METHODS OF MODULATING CELL PROLIFERATION

CROSS-REFERENCE

[001] This application claims the benefit of U.S. Provisional Application No. 63/593,212, filed October 25, 2023, and U.S. Provisional Application No. 63/572,126, filed March 29, 2024, each incorporated herein by reference in its entirety.

SEQUENCE LISTING

[002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on October 21, 2024, is named 56690_781_601_SL.xml and is 4,097 bytes in size.

BACKGROUND

[003] Cancer (e.g., tumor, neoplasm, metastases) is the second leading cause of death worldwide estimated to be responsible for about 10 million deaths each year. Many types of cancers are marked with mutations in one or more proteins involved in various signaling pathways leading to unregulated growth of cancerous cells. In some cases, about 25 to 30 percent (%) of tumors are known to harbor Rat sarcoma (Ras) mutations. In particular, mutations in the Kirsten Ras oncogene (K-Ras) are one of the most frequent Ras mutations detected in human cancers, including lung adenocarcinomas (LUADs) and pancreatic ductal adenocarcinoma (PDAC).

[004] Ras proteins have long been considered "undruggable," due to, in part, high affinity to their substrate guanosine-5'-triphosphate (GTP) and/or their smooth surfaces without any obvious targeting region. The specific G12C Ras gene mutation has been identified as a druggable target to which a number of G12C specific inhibitors have been developed. However, such therapeutics are still of limited application, as the G12C mutation in Ras exhibits a much lower prevalence rate as compared to other known Ras mutations, such as G12D and G12V. Drug resistance and lack of durability impose further limitations to such therapeutics.

[005] Son of Sevenless 1 (SOS1), a homolog of SOS2 in mammalian cells, acts as a guanine nucleotide exchange factor (GEF) that promotes release of inactive GDP from RAS-family proteins to enable GTP binding. SOS1 has been implicated in cancer via its ability to activate RAS-family protein signaling. SOS1 interacts with the adaptor protein Grb2 and the resulting SOS1/Grb2 complex binds to activated/phosphorylated Receptor Tyrosine Kinases (e.g., EGFR, ErbB2, ErbB3, ErbB4,TrkA, TrkB, TrkC, RET, c-MET, VEGFR1/2/3). SOS1 is also recruited to other phosphorylated cell surface receptors such as the T cell Receptor (TCR), B cell Receptor (BCR) and monocyte colony-stimulating factor receptor. This localization of SOS1 to the plasma membrane, proximal to RAS-family proteins, enables SOS1 to promote RAS-family protein activation.

SUMMARY

[006] There exists a considerable need for identifying combination therapies to address the long-felt need to overcome various challenges or limitations associated with a single agent therapy, such as, potential resistance mechanism to the single agent, and/or undesired side effects associated with a therapeutically required effective amount of the single agent. In particular, there remains a considerable need for compositions and methods to reduce Ras pathway signaling and hence Ras-driven neoplasm or malignancy by combining Ras inhibitors with another therapeutic agent. Such compositions and methods can be particularly useful for treating a variety of diseases including, but not

limited to, cancers and neoplasia conditions. The present disclosure addresses these needs, and provides additional advantages applicable for diagnosis, prognosis, and treatment for a wide diversity of diseases.

[007] In an aspect is provided a method of reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS protein overexpression, the method comprising administering to the cells (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

[008] In an aspect is provided a method of downregulating KRAS signaling output in a plurality of cancer cells, comprising: (i) assessing KRAS mutation status in a biological sample comprising nucleic acid from a subject; and (ii) administering an effective dose of (a) a SOS1 inhibitor and an effective dose of (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, if a KRAS mutation is detected in the sample, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

[009] In embodiments, the cancer cells can be any cancerous cells of hematological or solid tumor origin, including but are not limited to non-small cell lung cancer cells, colorectal cancer cells, or pancreatic cancer cells.

[010] In embodiments, cancer cells of the subject comprise a KRAS G12C mutant protein. In embodiments, cancer cells of the subject comprise a KRAS G12S mutant protein. In embodiments, cancer cells of the subject comprise overexpression of KRAS protein. In embodiments, cancer cells of the subject are refractory to at least one KRAS G12C inhibitor.

[011] In embodiments, the method further comprises administering (c) an additional agent or additional therapy. In embodiments, the additional agent is a checkpoint immune blockade agent, a SHP2 inhibitor, a PI3K inhibitor, a CDK4/6 inhibitor, a RAF inhibitor, a MEK inhibitor, an ERK inhibitor, an EGFR inhibitor, or an AKT inhibitor. In embodiments, the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation.

[012] In embodiments, the administration of (a) and (b) synergistically reduces proliferation of the cancer cells with a synergistic value of at least 0.05 as ascertained by Bliss independence criterion.

[013] In an aspect is provided a method of treating cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

[014] In embodiments, the cancer is a mutant KRAS-mediated cancer. In embodiments, the KRAS inhibitor is a compound, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3) or any embodiment of the preceding formulae.

[015] In an aspect is provided a method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b), and wherein the administration of (a) and (b) synergistically reduces proliferation of the cancer cells with a synergistic value of at least 0.05 as ascertained by Bliss independence criterion.

[016] In embodiments, the synergistic value is ascertained by Bliss independence criterion in accordance with the formula:

$$Y_{AB,O} - Y_{AB,P}$$

wherein:

$Y_{AB,O}$ is observed percent growth inhibition of the cancer cells by the application of (a) and (b) comprising (a) at dose A and (b) at dose B;

$Y_{AB,P}$ is predicted percent growth inhibition of the cancer cells by the application of (a) and (b) comprising (a) at dose A and (b) at dose B, wherein $Y_{AB,P} = Y_A + Y_B - Y_A Y_B$;

Y_A is observed percent growth inhibition of the cancer cells by (a) alone at dose A;

Y_B is observed percent growth inhibition of the cancer cells by (b) alone at dose B; and

$Y_A Y_B$ is the product of Y_A and Y_B.

[017] In embodiments, the synergistic value is at least 0.1. In embodiments, the synergistic value is at least 0.4. In embodiments, the synergistic value is at least 1. In embodiments, the synergistic value is at least 5.

[018] In embodiments, the administration of (a) and (b) exhibits a synergistic effect. In embodiments, the synergistic effect is characterized by a synergistic value of at least 0.05 as ascertained by Bliss independence criterion. In embodiments, one or both of (a) and (b) are administered at a sub-therapeutic dose but achieve a therapeutic effect at least comparable to administering (a) or (b) alone at its therapeutically effective amount. In embodiments, KRAS inhibitor is administered at a dose less than about 25% the standard monotherapy dose.

[019] In an aspect is provided a method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SI-1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, and (iii) a pharmaceutically acceptable excipient.

[020] In an aspect is provided a method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

[021] In embodiments, the cancer is lung cancer. In embodiments, the cancer is a non-small cell lung cancer. In embodiments, the cancer is colorectal cancer. In embodiments, the cancer is pancreatic cancer. In embodiments, the cancer is a solid cancer.

[022] In embodiments, cancer cells of the subject comprise a KRAS G12C mutant protein. In embodiments, cancer cells of the subject comprise a KRAS G12S mutant protein. In embodiments, cancer cells of the subject comprise overexpression of KRAS protein. In embodiments, cancer cells of the subject are refractory to at least one KRAS G12C inhibitor.

[023] In embodiments, the subject exhibits relapse of the cancer. In embodiments, the subject has previously been treated with a KRAS G12C inhibitor. In embodiments, the subject is a naïve subject that has not been treated with a KRAS inhibitor prior to administering (a) and (b).

[024] In embodiments, the method further comprises administering (c) an additional agent or additional therapy. In embodiments, the additional agent is selected from an immunomodulatory agent, an anti-nausea agent, an antiemetic, a pain reliever, a chemotherapeutic agent, a SHP2 inhibitor, a PI3K inhibitor, a CDK4/6 inhibitor, a RAF inhibitor, a MEK inhibitor, an ERK inhibitor, an EGFR inhibitor, and an AKT inhibitor. In embodiments, the additional agent is selected from an immunomodulatory agent, a cytokine blockade agent, and a checkpoint immune blockade agent. In

embodiments, the additional agent is selected from an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-LAG3 antibody, an anti-TIM3 antibody, and combinations thereof. In embodiments, the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation.

[025] In embodiments, the administration of (a) and (b) reduces incidence of one or more adverse events associated with the SOS1 inhibitor or the KRAS inhibitor. In embodiments, the adverse event is selected from diarrhea, rash, nausea, vomiting, decreased appetite, fatigue, musculoskeletal pain, dyspnea, and acute kidney injury. In embodiments, the adverse event is selected from diarrhea, rash, and nausea.

[026] In embodiments, (a) and (b) are administered in the same formulation. In embodiments, (a) and (b) are administered in separate formulations.

[027] In embodiments of the methods described herein, (a) is administered prior to administering (b). In embodiments of the methods described herein, (a) is administered concurrently with administering (b). In embodiments of the methods described herein, (a) is administered subsequent to administering (b).

[028] In an aspect is provided a kit for use in reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS overexpression, the kit comprising: (1) a composition comprising a small molecule SOS1 inhibitor of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SI-1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or any embodiment of the preceding formulae; (2) a composition comprising a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae; and (3) instructions for using the composition(s) of (1) and (2).

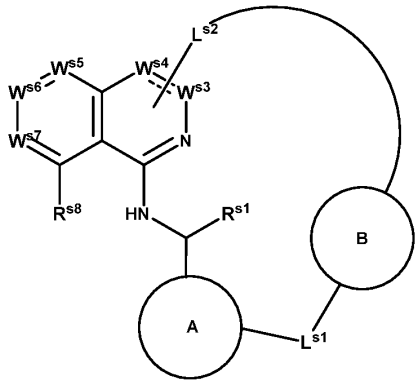
[029] In an aspect is provided a kit for use in reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS overexpression, the kit comprising: (1) a composition comprising a small molecule SOS1 inhibitor of Formula (SI-1); (2) a composition comprising a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae; and (3) instructions for using the composition(s) of (1) and (2).

[030] In embodiments of the kit, the SOS1 inhibitor and the KRAS inhibitor are formulated in the same unit dosage form. In embodiments of the kit, the SOS1 inhibitor and the KRAS inhibitor are formulated in different unit dosage forms.

[031] In an aspect is provided a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SI-1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, and (iii) a pharmaceutically acceptable excipient.

[032] In an aspect is provided a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, and (iii) a pharmaceutically acceptable excipient.

[033] In embodiments of the methods described herein, the SOS1 inhibitor is a compound of Formula (SI-1):



(SI-1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from C_{5-7} carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R^{s11};

is absent or selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

W^{s3} is selected from $N(R^{s3b})$, N, $C(R^{s3})$, and C(O);

W^{s4} is selected from $N(R^{s4b})$, N, $C(R^{s4})$, and C(O);

W^{s5} is selected from $N(R^{s5b})$, N, and $C(R^{s5})$;

W^{s6} is selected from $C(R^{s6})$ and C(O);

W^{s7} is $C(R^{s7})$;

R^{s1} is C_{1-3} alkyl optionally substituted with one or more R^{s11c};

R^{s8} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is

independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, and R^{s5b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s11} and R^{s11a} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11c} is independently selected at each occurrence from halogen, $-OR^{s12}$, and $-N(R^{s12})(R^{s13})$;

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are

optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

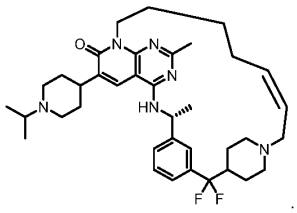
R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

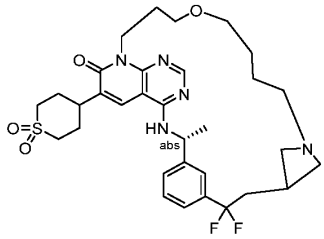
R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

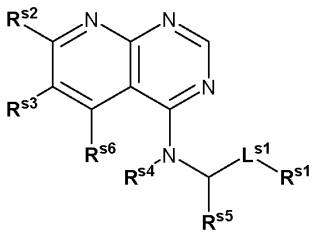
------ indicates a single or double bond such that all valences are satisfied.

[034] In embodiments, the SOS1 inhibitor is selected from BI-3406, MRTX0902, BAY 293, RMC-5845, and BI-1701963.

[035] In embodiments, the SOS1 inhibitor is  .

[036] In embodiments, the SOS1 inhibitor is  .

[037] In embodiments of the methods described herein, the SOS1 inhibitor is a compound of Formula (SIV-1):



(SIV-1),

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

L^{s1} is a bond;

R^{s1} is 6- to 10-membered aryl, wherein the 6- to 10-membered aryl is optionally substituted with one or more independently selected R^{s10} substituents;

R^{s2} is halogen or OR^{s2a};

R^{s2a} is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl is optionally substituted with one, two, or three independently selected R^{s20a} substituents;

R^{s3} is halogen, C_{1-6} alkyl, C_{3-14} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein the C_{1-6} alkyl, C_{3-14} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl is optionally substituted with one, two, or three independently selected R^{s20b} substituents;

R^{s4} is H, C_{1-6} alkyl, or C_{1-6} haloalkyl;

R^{s5} is H, C_{1-6} alkyl, or C_{1-6} haloalkyl;

R^{s6} is H, halogen, CN, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one, two, or three independently selected R^{s20c} substituents;

each R^{s10} is independently halogen, CN, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein each C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three independently selected R^{s20d} substituents;

each R^{s20a} is independently halogen, CN, C_{1-6} alkyl, CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OCH_2C(O)OR^{s22}$, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, $S(O)_2NR^{s22}R^{s23}$, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$; and

wherein each CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$;

each R^{s20b} is independently halogen, CN, C_{1-6} alkyl, CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OCH_2C(O)OR^{s22}$, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, $S(O)_2NR^{s22}R^{s23}$, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$; and

wherein each CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$;

each R^{s20c} is independently halogen, CN, C_{1-6} alkyl, CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OCH_2C(O)OR^{s22}$, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, $S(O)_2NR^{s22}R^{s23}$, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$; and

wherein each CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$;

each R^{s20d} is independently halogen, CN, C_{1-6} alkyl, CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OCH_2C(O)OR^{s22}$, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, $S(O)_2NR^{s22}R^{s23}$, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$; and

wherein each CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$;

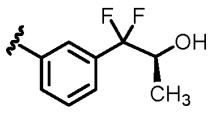
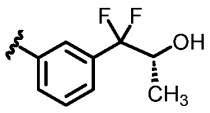
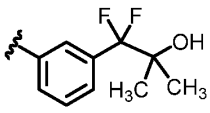
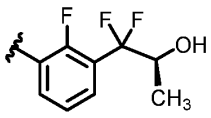
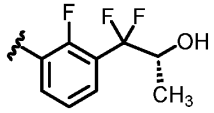
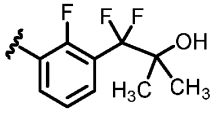
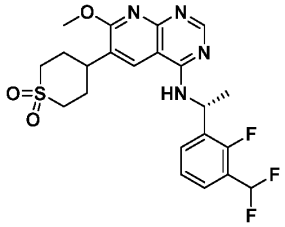
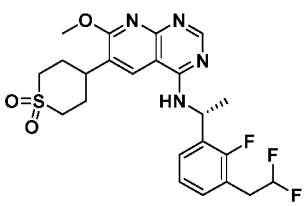
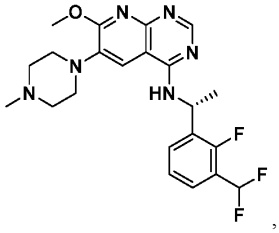
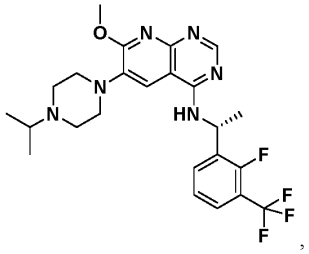
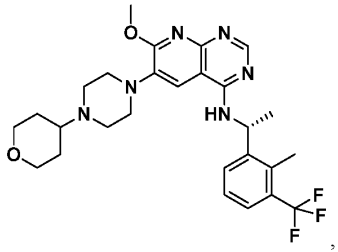
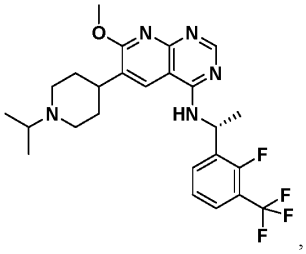
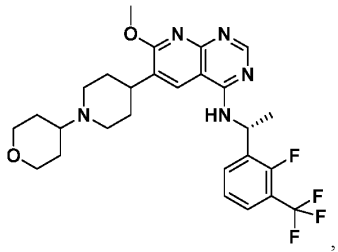
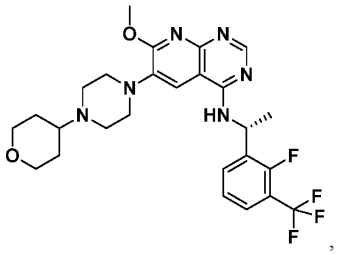
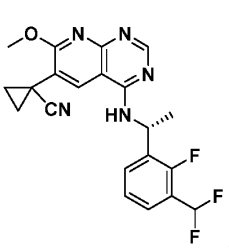
each R^{s21} is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein each C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen and C_{1-6} alkyl;

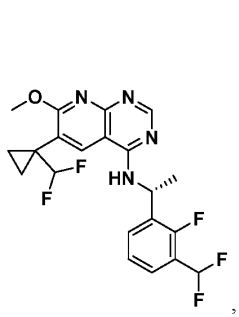
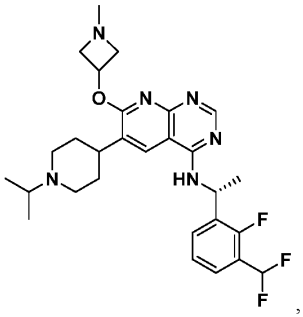
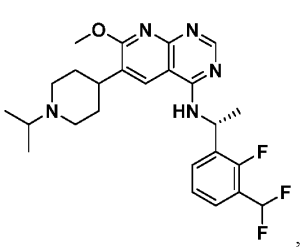
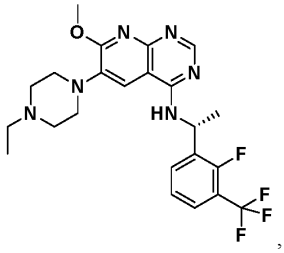
each R^{s22} is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein each C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen and C_{1-6} alkyl;

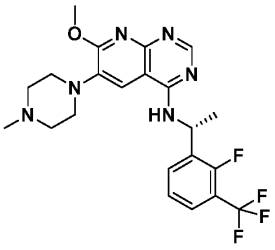
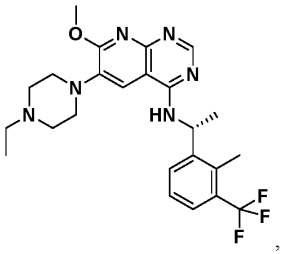
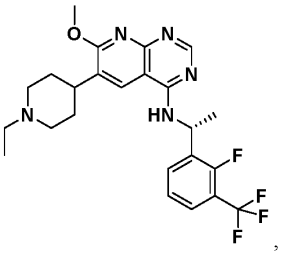
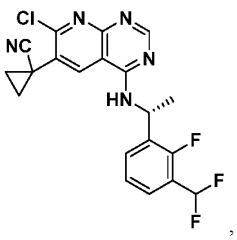
each R^{s23} is independently H or C_{1-6} alkyl;

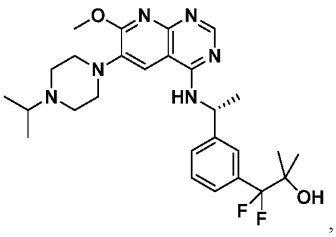
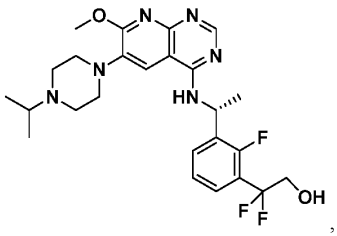
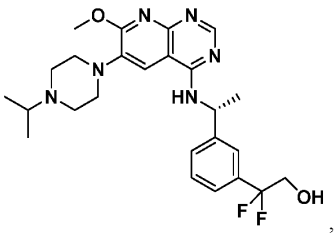
each R^{s24} is independently H or C_{1-6} alkyl; and

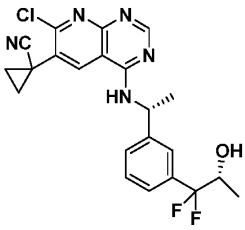
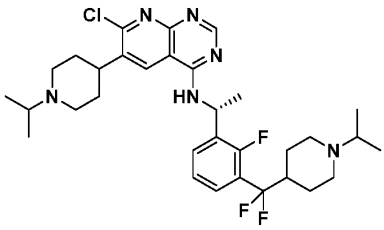
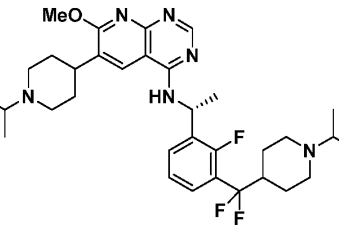
each R^{s25} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein each C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl.

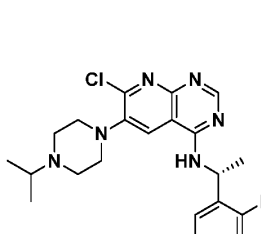
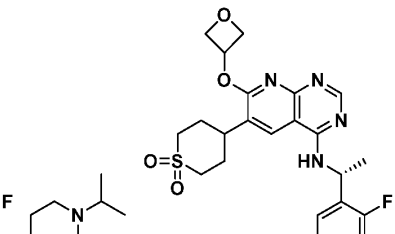
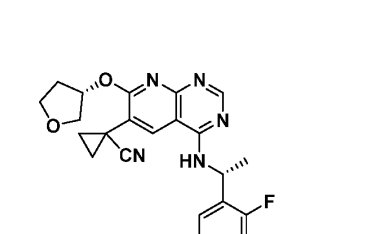
[038] In embodiments, R^{s3} is C_{2-9} heterocycloalkyl, wherein the C_{2-9} heterocycloalkyl is optionally substituted with one, two, or three independently selected R^{s20b} substituents. In embodiments, R^{s3} is C_{3-10} cycloalkyl, wherein the C_{3-10} cycloalkyl is optionally substituted with one, two, or three independently selected R^{s20b} substituents. In embodiments, R^{s1} is:  ,  ,  ,  ,  , or  . In embodiments, the SOS1 inhibitor is a compound selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,

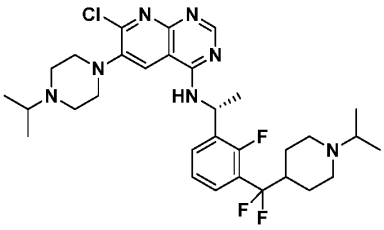
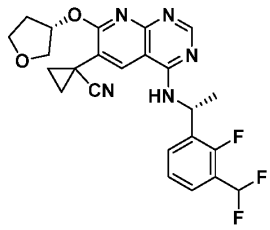
 ,  ,  ,  ,

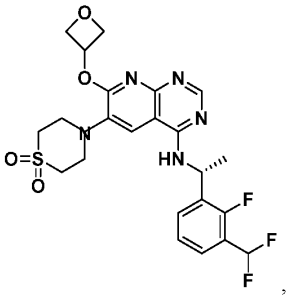
 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 , ,  ,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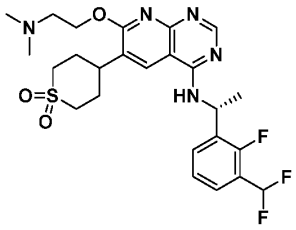
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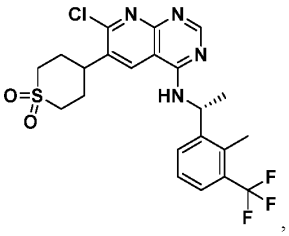
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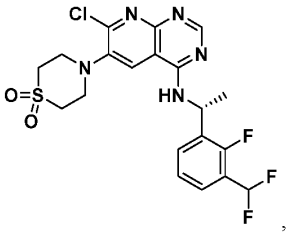
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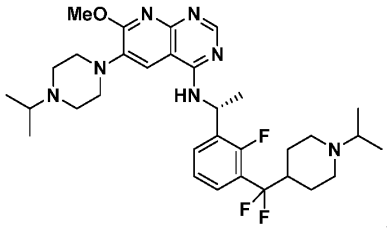
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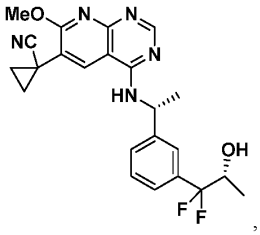
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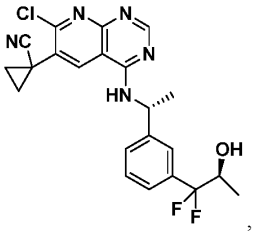
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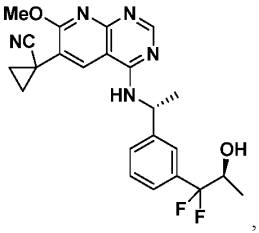
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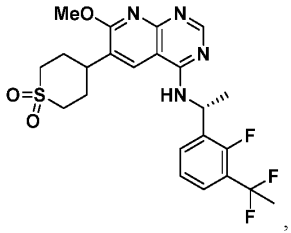
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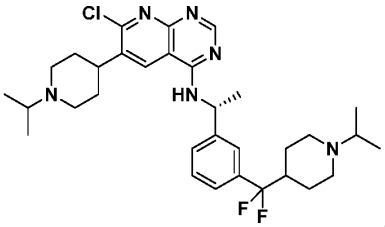
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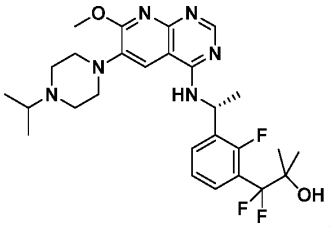
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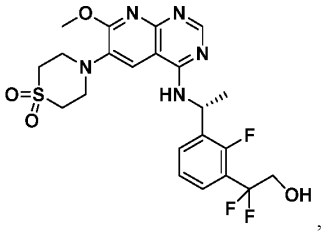
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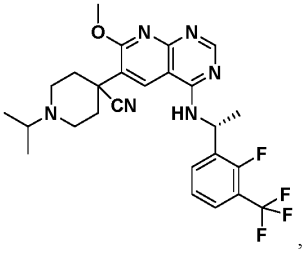
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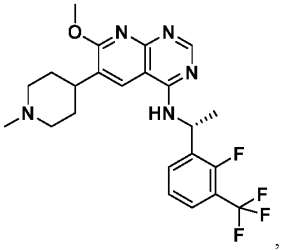
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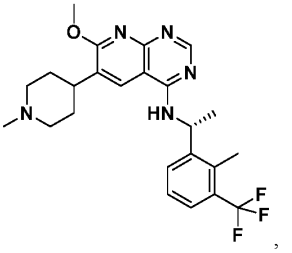
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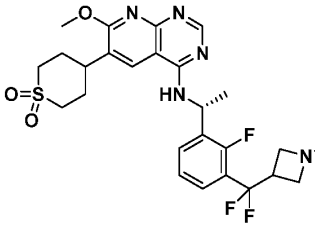
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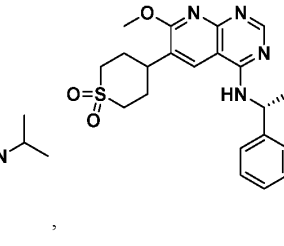
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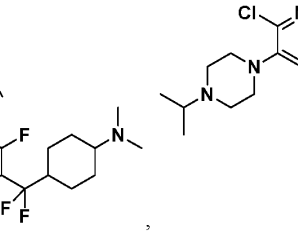
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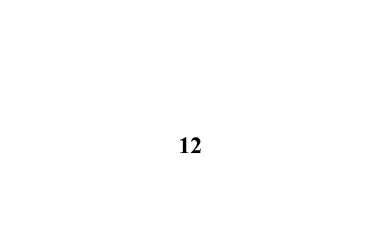
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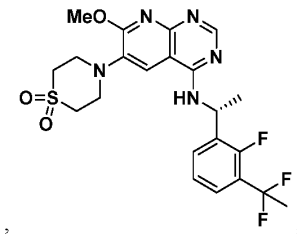
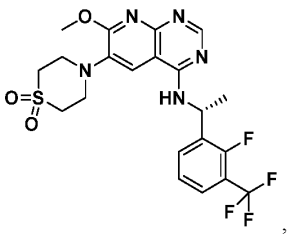
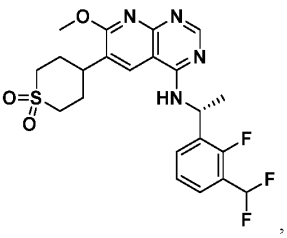
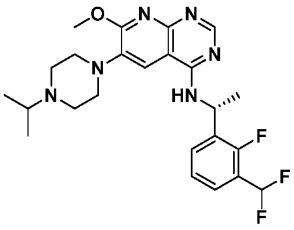
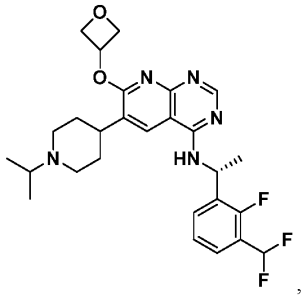
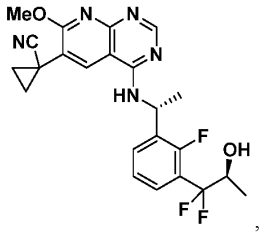
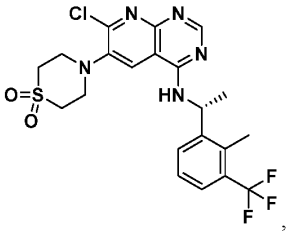
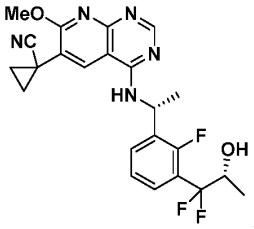
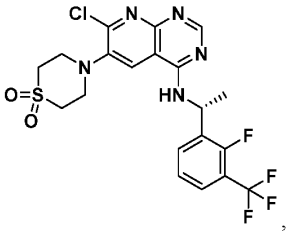
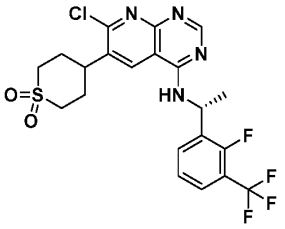
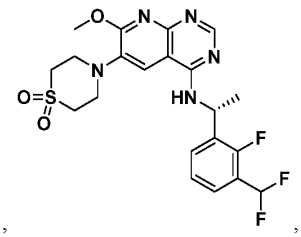
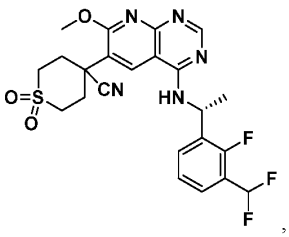
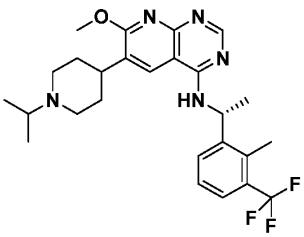
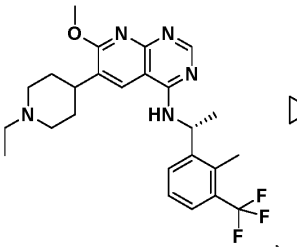
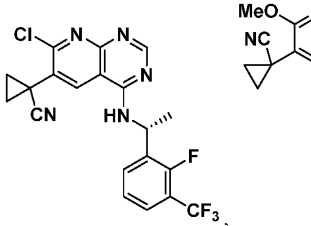
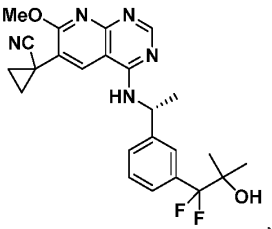
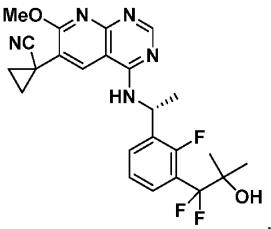
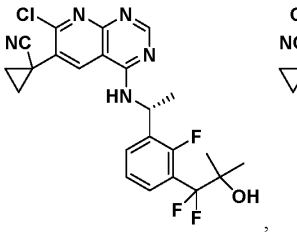

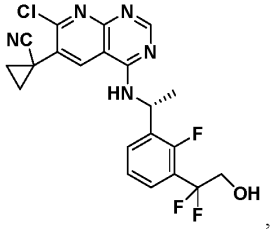
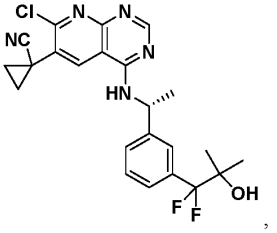
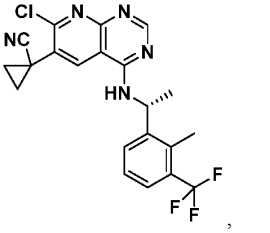

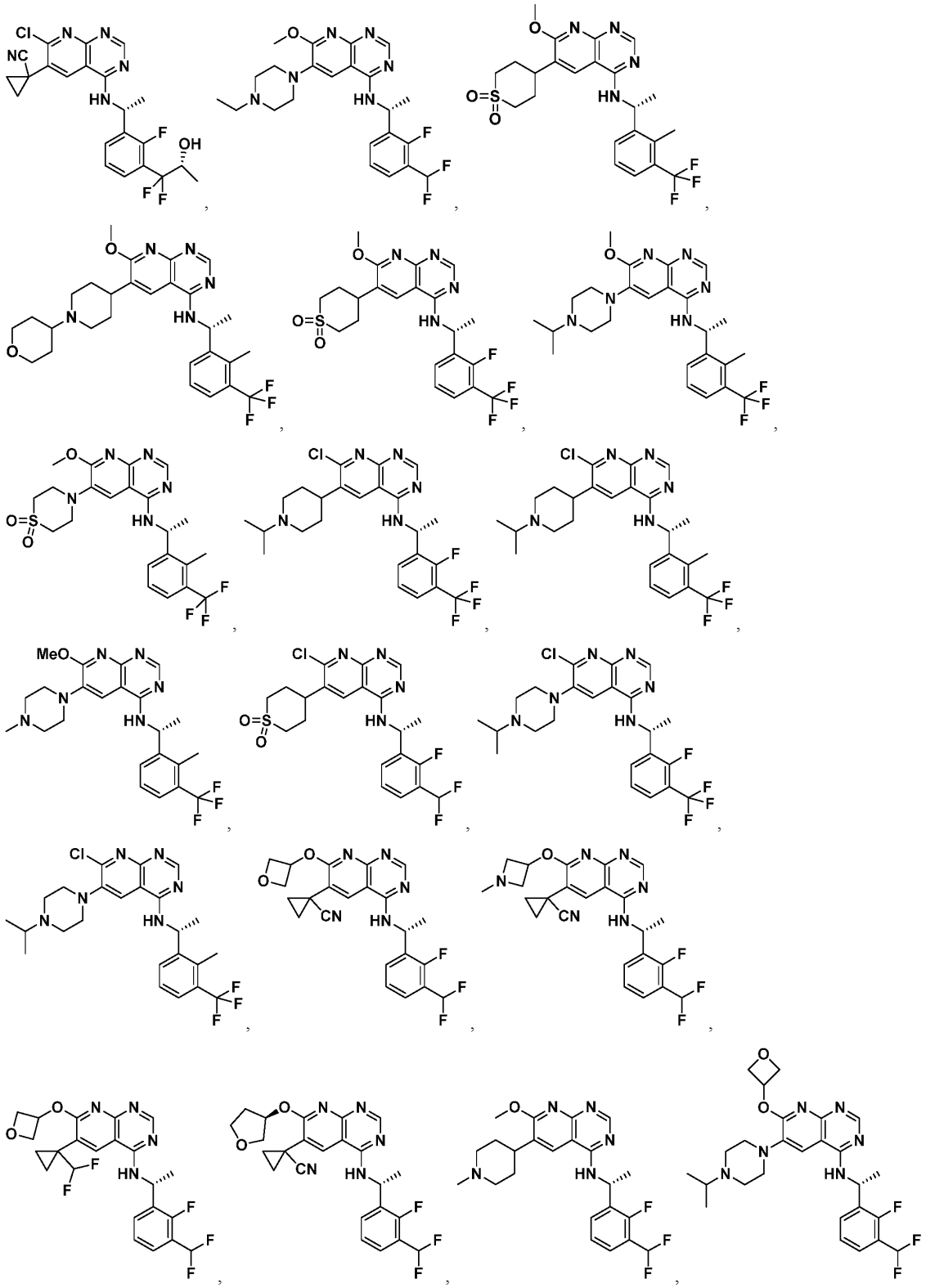

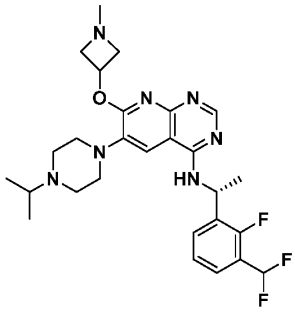
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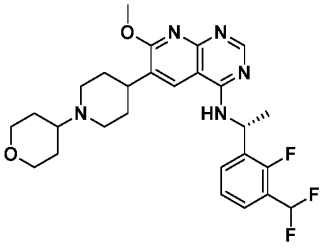
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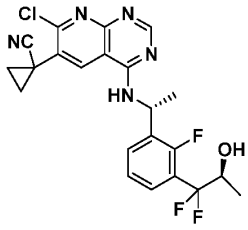
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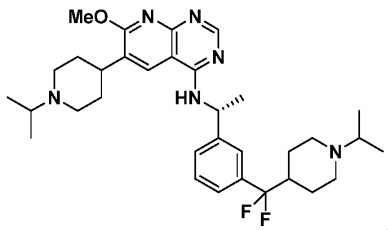
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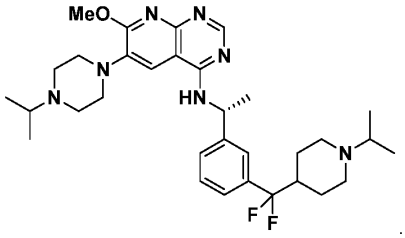
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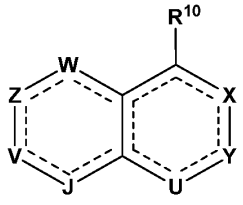
[039] In embodiments of the methods described herein, the KRAS inhibitor is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:


Formula (I);

wherein

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

Z is N, $C(R^{8})$, $N(R^{8b})$, $C(R^{8})(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

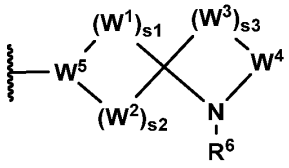
V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

Y is N, $C(R^{2})$, $C(R^{2})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$;

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^{7}-R^{7}$;

L^{7} is a bond, -O-, $-N(R^{14})-$, -C(O)-, -S-, $-S(O)_2-$, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^{7} is  ;

W^{1} and W^{3} are independently selected from $N(R^{1})$, $N(R^{4})$, $C(R^{1})(R^{1})$, $C(R^{1})(R^{4})$, $C(R^{4})(R^{4})$, C(O), S, O, S(O), and $S(O)_2$;

W^{2} is independently selected from a $N(R^{1})$, $N(R^{4})$, $C(R^{1})(R^{1})$, $C(R^{1})(R^{4})$, $C(R^{4})(R^{4})$, C(O), S, O, S(O), and $S(O)_2$;

W^{4} is selected from $C(R^{1})(R^{1})$, $C(R^{1})(R^{4})$, $C(R^{4})(R^{4})$, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is 1 and s2 is 0, 2, or 3; s1 is 2 and s2 is 0, 1, or 3; s1 is 3 and s2 is 0 to 3; s1 is 4 and s2 is 0 to 3; s1 is 5 and s2 is 0 to 3; or s1 is 6 and s2 is 0 to 3;

s3 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, $=C(R^{21b})_2$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is -L^2-R^5, wherein R^6 is optionally capable of forming a covalent bond with a RAS amino acid;

L^2 is a bond, -O-, -$N(R^{4d})$-, -C(O)-, -S-, -$S(O)_2$-, -S(O)-, -$P(O)R^{4d}$-, -$CR^{4c}R^{4c}$-, -$OCR^{4c}R^{4c}$-, -$N(R^{4d})CR^{4c}R^{4c}$-, -$C(O)CR^{4c}R^{4c}$-, -$SCR^{4c}R^{4c}$-, -$S(O)_2CR^{4c}R^{4c}$-, -$S(O)CR^{4c}R^{4c}$-, -$P(O)R^{4d}CR^{4c}R^{4c}$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}$, -$CR^{4c}R^{4c}O$-, -$CR^{4c}R^{4c}N(R^{4d})$-, -$CR^{4c}R^{4c}C(O)$-, -$CR^{4c}R^{4c}S$-, -$CR^{4c}R^{4c}S(O)_2$-, -$CR^{4c}R^{4c}S(O)$-, -$CR^{4c}R^{4c}P(O)R^{4d}$-, -$N(R^{4d})C(O)$-, -$N(R^{4d})S(O)_2$-, -$N(R^{4d})S(O)$-, -$N(R^{4d})P(O)R^{4d}$-, -$C(O)N(R^{4d})$-, -$S(O)_2N(R^{4d})$-, -$S(O)N(R^{4d})$-, -$P(O)R^{4d}N(R^{4d})$-, -OC(O)-, -$OS(O)_2$-, -OS(O)-, -$OP(O)R^{4d}$-, -C(O)O-, -$S(O)_2O$-, -S(O)O-, -$P(O)R^{4d}O$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}$-, -$OCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$SCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$CR^{4c}R^{4c}CR^{4c}R^{4c}O$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)$-, or -$CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}$-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, -$OC(O)R^{14a}$, -$N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14a}$, and -$N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, and -$OC(O)R^{14a}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-}

$_{6}$alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

R^5 is a 5 or 6 membered partially unsaturated heterocycloalkyl or a 5 or 6 membered heteroaryl, each optionally substituted with one, two or three R^{20k}, wherein the partially unsaturated 5 or 6 membered heterocycloalkyl or 5 or 6 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and the 5 or 6 membered partially unsaturated heterocycloalkyl or 5 or 6 membered heteroaryl is each bonded to L^2 through a ring nitrogen;

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is -L^1-R^{19};

R^{17b} is -L^{1b}-R^{19};

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, -$N(R^{14})$-, -C(O)-, -$N(R^{14})C(O)$-, -$C(O)N(R^{14})$-, -S-, -$S(O)_2$-, -S(O)-, -$S(O)_2N(R^{14})$-, -$S(O)N(R^{14})$-, -$N(R^{14})S(O)$-, -$N(R^{14})S(O)_2$-, -$OCON(R^{14})$-, -$N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, -$C(O)N(R^{14})$-, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered

heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12''})(R^{13})$, $-N=(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{4-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, and $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, –

(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -$C(O)OR^{12'}$, -$OC(O)N(R^{12'})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12'})(R^{13})$, -$C(O)C(O)N(R^{12'})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, -$CH_2C(O)N(R^{12'})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12'})(R^{13})$, –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the

nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, C_{1-9}heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $=C(R^{21b})_2$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{21}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{21}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-}

$_9$heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

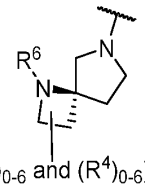
each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

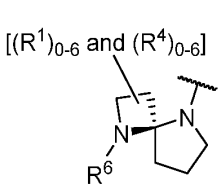
------ indicates a single or double bond such that all valences are satisfied.

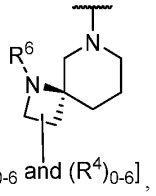
[040] In embodiments, R^5 is a 5 membered heteroaryl optionally substituted with one, two or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and the 5 membered heteroaryl is bonded to L^2 through a ring nitrogen. In embodiments, L^2 is -C(O)-; and R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and L^2 is directly bonded to an N ring atom of R^5.

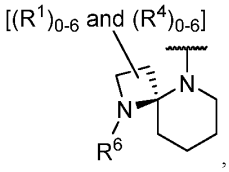
[041] In embodiments, L^7 is a bond.

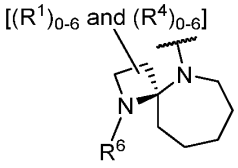
[042] In embodiments, s1 is 2 and s2 is 0, 1, or 3.

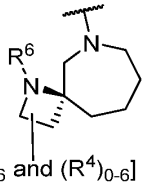
[043] In embodiments, R^7 is selected from 

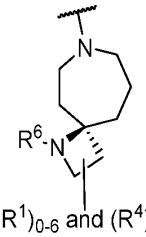
, 

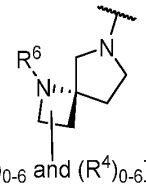
, 

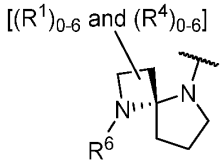
, 

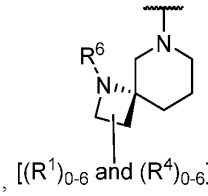
, 

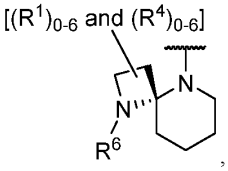
, 

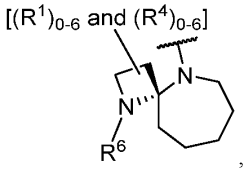
, 

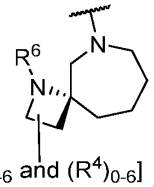
, 

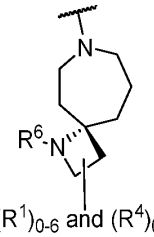
, 

, 

, 

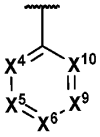
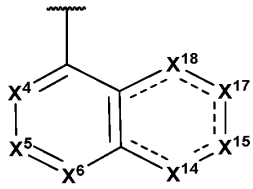
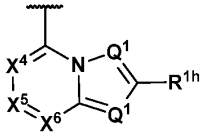
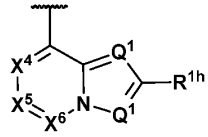
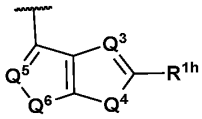
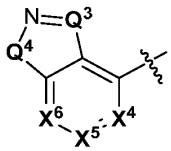
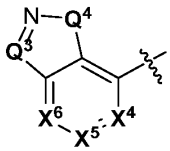
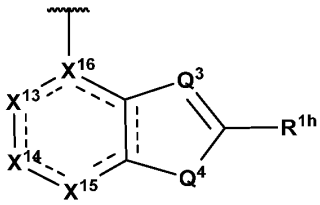
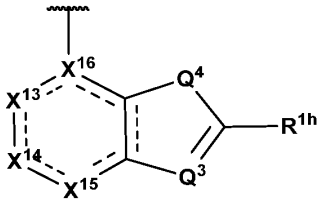
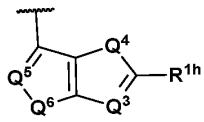
, 

, 

, and 

; wherein R^1 and R^4 substituents may be bonded to either spirocyclic ring.

[044] In embodiments, R^{17} is $-L^1-R^{19}$ or $-L^{1b}-R^{19}$; L^1 is a bond, and L^{1b} is a bond.

[045] In embodiments, R^{19} is:  ,  ,  ,  ,  ,  ,  ,  ,  , or  ;

Q^1, Q^3, and Q^5 are independently selected from N and $C(R^{1d})$;

Q^4 and Q^6 are independently selected from O, S, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

X^4, X^5, X^6, X^9, X^{10} are independently selected from $C(R^{1a})$ and N;

X^{13} is selected from a bond, $C(R^{1a})$, N, C(O), $C(R^{1a})(R^{1b})$, $C(O)C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})N(R^{1c})$, and $N(R^{1c})$;

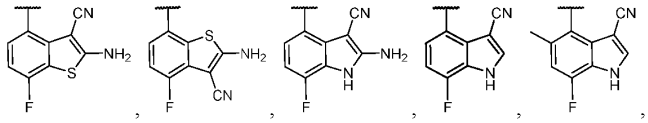
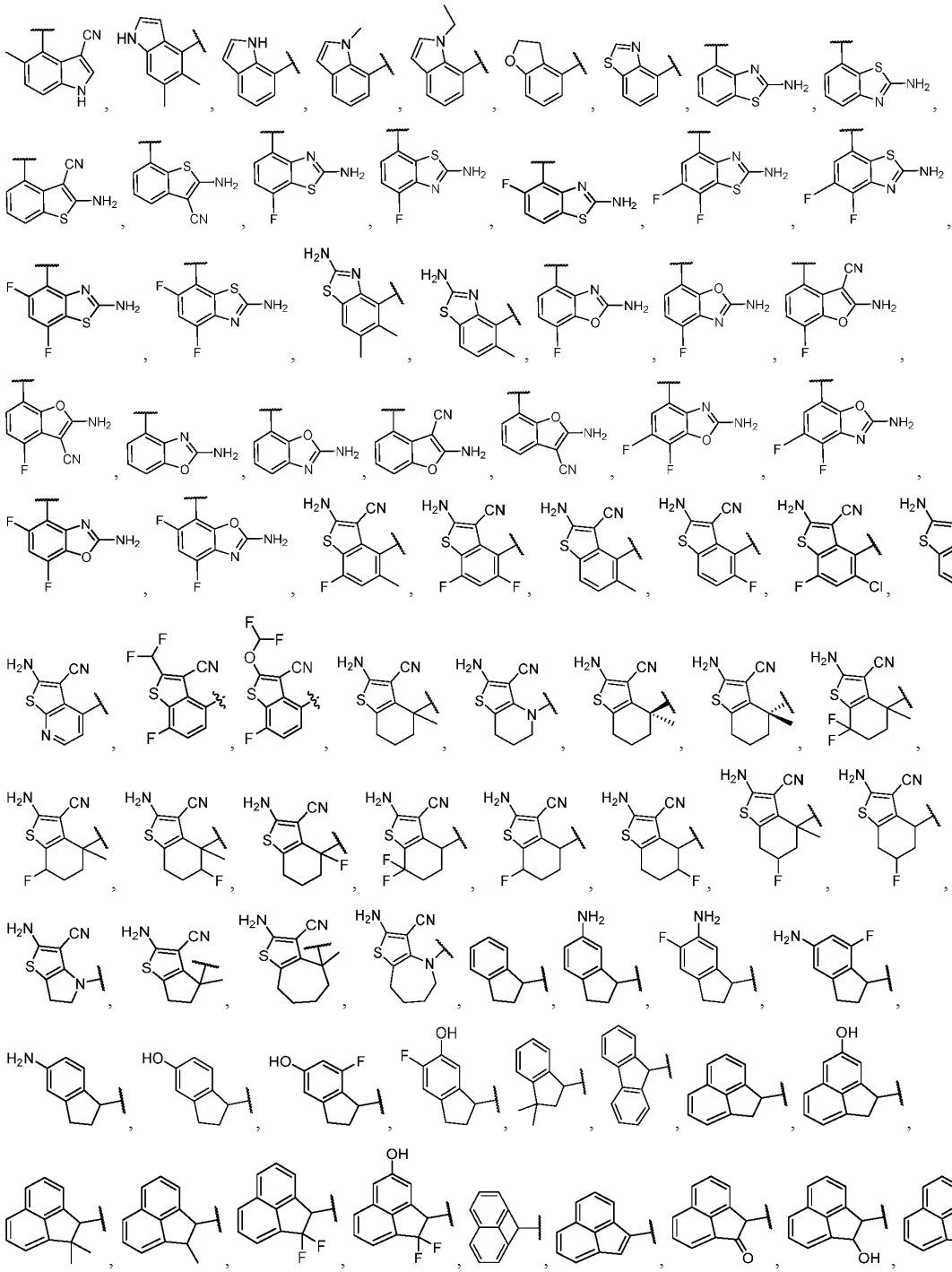
X^{14}, X^{15}, X^{17}, X^{18} are independently selected from a C(O), $C(R^{1a})$, N, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

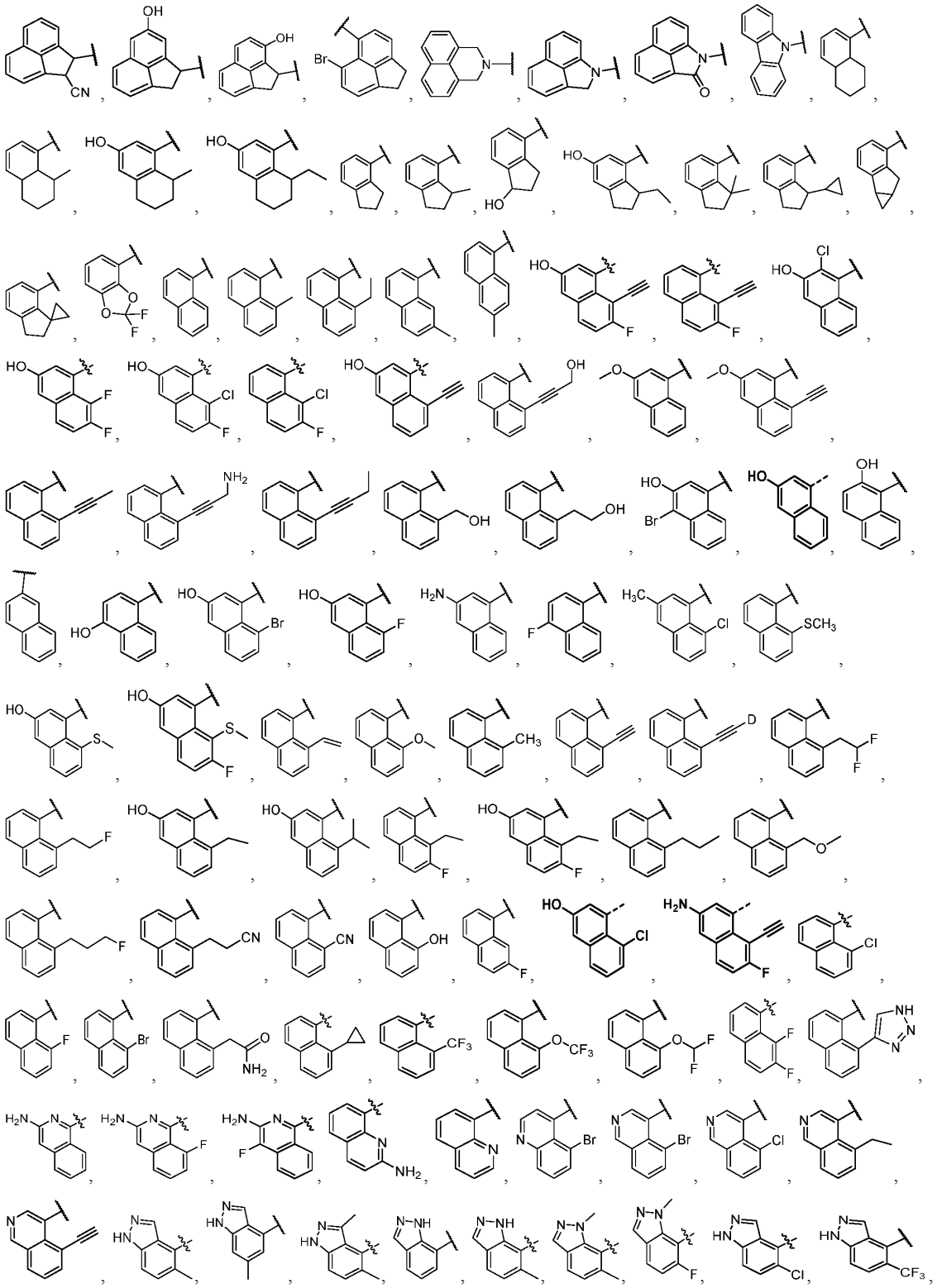
X^{16} are independently selected from C, N, and $C(R^{1a})$;

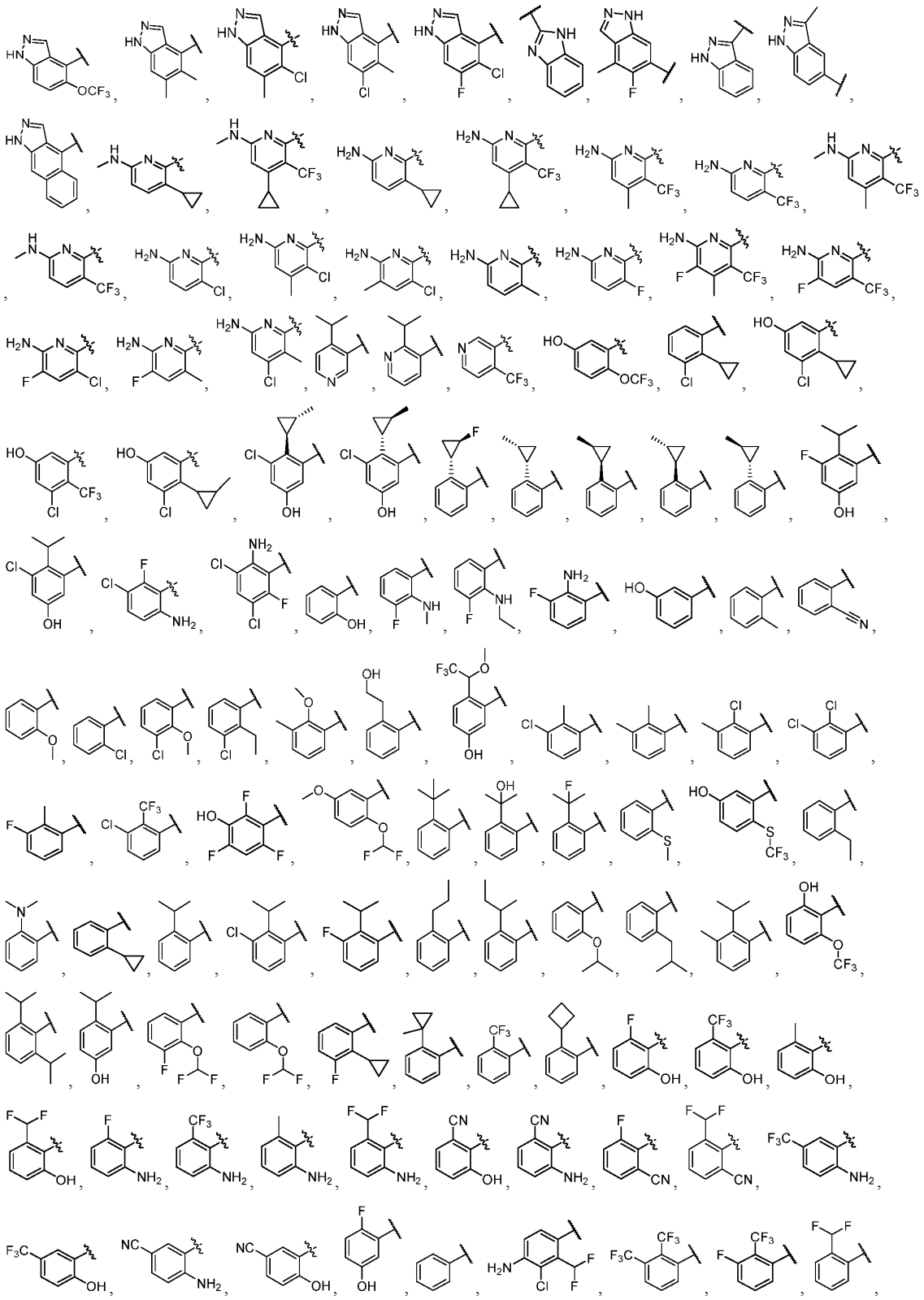
each R^{1a}, R^{1b}, R^{1d}, and R^{1h} are each independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1a} and R^{1b} bonded to the same carbon are joined to form a 3-10 membered heterocycloalkyl ring or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or two R^{1a} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, C_{6-10}aryl ring, 5-12 membered heteroaryl ring, or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or R^{1h} and one of R^{1a}, R^{1b}, R^{1c}, and R^{1d} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, and C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; and

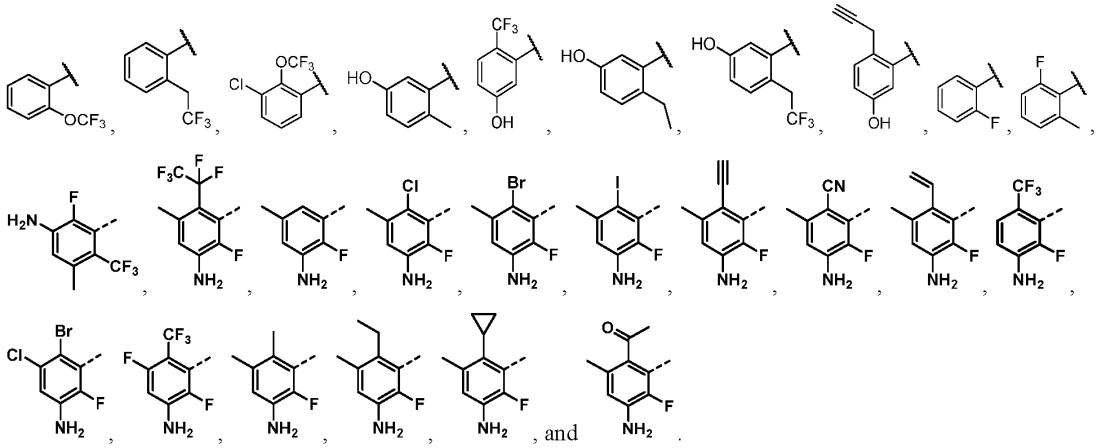
each R^{1c} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-}

$_9$heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}.

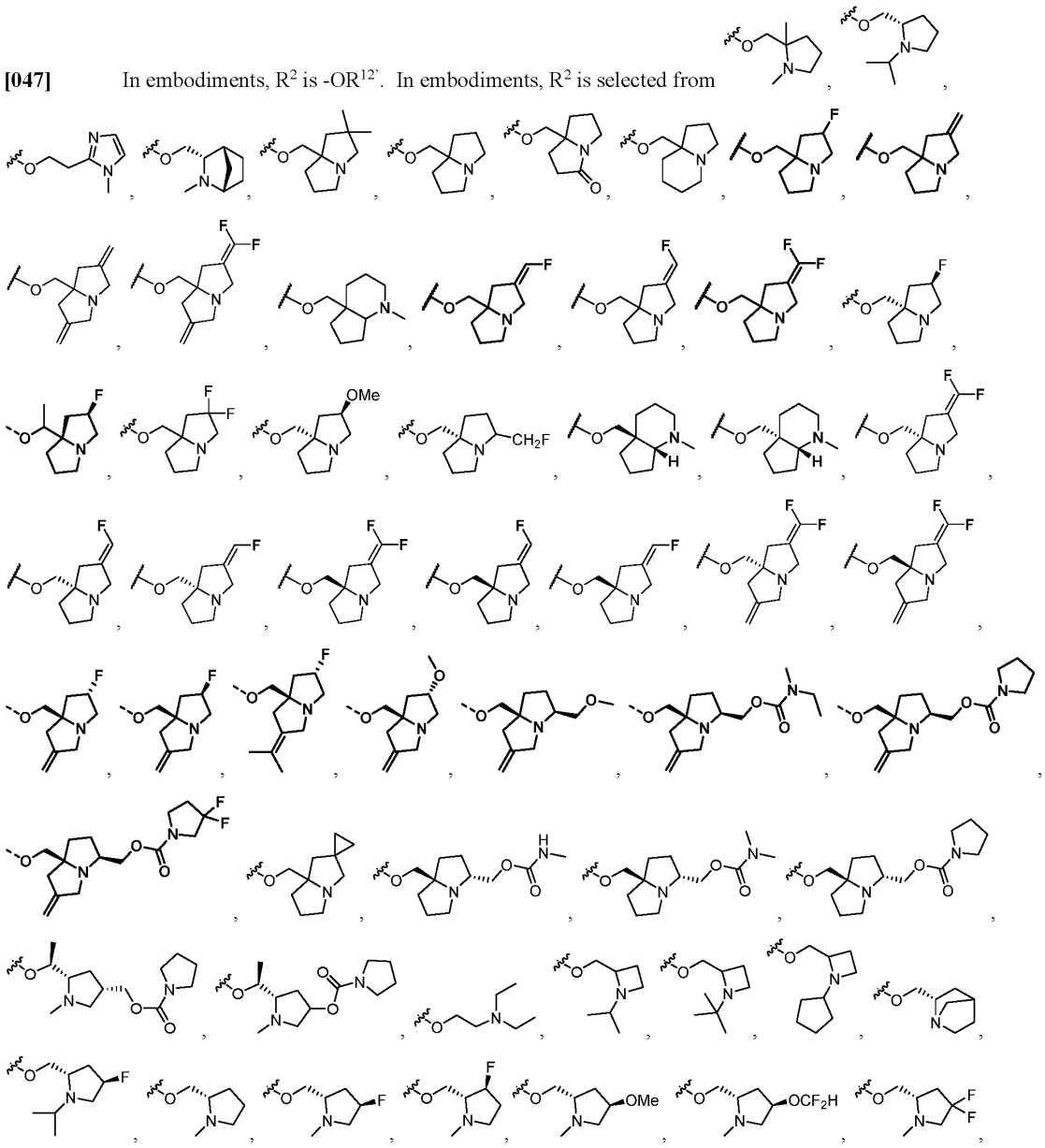
[046] In embodiments, R^{19} is selected from 


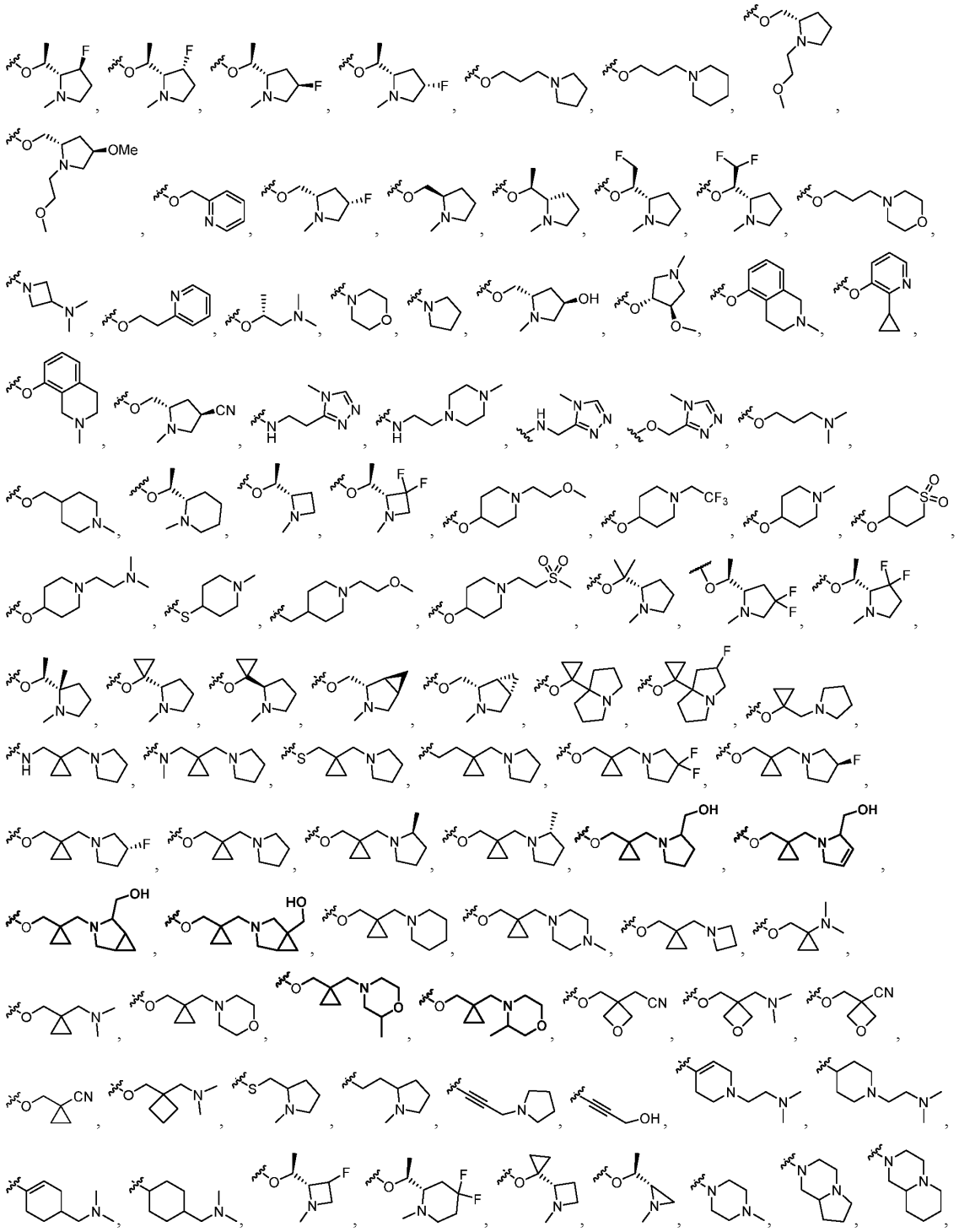


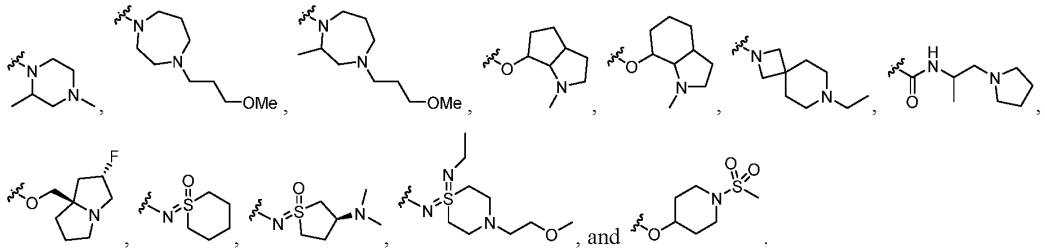




[047] In embodiments, R^2 is $-OR^{12'}$. In embodiments, R^2 is selected from







[048] In embodiments of the methods described herein, wherein the KRAS inhibitor is a compound of Formula (I) as recited above, or a pharmaceutically acceptable salt or solvate thereof;

W is a $C(R^{18})$ or C(O); Z is N, $C(R^8)$, or $N(R^{8b})$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^2)$; U is N; X is N;

L^1 is a bond;

L^7 is a bond;

W^1, W^2, and W^3 are independently selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, and O; W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$; W^5 is selected from N and CH;

L^2 is -C(O)-; R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N ring atom of R^5;

R^2 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12'}$, $-SR^{12'}$, and $-N(R^{12''})(R^{13})$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20d};

R^8 is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12}$, $-SR^{12}$, and $-N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20e};

R^{8b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20e};

R^{16} is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12}$, $-SR^{12}$, and $-N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20g};

R^{18} is hydrogen; and

all other variables are as described for a compound of Formula (I) as recited in the method above.

[049] In embodiments of the methods described herein, wherein the KRAS inhibitor is a compound of Formula (I) as recited above, or a pharmaceutically acceptable salt or solvate thereof;

W^1, W^2, and W^3 are independently selected from CH_2 and O; W^4 is CH_2; W^5 is selected from N and CH;

R^2 is $-OR^{12'}$;

R^8 is independently selected halogen and C_{1-6}haloalkyl;

R^{8b} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20e};

R^{16} is halogen; and

all other variables are as described for a compound of Formula (I), as recited in the method or embodiment thereof, of the two paragraphs immediately above.

[050] In an aspect is provided a kit for use in reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS overexpression, the kit comprising:

(1) a composition comprising a SOS1 inhibitor of Formula (SI-1);

(2) a composition comprising a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H); and

(3) instructions for using the composition(s) of (1) and (2).

[051] In an aspect is provided a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

[052] In an aspect is provided a method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

[053] In an aspect is provided a kit for use in reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS overexpression, the kit comprising:

(1) a composition comprising a SOS1 inhibitor of Formula (SIV-1);

(2) a composition comprising a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H); and

(3) instructions for using the composition(s) of (1) and (2).

[054] In an aspect is provided a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SIV-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

[055] In an aspect is provided a method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SIV-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

[056] In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Table 2a, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Table 2b, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Table 1a, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Table 1b, or a pharmaceutically acceptable salt or solvate thereof.

INCORPORATION BY REFERENCE

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

individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF DRAWINGS

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

[059] **FIG. 1A** shows a degree of growth inhibition of H358 cells (KRAS-G12C mutant) cells upon treatment with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A, at various concentrations) alone, (ii) a subject KRAS inhibitor (e.g., Compound K) alone, or (iii) a combination of (i) and (ii) at various concentrations.

[060] **FIG. 1B** shows a degree of synergy across the drug combinations in **FIG. 1A**, as calculated using the BLISS independence model.

[061] **FIG. 2A** shows a degree of growth inhibition of H2122 (KRAS-G12C mutant) cells upon treatment with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A, at various concentrations) alone, (ii) a subject KRAS inhibitor (e.g., Compound K) alone, or (iii) a combination of (i) and (ii) at various concentrations.

[062] **FIG. 2B** shows a degree of synergy across the combinations in **FIG. 2A**, as calculated using the BLISS independence model.

[063] **FIG. 3A** shows a degree of growth inhibition of LU99 (KRAS-G12C mutant) cells upon treatment with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A, at various concentrations) alone, (ii) a subject KRAS inhibitor (e.g., Compound K) alone, or (iii) a combination of (i) and (ii) at various concentrations.

[064] **FIG. 3B** shows a degree of synergy across the combinations in **FIG. 3A**, as calculated using the BLISS independence model.

[065] **FIG. 4** shows results of a study in which mice bearing CR9528 PDX tumors (colorectal cancer exhibiting a KRAS G12C mutation) were treated with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A) alone, (ii) a subject KRAS inhibitor (e.g., Compound K) alone, or (iii) a combination of (i) and (ii). The results demonstrate that the SOS1 inhibitor disclosed herein synergistically reduces tumor volume in combination with a KRAS inhibitor in the tumor model.

[066] **FIG. 5** shows results of a study in which mice bearing SW837 xenograft tumors (colorectal cancer exhibiting a KRAS G12C mutation) were treated with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A) alone, (ii) a subject KRAS inhibitor (e.g., Compound K) alone, or (iii) a combination of (i) and (ii). The results demonstrate that the SOS1 inhibitor disclosed herein synergistically reduces tumor volume in combination with a KRAS inhibitor in the tumor model.

[067] **FIG. 6** shows results of a study in which mice bearing LU1147 PDX tumors (NSCLC exhibiting a KRAS G12C mutation) were treated with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A) alone, (ii) a subject KRAS inhibitor (e.g., Compound K) alone, or (iii) a combination of (i) and (ii). The results demonstrate that the SOS1 inhibitor disclosed herein synergistically reduces tumor volume in combination with a KRAS inhibitor in the tumor model.

DETAILED DESCRIPTION

[068] The practice of some embodiments disclosed herein employ, unless otherwise indicated, conventional techniques of immunology, biochemistry, chemistry, molecular biology, microbiology, cell biology, genomics and recombinant DNA, which are within the skill of the art. See for example Sambrook and Green, Molecular Cloning: A

Laboratory Manual, 4th Edition (2012); the series Current Protocols in Molecular Biology (F. M. Ausubel, et al. eds.); the series Methods In Enzymology (Academic Press, Inc.); PCR 2: A Practical Approach (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)); Antibodies, A Laboratory Manual (Harlow and Lane, eds. (1988)); and Culture of Animal Cells: A Manual of Basic Technique and Specialized Applications, 6th Edition (R.I. Freshney, ed. (2010)).

[069] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood to which the claimed subject matter belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. All patents, patent applications, publications and published nucleotide and amino acid sequences (*e.g.*, sequences available in GenBank or other databases) referred to herein are incorporated by reference. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[070] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[071] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[072] Definition of standard chemistry terms may be found in reference works, including but not limited to, Carey and Sundberg "Advanced Organic Chemistry 4th Ed." Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology.

[073] It is to be understood that the methods and compositions described herein are not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the methods, compounds, compositions described herein.

[074] The term "C_{x-y}" or "C_x-C_y" when used in conjunction with a chemical moiety, such as alkyl, alkenyl, or alkynyl, is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y} alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups, that contain from x to y carbons in the chain.

[075] "Alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including linear and branched alkyl groups. An alkyl group may contain from one to twelve carbon atoms (e.g., C_{1-12} alkyl), such as one to eight carbon atoms (C_{1-8} alkyl) or one to six carbon atoms (C_{1-6} alkyl). Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl, and decyl. An alkyl group is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more substituents such as those substituents described herein.

[076] An "alkoxy" refers to a "-O-alkyl" group, where alkyl is as defined herein.

[077] "Haloalkyl" refers to an alkyl group that is substituted by one or more halogens. Exemplary haloalkyl groups include trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-

fluoropropyl, and 1,2-dibromoethyl.

[078] "Alkenyl" refers to substituted or unsubstituted hydrocarbon groups, including linear and branched alkenyl groups, containing at least one double bond. An alkenyl group may contain from two to twelve carbon atoms (e.g., C_{2-12} alkenyl), such as two to eight carbon atoms (C_{2-8} alkenyl) or two to six carbon atoms (C_{2-6} alkenyl). Exemplary alkenyl groups include ethenyl (i.e., vinyl), prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents such as those substituents described herein.

[079] "Alkynyl" refers to substituted or unsubstituted hydrocarbon groups, including linear and branched alkynyl groups, containing at least one triple bond. An alkynyl group may contain from two to twelve carbon atoms (e.g., C_{2-12} alkynyl), such as two to eight carbon atoms (C_{2-8} alkynyl) or two to six carbon atoms (C_{2-6} alkynyl). Exemplary alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents such as those substituents described herein.

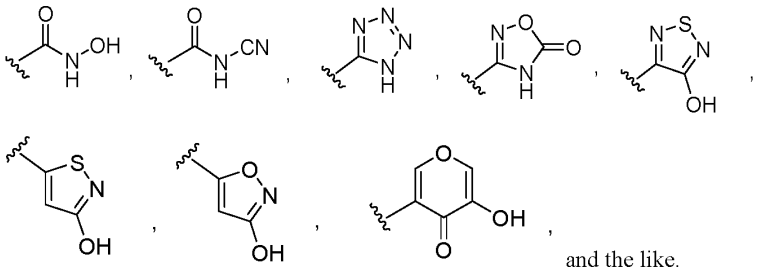
[080] "Alkylene" or "alkylene chain" refers to substituted or unsubstituted divalent saturated hydrocarbon groups, including linear alkylene and branched alkylene groups, that contain from one to twelve carbon atoms (e.g., C_{1-12} alkylene), such as one to eight carbon atoms (C_{1-8} alkylene) or one to six carbon atoms (C_{1-6} alkylene). Exemplary alkylene groups include methylene, ethylene, propylene, and n-butylene. Similarly, "alkenylene" and "alkynylene" refer to alkylene groups, as defined above, which comprise one or more carbon-carbon double or triple bonds, respectively. The points of attachment of the alkylene, alkenylene or alkynylene chain to the rest of the molecule can be through one carbon or any two carbons of the chain. Unless stated otherwise specifically in the specification, an alkylene, alkenylene, or alkynylene group is optionally substituted by one or more substituents such as those substituents described herein.

[081] "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" refer to substituted or unsubstituted alkyl, alkenyl and alkynyl groups, respectively, in which one or more, such as 1, 2 or 3, of the carbon atoms are replaced with a heteroatom, such as O, N, P, Si, S, or combinations thereof. Any nitrogen, phosphorus, and sulfur heteroatoms present in the chain may optionally be oxidized, and any nitrogen heteroatoms may optionally be quaternized. If given, a numerical range refers to the chain length in total. For example, a 3- to 8-membered heteroalkyl group has a chain length of 3 to 8 atoms. Connection to the rest of the molecule may be through either a heteroatom or a carbon in the heteroalkyl, heteroalkenyl, or heteroalkynyl chain. Unless stated otherwise specifically in the specification, a heteroalkyl, heteroalkenyl, or heteroalkynyl group is optionally substituted by one or more substituents such as those substituents described herein.

[082] "Heteroalkylene", "heteroalkenylene" and "heteroalkynylene" refer to substituted or unsubstituted alkylene, alkenylene and alkynylene groups, respectively, in which one or more, such as 1, 2 or 3, of the carbon atoms are replaced with a heteroatom, such as O, N, P, Si, S, or combinations thereof. Any nitrogen, phosphorus, and sulfur heteroatoms present in the chain may optionally be oxidized, and any nitrogen heteroatoms may optionally be quaternized. If given, a numerical range refers to the chain length in total. For example, a 3- to 8-membered heteroalkylene group has a chain length of 3 to 8 atoms. The points of attachment of the heteroalkylene, heteroalkenylene or heteroalkynylene chain to the rest of the molecule can be through either one heteroatom or one carbon, or any two heteroatoms, any two carbons, or any one heteroatom and any one carbon in the heteroalkylene, heteroalkenylene or heteroalkynylene chain. Unless stated otherwise specifically in the specification, a heteroalkylene, heteroalkenylene, or heteroalkynylene group is optionally substituted by one or more substituents such as those

substituents described herein.

[083] "Carboxy" refers to -CO_2H. In some embodiments, carboxy moieties may be replaced with a "carboxylic acid bioisostere", which refers to a functional group or moiety that exhibits similar physical and/or chemical properties as a carboxylic acid moiety. A carboxylic acid bioisostere has similar biological properties to that of a carboxylic acid group. A compound with a carboxylic acid moiety can have the carboxylic acid moiety exchanged with a carboxylic acid bioisostere and have similar physical and/or biological properties when compared to the carboxylic acid-containing compound. For example, in one embodiment, a carboxylic acid bioisostere would ionize at physiological pH to roughly the same extent as a carboxylic acid group. Examples of bioisosteres of a carboxylic acid include, but are not limited to,



and the like.

[084] "Carbocycle" refers to a saturated, unsaturated or aromatic ring in which each atom of the ring is a carbon atom. Carbocycle may include C_{3-10} monocyclic rings, C_{6-12} bicyclic rings, C_{6-12} spirocyclic rings, and C_{6-12} bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. In some embodiments, the carbocycle is a C_{6-12} aryl group, such as C_{6-10} aryl. In some embodiments, the carbocycle is a C_{6-12} cycloalkyl group. In some embodiments, the carbocycle is a C_{6-12} cycloalkenyl group. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, are included in the definition of carbocycle. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantly, phenyl, indanyl, and naphthyl. Unless state otherwise specifically in the specification, a carbocycle is optionally substituted by one or more substituents such as those substituents described herein.

[085] The term "cycloalkyl" refers to a monocyclic i) carbocyclic saturated or partially unsaturated non-aromatic ring or a ii) polycyclic ring system (e.g., bicyclic or tricyclic) wherein 1) at least one ring is carbocyclic saturated or partially unsaturated and non-aromatic, 2) a bond to the remainder of the compound is directly bonded to a carbocyclic saturated or partially unsaturated non-aromatic ring of the ring system, and 3) the carbocyclic saturated or partially unsaturated non-aromatic ring of the ring system of 2) is not directly bonded (e.g., fused or spirocyclic) to a heterocycloalkyl ring in the polycyclic ring system. Cycloalkyls may be saturated or partially unsaturated. In some embodiments, a cycloalkyl ring is a spirocyclic cycloalkyl ring. In embodiments, a cycloalkyl is a monocyclic ring. In embodiments, a cycloalkyl is a fused ring polycyclic system. In embodiments, a cycloalkyl is a bridged ring polycyclic system. In embodiments, a cycloalkyl is a spirocyclic polycyclic ring system. In some embodiments, cycloalkyl groups include groups having from 3 to 10 ring atoms. Depending on the structure, a cycloalkyl group can be a monoradical or a diradical (i.e., a cycloalkylene group).

[086] "Heterocycle" refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms, for example 1, 2 or 3 heteroatoms selected from O, S and N. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, 6- to 12-membered spirocyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic heterocycle may be selected from saturated, unsaturated, and aromatic rings. The heterocycle may be attached to the rest of the molecule through any atom of the heterocycle, valence permitting, such as a carbon or nitrogen atom of

the heterocycle. In some embodiments, the heterocycle is a 5- to 10-membered heteroaryl group, such as 5- or 6-membered heteroaryl. In some embodiments, the heterocycle is a 3- to 12-membered heterocycloalkyl group. In an exemplary embodiment, a heterocycle, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Exemplary heterocycles include pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiophenyl, oxazolyl, thiazolyl, morpholinyl, indazolyl, indolyl, and quinolinyl. Unless stated otherwise specifically in the specification, a heterocycle is optionally substituted by one or more substituents such as those substituents described herein.

[087] A "heterocycloalkyl" group or "heteroalicyclic" group refers to a cycloalkyl group, wherein at least one skeletal ring atom of a saturated or partially unsaturated non-aromatic ring is a heteroatom selected from nitrogen, oxygen, phosphorus, and sulfur. A heterocycloalkyl refers to a monocyclic saturated or partially unsaturated non-aromatic ring including one or more heteroatoms or a polycyclic ring system (e.g., bicyclic or tricyclic) wherein 1) at least one ring is saturated or partially unsaturated, non-aromatic, and includes one or more heteroatoms and 2) a bond to the remainder of the compound is directly bonded to a ring of the ring system that is a saturated or partially unsaturated and non-aromatic ring that includes one or more heteroatoms or a non-aromatic ring directly bonded (e.g., fused) to a saturated or partially unsaturated and non-aromatic ring that includes one or more heteroatoms of the ring system. Heterocycloalkyls may be saturated or partially unsaturated. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In some embodiments, a heterocycloalkyl ring is a spirocyclic heterocycloalkyl ring. In embodiments, a heterocycloalkyl is a monocyclic ring. In embodiments, a heterocycloalkyl is a fused ring polycyclic system. In embodiments, a heterocycloalkyl is a bridged ring polycyclic system. In embodiments, a heterocycloalkyl is a spirocyclic polycyclic ring system. Unless otherwise noted, heterocycloalkyls have from 2 to 13 carbons in the ring or ring system. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Depending on the structure, a heterocycloalkyl group can be a monoradical or a diradical (i.e., a heterocycloalkylene group).

[088] "Heteroaryl" refers to a 5- to 12-membered aromatic ring that comprises at least one heteroatom, such as 1, 2 or 3 heteroatoms, selected from O, S and N. As used herein, the heteroaryl ring may be selected from monocyclic or bicyclic—including fused, spirocyclic and bridged ring systems—wherein at least one of the rings in the ring system is aromatic. The heteroatom(s) in the heteroaryl may optionally be oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the heteroaryl, valence permitting, such as a carbon or nitrogen atom of the heteroaryl. Examples of heteroaryl groups include, but are not limited to, azepinyl, benzimidazolyl, benzisothiazolyl, benzisoxazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, furanyl, imidazolyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, purinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroquinolinyl, thiadiazolyl, thiazolyl, and thienyl groups. Unless stated otherwise specifically in the specification, a heteroaryl is optionally substituted by one or more substituents such as those substituents described herein.

[089] Unless stated otherwise, hydrogen atoms are implied in structures depicted herein as necessary to satisfy the valence requirement.

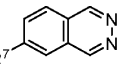
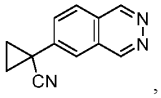
[090] The term "oxo" refers to the =O radical.

[091] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the

atoms joined by the bond are considered to be part of larger substructure.

[092] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[093] The suffix "-di-yl" will be understood to mean the substituent or linker is a divalent substituent or linker.

[094] A waved line "〰" drawn across a bond or a dashed bond "- - -" are used interchangeably herein to denote where a bond disconnection or attachment occurs. For example, in the structure  , if R^7 is 1-cyclopropyl-1-carbonitrile as in  , then R^7 may be depicted as " " or " ".

[095] As used herein, the substituent "R" appearing by itself and without a number designation refers to a substituent selected from among from alkyl, haloalkyl, heteroalkyl, alkenyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon), and heterocycloalkyl.

[096] The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons or heteroatoms of the structure. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, heteroatoms such as nitrogen may have any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

[097] In embodiments, a compound disclosed herein, is optionally substituted by one or more, such as 1, 2 or 3 substituents selected from:

halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

R^{21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{24} is independently selected at each occurrence from H and C_{1-6} alkyl; and

R^{25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

[098] In some embodiments, a compound disclosed herein, is optionally substituted by one or more, such as 1, 2 or 3 substituents selected from:

halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, -CH_2-(3- to 10-membered heterocycle), -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{21}, -SR^{21}, and -$N(R^{22})(R^{23})$;

R^{21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{24} is independently selected at each occurrence from H and C_{1-6} alkyl; and

R^{25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

[099] In embodiments, a compound disclosed herein, is optionally substituted by one or more, such as 1, 2 or 3 substituents selected from:

halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, -CH_2-(3- to 10-membered heterocycle), -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, -$OCH_2C(O)OR^{s22}$, and -$OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, and -$OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl; and

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

[100] In some embodiments, a compound disclosed herein, is optionally substituted by one or more, such as 1, 2 or 3 substituents selected from:

halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2$-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, $-CH_2$-(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2$-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and $-CH_2$-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, and $-N(R^{s22})(R^{s23})$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl; and

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

[101] In some embodiments, a compound disclosed herein, such as a compound of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), (H), (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), is optionally substituted by one or more, such as 1, 2 or 3 substituents selected from halogen, oxo, =NH, -CN, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2$-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, $-CH_2$-(3- to 10-membered heterocycle), -OH, $-OCH_3$, $-OCH_2CH_3$, $-NH_2$, $-NHCH_3$, and $-NHCH_2CH_3$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2$-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and $-CH_2$-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, $-NO_2$, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-NH_2$, $-NHCH_3$, and $-NHCH_2CH_3$.

[102] The term "halo" or, alternatively, "halogen" means fluoro, chloro, bromo and iodo.

[103] The abbreviations "Fmoc", "Ac", "Bn", "PMB", "Tr", "Ts", "Boc", and "Cbz" are used in accordance with their well understood common meanings in Chemistry and mean the monovalent chemical substituents fluorenylmethyloxycarbonyl, acetyl, benzyl, p-methoxybenzyl, trityl or triphenylmethyl, tosyl, tert-butyloxycarbonyl, and carbobenzyloxy, respectively.

[104] The term "haloalkyl" refers to an alkyl group that is substituted with one or more halogens. The halogens may the same or they may be different. Non-limiting examples of haloalkyls include $-CH_2Cl$, $-CF_3$, $-CHF_2$, $-CH_2CF_3$, $-CF_2CF_3$, and the like.

[105] The terms "fluoroalkyl" and "fluoroalkoxy" include alkyl and alkoxy groups, respectively, that are substituted with one or more fluorine atoms. Non-limiting examples of fluoroalkyls include $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CF(CH_3)_3$, and the like. Non-limiting examples of fluoroalkoxy groups, include $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-OCF_2CF_2CF_3$, $-OCF(CH_3)_2$, and the like.

[106] ~~~ indicates the location of attachment (e.g., location of a bond to another atom) of the depicted chemical formula or atom to a substituent, a further component of a molecule, or an atom. ~~~ may equivalently be located at the end of a bond or overlapping a bond. A waved line ~~~ drawn across a bond or at the end of a bond and a dashed bond "- - -" are used interchangeably herein to denote where a bond disconnection or attachment occurs.

[107] "About" as used herein when referring to a measurable value such as an amount, a duration, and the like, is meant to encompass variations of ± 10% of a stated number or value.

[108] It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted", references to chemical moieties herein are understood to include substituted variants. For example, reference to a "heteroaryl" group or moiety implicitly includes both substituted and unsubstituted variants.

[109] Where bivalent substituent groups are specified herein by their conventional chemical formulae, written from left to right, they are intended to encompass the isomer that would result from writing the structure from right to left, e.g., $-CH_2O-$ is also intended to encompass $-OCH_2-$.

[110] "Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, an "optionally substituted" group may be either unsubstituted or substituted.

[111] Compounds of the present disclosure also include crystalline and amorphous forms of those compounds, pharmaceutically acceptable salts, and active metabolites having the same type of activity, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, amorphous forms of the compounds, and mixtures thereof.

[112] The compounds described herein may exhibit their natural isotopic abundance, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^1H (protium), ^2H (deuterium), and ^3H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increased in vivo half-life and/or exposure, or may provide a compound useful for investigating in vivo routes of drug elimination and metabolism. Examples of isotopes that may be incorporated into compounds of the present disclosure include, but are not limited to, ^2H, ^3H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{36}Cl, and ^{18}F. Of particular interest are compounds of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C),

(D), (E), (F), (G), (H), (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or embodiments of any of the preceding formulae, enriched in tritium or carbon-14, which can be used, for example, in tissue distribution studies; compounds of the disclosure enriched in deuterium—especially at a site of metabolism—resulting, for example, in compounds having greater metabolic stability; and compounds of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), (H), (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or embodiments of any of the preceding formulae, enriched in a positron emitting isotope, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, which can be used, for example, in Positron Emission Topography (PET) studies. Isotopically-enriched compounds may be prepared by conventional techniques well known to those skilled in the art.

[113] As used herein, the phrase "of the formula", "having the formula" or "having the structure" is not intended to be limiting and is used in the same way that the term "comprising" is commonly used. For example, if one structure is depicted, it is understood that all stereoisomer and tautomer forms are encompassed, unless stated otherwise.

[114] Certain compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms, the asymmetric centers of which can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. In some embodiments, in order to optimize the therapeutic activity of the compounds of the disclosure, e.g., to treat cancer, it may be desirable that the carbon atoms have a particular configuration (e.g., (R,R), (S,S), (S,R), or (R,S)) or are enriched in a stereoisomeric form having such configuration. The compounds of the disclosure may be provided as racemic mixtures. Accordingly, the disclosure relates to racemic mixtures, pure stereoisomers (e.g., enantiomers and diastereomers), stereoisomer-enriched mixtures, and the like, unless otherwise indicated. When a chemical structure is depicted herein without any stereochemistry, it is understood that all possible stereoisomers are encompassed by such structure. Similarly, when a particular stereoisomer is shown or named herein, it will be understood by those skilled in the art that minor amounts of other stereoisomers may be present in the compositions of the disclosure unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers. Individual stereoisomers may be obtained by numerous methods that are known in the art, including preparation using chiral synthons or chiral reagents, resolution using chiral chromatography using a suitable chiral stationary phase or support, or by chemically converting them into diastereomers, separating the diastereoisomers by conventional means such as chromatography or recrystallization, then regenerating the original stereoisomer.

[115] Additionally, where applicable, all cis-trans or E/Z isomers (geometric isomers), tautomeric forms and topoisomeric forms of the compounds described herein are included with the scope of the disclosure unless otherwise specified.

[116] The term "pharmaceutically acceptable" refers to a material that is not biologically or otherwise unacceptable when used in the subject compositions and methods. For example, the term "pharmaceutically acceptable carrier" refers to a material—such as an adjuvant, excipient, glidant, sweetening agent, diluent, preservative, dye, colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent or emulsifier—that can be incorporated into a composition and administered to a patient without causing unacceptable biological effects or interacting in an unacceptable manner with other components of the composition. Such pharmaceutically acceptable materials typically have met the required standards of toxicological and manufacturing testing, and include those materials identified as suitable inactive ingredients by the U.S. Food and Drug Administration.

[117] The terms "salt" and "pharmaceutically acceptable salt" refer to a salt prepared from a base or an acid. Pharmaceutically acceptable salts are suitable for administration to a patient, such as a mammal (for example, salts having acceptable mammalian safety for a given dosage regime). Salts can be formed from inorganic bases, organic bases, inorganic acids and organic acids. In addition, when a compound contains both a basic moiety, such as an amine, pyridine or imidazole, and an acidic moiety, such as a carboxylic acid or tetrazole, zwitterions may be formed and are included within the term "salt" as used herein. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[118] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc., and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 66:1-19 (1997)). Acid addition salts of basic compounds are, in some embodiments, prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[119] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts are, in some embodiments, formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, N,N-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, N-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. See Berge et al., supra.

[120] As used herein, "treating" or "treatment" refers to an approach for obtaining beneficial or desired results with respect to a disease, disorder, or medical condition (such as cancer) in a subject, including but not limited to the following: (a) ameliorating the disease or medical condition, e.g., eliminating or causing regression of the disease or

medical condition in a subject; (b) suppressing the disease or medical condition, e.g., slowing or arresting the development of the disease or medical condition in a subject; or (c) alleviating symptoms of the disease or medical condition in a subject. For example, "treating cancer" would include preventing cancer from reoccurring, ameliorating cancer, suppressing cancer, and alleviating the symptoms of cancer. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder.

[121] A "therapeutic effect", as that term is used herein, encompasses a therapeutic benefit and/or prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof. In embodiments, a "therapeutic effect" does not include a prophylactic benefit. In embodiments, a "therapeutic effect" includes slowing, halting, or reversing the progression of a disease or condition, or any combination thereof. In embodiments, a "therapeutic effect" includes reducing or eliminating one or more symptoms of a disease or condition. In embodiments, a "therapeutic effect" includes reducing or eliminating a disease or condition.

[122] The terms "administer", "administering", "administration", and derivatives thereof refer to the methods that may be used to enable delivery of a composition to the desired site of biological action. These methods include, but are not limited to parenteral administration (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular, intrathecal, intranasal, intravitreal, infusion and local injection), transmucosal injection, oral administration, administration as a suppository, and topical administration. Administration is by any route, including parenteral. Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transplantation, etc. One skilled in the art will know of additional methods for administering a therapeutically effective amount of a composition of the present disclosure for preventing or relieving one or more symptoms associated with a disease.

[123] The term "effective amount" or "therapeutically effective amount" or "therapeutically effective dose" refers to the amount of an agent that is sufficient to effect beneficial or desired results. The therapeutically effective amount may vary depending upon one or more of: the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. An effective amount of an active agent may be administered in a single dose or in multiple doses. A component may be described herein as having at least an effective amount, or at least an amount effective, such as that associated with a particular goal or purpose, such as any described herein. The term "effective amount" also applies to a dose that will provide an image for detection by an appropriate imaging method. The specific dose may vary depending on one or more of: the particular agent chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to be imaged, and the physical delivery system in which it is carried.

[124] The terms "sub-therapeutic amount", "sub-effective amount", and "sub-therapeutic dose" are used interchangeably and refer to the amount of an agent that is less than the effective amount for that agent, but when combined with an effective or sub-therapeutic amount of a different agent can produce a desired result, due to, for example, synergy in the resulting efficacious effects and/or reduced side effects by the combination of (i) the sub-therapeutic amount of the agent and (ii) the different agent (e.g., one or more different agents). For example, an agent

can be approved for clinical use for a specified indication at a defined dose or range thereof (e.g., 150 milligrams per day (mg/d)) over the course of one or more administrations, and a sub-therapeutic amount of such agent can be lower than the approved dose or range thereof by at least about 0.1-fold, 0.2-fold, 0.5-fold, 1-fold, 2-fold, 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, 200-fold, 500-fold, 1,000-fold, 2,000-fold, 5,000-fold, 10,000-fold, 20,000-fold, 50,000-fold, 100,000-fold, or more. The sub-therapeutic amount of such agent can be lower than the approved dose or range thereof by at most about 100,000-fold, 50,000-fold, 20,000-fold, 10,000-fold, 5,000-fold, 2,000-fold, 1,000-fold, 500-fold, 200-fold, 100-fold, 50-fold, 20-fold, 10-fold, 5-fold, 2-fold, 1-fold, 0.5-fold, 0.2-fold, 0.1-fold or less. A sub-therapeutic amount of an agent can be achieved by reducing the amount of the agent per dosage and/or by reducing the number of administrations (or cycles) of the agent to the subject.

[125] The term "synergistic" or "synergizing" effect refers to when a desired effect (e.g., one or more different effects) of a combination (or combination treatment) comprising two or more different therapeutic components (e.g., two or more different therapies, two or more therapeutic agents, etc.) is greater than (i) the effect of each therapeutic component alone and/or (ii) the sum of the effect of each therapeutic component alone when administered individually (e.g., the sum of individual effects). The synergistic effect can be at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 150%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1,000%, 5,000%, or more than (i) the effect of each therapeutic component alone and/or (ii) the sum of individual effects. The effect can be any measurable effect including but not limited to an enhancement of a therapeutic effect of an individual component within the combination or a reduction in a side effect of an individual component within the combination. In some embodiments, the effect is a pharmacodynamic effect, such as phosphorylated ERK (p-ERK) and/or DUSP6 inhibition, optionally assessed in whole blood. To yield the synergistic effect, the two or more different therapeutic components of the combination treatment as disclosed herein can be administered concurrently or sequentially, as separate components or as a unit dosage. For example, a synergistic effect of a combination comprising a first agent and a second agent can yield a desired therapeutic outcome (e.g., in treating cancer) that is comparable (e.g., substantially the same) or better than (i) the therapeutic outcome of each therapeutic component alone at the therapeutically effective amount and/or (ii) the sum of individual effects, where either or both of the first and the second agent are administered in a respective sub-therapeutic amount. In another example, a synergistic effect of a combination comprising a first agent and a second agent can yield a desired therapeutic outcome (e.g., reducing side effect of either one of the agent) that is comparable (e.g., substantially the same) or better than the therapeutic outcome of each therapeutic component alone.

[126] The term "IC50" refers to the half maximal inhibitory amount (e.g., concentration) of an inhibitor in inhibiting a biological or biochemical effect. IC50 can be a quantitative measure that indicates how much of a particular inhibitor is needed to inhibit a given biological or biochemical effect (e.g., expression and/or activity level of a gene/protein of interest, growth, or growth rate of a cell, etc.) by substantially half (e.g., about 50%). For example, determination of IC50 can be made by determining and constructing a dose-response curve and examining the effect of different concentrations of an inhibitor on reducing cell growth (e.g., inhibiting proliferation of cancer cells), and determining the concentration of the inhibitor at which 50% inhibition of cell growth is observed.

[127] The term "combination", as applied to agents including inhibitors disclosed herein, refers to the use of two or more agents (e.g., a SOS1 inhibitor and at least another inhibitor against a different signaling molecule (e.g., a RAS or KRAS inhibitor)) *in vitro*, *in vivo*, or *ex-vivo*. The two or more agents in combination can be formulated in one single formulation, or in separate formulation(s). A combination treatment or therapy with two or more agents can be carried out conjunctively in any temporal order, administered simultaneously or separately.

[128] The term "conjunction" refers to a temporal aspect of the use of two or more agents (e.g., a SOS1 inhibitor and at least another inhibitor against a different signaling molecule (e.g., a RAS or KRAS inhibitor)) *in vitro*, *in vivo*, or *ex-vivo*. For example, one agent of a set of agents of interest can be administered prior to, subsequent to, or concurrently with the administration of a second agent of the set. Simultaneous administration can be effectuated by simultaneously administering multiple agents as separate agents, or as a unit dosage comprising the multiple agents.

[129] The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound having the ability to inhibit a biological function (e.g., activity, expression, binding, protein-protein interaction) of a target protein (e.g., SOS1, RAS, or KRAS). Accordingly, the terms "antagonist" and "inhibitor" are defined in the context of the biological role of the target protein. While preferred antagonists herein specifically interact with (e.g., bind to) the target, compounds that inhibit a biological activity of the target protein by interacting with other members of the signal transduction pathway of which the target protein is a member are also specifically included within this definition.

[130] The term "selective inhibition" or "selectively inhibit" refers to the ability of a biologically active agent to preferentially reduce the target signaling activity as compared to off-target signaling activity, via direct or indirect interaction with the target.

[131] The terms "subject", "individual", and "patient" are used interchangeably herein to refer to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics and veterinary applications. In some embodiments, the subject is a mammal, such as a human. "Mammal" includes humans and both domestic animals such as laboratory animals and household pets (e.g., cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like. Tissues, cells, and their progeny of a biological entity obtained in vivo or cultured in vitro are also encompassed.

[132] The terms "therapeutic agent", "therapeutic capable agent" or "treatment agent" are used interchangeably and refer to a molecule or compound that confers some beneficial effect upon administration to a subject. The beneficial effect includes enablement of diagnostic determinations; amelioration of a disease, symptom, disorder, or pathological condition; reducing or preventing the onset of a disease, symptom, disorder or condition; and generally counteracting a disease, symptom, disorder or pathological condition.

[133] The terms "polypeptide", "peptide" and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component. As used herein the term "amino acid" refers to either natural and/or unnatural or synthetic amino acids, including glycine and both the D or L optical isomers, and amino acid analogs and peptidomimetics.

[134] The terms "polynucleotide", "nucleotide", "nucleotide sequence", "nucleic acid" and "oligonucleotide" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, short interfering RNA (siRNA), short-hairpin RNA (shRNA), micro-RNA (miRNA), ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise one or more modified nucleotides, such as methylated nucleotides and nucleotide analogs, such as peptide nucleic acid

(PNA), morpholino and locked nucleic acid (LNA), glycol nucleic acid (GNA), threose nucleic acid (TNA), 2'-fluoro, 2'-OMe, and phosphorothiolated DNA. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component or other conjugation target.

[135] The term "nucleic acid agent" refers to an inhibitory agent capable of downregulating (e.g., reducing or inhibiting) expression and/or activity of a target moiety (e.g., a protein or a gene encoding thereof). In some embodiments, a nucleic acid agent may consist of a nucleic acid molecule. In some embodiments, a nucleic acid agent may comprise a nucleic acid molecule. In some embodiments, a nucleic acid agent may comprise a nucleic acid molecule and a non-nucleic acid molecule. The nucleic acid molecule and the non-nucleic acid molecule may be operatively coupled to each other to yield the inhibitory effect on the target moiety. The nucleic acid molecule and the non-nucleic acid molecule may be coupled (e.g., covalently and/or non-covalently) to each other. In some cases, the nucleic acid molecule and the non-nucleic acid molecule can be linked to each other via a linker. In some cases, the nucleic acid molecule can be configured to bind to the non-nucleic acid molecule. In some cases, the non-nucleic acid molecule can be configured to bind to the nucleic acid molecule. Non-limiting examples of the non-nucleic acid molecule include a small molecule, a polypeptide (e.g., an enzyme), etc. In some cases, the non-nucleic acid molecule is a nuclease, e.g., an endonuclease.

[136] As used herein, "expression" refers to the process by which a polynucleotide is transcribed from a DNA template (such as into and mRNA or other RNA transcript) and/or the process by which a transcribed mRNA is subsequently translated into peptides, polypeptides, or proteins. Transcripts and encoded polypeptides may be collectively referred to as "gene product." If the polynucleotide is derived from genomic DNA, expression may include splicing of the mRNA in a eukaryotic cell.

[137] An "antigen" is a moiety or molecule that contains an epitope, and, as such, also specifically binds to an antibody. An "antigen binding unit" may be whole or a fragment (or fragments) of a full-length antibody, a structural variant thereof, a functional variant thereof, or a combination thereof. A full-length antibody may be, for example, a monoclonal, recombinant, chimeric, deimmunized, humanized and human antibody. Examples of a fragment of a full-length antibody may include, but are not limited to, variable heavy (VH), variable light (VL), a heavy chain found in camelids, such as camels, llamas, and alpacas (VHH or V_HH), a heavy chain found in sharks (V-NAR domain), a single domain antibody (sdAb, e.g., "nanobody") that comprises a single antigen-binding domain, Fv, Fd, Fab, Fab', F(ab')2, and "r IgG" (or half antibody). Examples of modified fragments of antibodies may include, but are not limited to scFv, di-scFv or bi(s)-scFv, scFv-Fc, scFv-zipper, scFab, Fab2, Fab3, diabodies, single chain diabodies, tandem diabodies (Tandab's), tandem di-scFv, tandem tri-scFv, minibodies (e.g., (VH-VL-CH3)2, (scFv-CH3)2, ((scFv)2-CH3+CH3), ((scFv)2-CH3) or (scFv-CH3-scFv)2), and multibodies (e.g., triabodies or tetrabodies).

[138] The term "antibody" and "antibodies" encompass any antigen binding units, including without limitation: monoclonal antibodies, human antibodies, humanized antibodies, camelised antibodies, chimeric antibodies, and any other epitope-binding fragments.

[139] The term "diseased cell" refers to the state of a cell, tissue, or organism that diverges from the normal or healthy state. A diseased cell may result from the influence of a pathogen, a toxic substance, irradiation, or cell internal deregulation (e.g., genetic mutation). In an example, a diseased cell is a cell that has been infected with a pathogenic virus. In an example, a diseased cell is a malignant cell or neoplastic cell that may constitute or give rise to cancer in a subject (e.g., a mammal such as a human subject).

[140] "Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein (e.g., a compound of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), (H), (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or embodiments of any of the preceding formulae). Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some aspects, a prodrug is inactive when administered to a subject but is converted in vivo to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam); Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," (1987) A.C.S. Symposium Series, Vol. 14; and Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press each of which is incorporated in full by reference herein). The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound in vivo when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, are typically prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of a hydroxy functional group, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound, and the like.

[141] The term "in vivo" refers to an event that takes place in a subject's body. The term "ex vivo" refers to an event that first takes place outside of the subject's body for a subsequent in vivo application into a subject's body. For example, an ex vivo preparation may involve preparation of cells outside of a subject's body for the purpose of introduction of the prepared cells into the same or a different subject's body. The term "in vitro" refers to an event that takes place outside of a subject's body. For example, an in vitro assay encompasses any assay run outside of a subject's body. In vitro assays encompass cell-based assays in which cells alive or dead are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

[142] The disclosure is also meant to encompass the in vivo metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the disclosure includes compounds produced by a process comprising administering a compound disclosed herein to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabeled compound of the disclosure in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to a human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

[143] The term "Ras" or "RAS" refers to a protein in the Rat sarcoma (Ras) superfamily of small GTPases, such as in the Ras subfamily. The Ras superfamily includes, but is not limited to, the Ras subfamily, Rho subfamily, Rab subfamily, Rap subfamily, Arf subfamily, Ran subfamily, Rheb subfamily, RGK subfamily, Rit subfamily, Miro subfamily, and Unclassified subfamily. In some embodiments, a Ras protein is selected from the group consisting of KRAS (K-Ras or K-ras or Kras), HRAS (or H-Ras), NRAS (or N-Ras), MRAS (or M-Ras), ERAS (or E-Ras), RRAS2 (or R-Ras2), RALA (or RalA), RALB (or RalB), RIT1, and any combination thereof, such as from KRAS, HRAS,

NRAS, RALA, RALB, and any combination thereof.

Methods

[144] In an aspect is provided a method of reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS protein overexpression, the method comprising administering to the cells (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

[145] In an aspect is provided a method of downregulating KRAS signaling output in a plurality of cancer cells, comprising: (i) assessing KRAS mutation status in a biological sample comprising nucleic acid from the subject; and (ii) administering an effective dose of (a) a SOS1 inhibitor and an effective dose of (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, if a KRAS mutation is detected in the sample, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b). In embodiments of the method, the KRAS mutation is a G12C mutation. In embodiments of the method, the KRAS mutation is a G12S mutation. In embodiments of the method, the KRAS mutation is a G12D mutation. In embodiments of the method, the KRAS mutation is a G12V mutation.

[146] In embodiments, the cancer cells are non-small cell lung cancer cells, colorectal cancer cells, or pancreatic cancer cells.

[147] In embodiments, cancer cells of the subject comprise a KRAS G12C mutant protein. In embodiments, cancer cells of the subject comprise a KRAS G12S mutant protein. In embodiments, cancer cells of the subject comprise overexpression of KRAS protein. In embodiments, cancer cells of the subject are refractory to at least one KRAS G12C inhibitor.

[148] In embodiments, the method further comprises administering (c) an additional agent or additional therapy. Suitable agents that can be administered in combination with (a) the SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, include other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, immunomodulatory agents, steroids, chemotherapeutic agents, and combinations thereof. In embodiments, the additional agent is a checkpoint immune blockade, a SHP2 inhibitor, a PI3K inhibitor, a CDK4/6 inhibitor, a RAF inhibitor, a MEK inhibitor, an ERK inhibitor, or an AKT inhibitor. In embodiments, the additional agent is an EGFR inhibitor. In embodiments, the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation.

[149] In embodiments, the administration of (a) and (b) synergistically reduces proliferation of the cancer cells with a synergistic value of at least 0.05 as ascertained by Bliss independence criterion.

[150] In an aspect is provided a method of treating cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

[151] In embodiments, the cancer is a mutant KRAS-mediated cancer. In embodiments, the KRAS inhibitor is a compound, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3) or any embodiment of the preceding formulae.

[152] A KRAS-mediated disease or condition may be any disease or condition in which the KRAS signaling pathway contributes to the progression of the disease or condition. In some embodiments, the disease or condition is

characterized by aberrant activity of KRAS, optionally due to KRAS amplification, KRAS overexpression, and/or occurrence of one or more KRAS mutations (a mutant KRAS-mediated disease or condition).

[153] In an aspect is provided a method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b), and wherein the administration of (a) and (b) synergistically reduces proliferation of the cancer cells with a synergistic value of at least 0.05 as ascertained by Bliss independence criterion.

[154] In embodiments, the synergistic value is ascertained by Bliss independence criterion in accordance with the formula:

$$Y_{AB,O} - Y_{AB,P}$$

wherein:

$Y_{AB,O}$ is observed percent growth inhibition of the cancer cells by the application of (a) and (b) comprising (a) at dose A and (b) at dose B;

$Y_{AB,P}$ is predicted percent growth inhibition of the cancer cells by the application of (a) and (b) comprising (a) at dose A and (b) at dose B, wherein $Y_{AB,P} = Y_A + Y_B - Y_A Y_B$;

Y_A is observed percent growth inhibition of the cancer cells by (a) alone at dose A;

Y_B is observed percent growth inhibition of the cancer cells by (b) alone at dose B; and

$Y_A Y_B$ is the product of Y_A and Y_B.

[155] In embodiments, the synergistic value is at least 0.1. In embodiments, the synergistic value is at least 0.4. In embodiments, the synergistic value is at least 1. In embodiments, the synergistic value is at least 5.

[156] In embodiments, the administration of (a) and (b) exhibits a synergistic effect. In embodiments, the synergistic effect is characterized by a synergistic value of at least 0.05 as ascertained by Bliss independence criterion. In embodiments, one or both of (a) and (b) are administered at a sub-therapeutic dose but achieve a therapeutic effect at least comparable to administering (a) or (b) alone at its therapeutically effective amount. In embodiments, KRAS inhibitor is administered at a dose less than about 25% the standard monotherapy dose.

[157] In an aspect is provided a method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SI-1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, and (iii) a pharmaceutically acceptable excipient.

[158] In an aspect is provided a method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

[159] In embodiments, the cancer is lung cancer. In embodiments, the cancer is a non-small cell lung cancer. In embodiments, the cancer is colorectal cancer. In embodiments, the cancer is pancreatic cancer. In embodiments, the cancer is a solid cancer.

[160] In embodiments, cancer cells of the subject comprise a KRAS G12C mutant protein. In embodiments, cancer cells of the subject comprise a KRAS G12S mutant protein. In embodiments, cancer cells of the subject comprise overexpression of KRAS protein. In embodiments, cancer cells of the subject are refractory to at least one KRAS G12C inhibitor.

[161] In embodiments, the subject exhibits relapse of the cancer. In embodiments, the subject has previously been treated with a KRAS G12C inhibitor. In embodiments, the subject is a naïve subject that has not been treated with a KRAS inhibitor prior to administering (a) and (b).

[162] In embodiments, the method further comprises administering (c) an additional agent or additional therapy. Suitable agents that can be administered in combination with (a) the SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, include other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, immunomodulatory agents, steroids, chemotherapeutic agents, and combinations thereof. In embodiments, the additional agent is selected from an immunomodulatory agent, an anti-nausea agent, an antiemetic, a pain reliever, a chemotherapeutic agent, a SHP2 inhibitor, a PI3K inhibitor, a CDK4/6 inhibitor, a RAF inhibitor, a MEK inhibitor, an ERK inhibitor, and an AKT inhibitor. In embodiments, the additional agent is an EGFR inhibitor. In embodiments, the additional agent is selected from an immunomodulatory agent, a cytokine blockade agent, and a checkpoint immune blockade agent. In embodiments, the additional agent is selected from an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-LAG3 antibody, an anti-TIM3 antibody, and combinations thereof. In embodiments, the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation.

[163] In embodiments, the administration of (a) and (b) reduces incidence of one or more adverse events associated with the SOS1 inhibitor or the KRAS inhibitor. In embodiments, the adverse event is selected from diarrhea, rash, nausea, vomiting, decreased appetite, fatigue, musculoskeletal pain, dyspnea, and acute kidney injury. In embodiments, the adverse event is selected from diarrhea, rash, and nausea.

[164] In embodiments, (a) and (b) are administered in the same formulation. In embodiments, (a) and (b) are administered in separate formulations.

[165] In embodiments of the methods described herein, (a) is administered prior to administering (b). In embodiments of the methods described herein, (a) is administered concurrently with administering (b). In embodiments of the methods described herein, (a) is administered subsequent to administering (b).

[166] In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the cancer is a solid tumor. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the cancer is a hematological cancer. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the cancer can be, without limitation, prostate cancer, brain cancer, colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, various lung cancers including non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS),

primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers, combinations of said cancers, or metastatic lesions of said cancers. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the cancer is a hematological cancer selected from one or more of chronic lymphocytic leukemia (CLL), acute leukemias, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and pre-leukemia. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the cancer is one or more cancers selected from the group consisting of chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-ALL), B cell acute lymphoblastic leukemia (B-ALL), and/or acute lymphoblastic leukemia (ALL).

[167] The presence of genetic aberration in a Ras gene (e.g., KRAS, NRAS, or HRAS) can be determined by a wide variety of nucleic acid assays. Exemplary nucleic acid assays include but are not limited to genotyping assays and sequencing methods. Sequencing methods can include next-generation sequencing, targeted sequencing, exome sequencing, whole genome sequencing, massively parallel sequencing, and the like. Several platforms for next generation sequencing are commercially available, including those marketed by Illumina and Pacific Biosciences. Additional nucleic acid assays include but not limited to in situ hybridization (e.g., FISH), polymerase chain reaction (PCR), quantitative PCR (qPCR), quantitative real-time PCR (qRT-PCR), and ligase chain reaction (LCR), all of which are applicable for detecting a genetic aberration in a Ras gene (e.g., KRAS, NRAS, or HRAS). Where desired, one or more nucleic acids can be employed to detect a genetic aberration in a Ras gene (e.g., KRAS, NRAS, or HRAS), including but not limited to translation, as well as genetic mutations within a Ras gene (e.g., KRAS, NRAS, or HRAS) via point mutation, insertion, deletion, or frameshift.

[168] In some embodiments, the step of assessing for presence of a genetic aberration associated with resistance to a KRAS inhibitor detects overexpression of a Ras gene (e.g., KRAS, NRAS, or HRAS). In some embodiments, the step of assessing detects a mutation in a Ras gene (e.g., KRAS, NRAS, or HRAS).

[169] In some embodiments, the step of assessing detects a mutation a Ras gene (e.g., KRAS, NRAS, or HRAS), including but not limited point mutations selected from the group consisting of G12D, G12R, G12S, G12V, G12W, G13D, Q61H, R68S, H95D, H95Q, H95R, and Y96C. In some embodiments, the step of assessing detects amplification of a Ras gene (e.g., KRAS, NRAS, or HRAS).

[170] A variety of techniques for protein analysis can also be applied for assessing the presence and/or overexpression of a Ras protein (e.g., KRAS, NRAS, HRAS, or mutants thereof such as G12C, G12D, G12R, G12S, G12V, G12W, G13D, Q61H, R68S, H95D, H95Q, H95R, or Y96C). Suitable protein assays include, without limitation, immunohistochemistry (IHC), ELISA (enzyme linked immunosorbent assays), "sandwich" immunoassays, immunoradiometric assays, in situ immunoassays, western blot analysis, immunoprecipitation assays, immunofluorescent assays, flow cytometry, confocal microscopy, enzymatic assays, surface plasmon resonance, and PAGE-SDS. One or more of these protein assays utilize antibodies or fragments thereof that exhibit specific binding to a Ras protein (e.g., KRAS, NRAS, HRAS, or mutants thereof such as G12C, G12D, G12R, G12S, G12V, G12W, G13D, Q61H, R68S, H95D, H95Q, H95R, or Y96C).

[171] In practicing a subject method, the presence of a Ras mutant protein (e.g., mutants or KRAS, NRAS, or HRAS, such as G12C, G12D, G12R, G12S, G12V, G12W, G13D, Q61H, R68S, H95D, H95Q, H95R, or Y96C) or overexpression of a Ras protein can be determined using any biological sample comprising the target cells (e.g., cancer cells from a subject under investigation) or constituents thereof (e.g., constituents such as cfDNA from the tumor tissue or cancer cells). The biological sample may be a liquid biological sample or a solid biological sample (in case of metastasis to other tissues) from the subject under investigation or treatment. The biological sample may be a biopsy sample that is fixed, paraffin-embedded, fresh, or frozen. The biological sample may be obtained by any suitable means, including but not limited to blood draw, needle aspiration, fine needle aspiration, core needle biopsy, vacuum assisted biopsy, large core biopsy, incisional biopsy, excisional biopsy, punch biopsy, shave biopsy, skin biopsy, surgical specimen, and venipuncture.

[172] Depending on the tumor tissue or cancer cells to be treated, the biological sample can be obtained from, without limitation, blood or plasma, skin, heart, lung, kidney, bone marrow, breast, pancreas, liver, muscle, smooth muscle, bladder, gall bladder, colon, intestine, brain, prostate, esophagus, thyroid, serum, saliva, urine, gastric and digestive fluid, tears, stool, semen, vaginal fluid, interstitial fluids derived from tumorous tissue, ocular fluids, sweat, mucus, earwax, oil, glandular secretions, spinal fluid, hair, fingernails, plasma, nasal swab or nasopharyngeal wash, spinal fluid, cerebral spinal fluid, tissue, throat swab, biopsy, placental fluid, amniotic fluid, cord blood, emphatic fluids, cavity fluids, sputum, pus, microbiota, meconium, breast milk, and/or other excretions or body tissues of the subject.

[173] In some embodiments, a biological sample comprises cell-free DNA (cfDNA) derived from a whole blood or plasma of the subject. A sample may be analyzed directly for its contents, or may be processed to purify one or more of its contents for analysis. In some embodiments, one or more components are purified from the sample for detecting the presence of a Ras mutant protein (e.g., mutants or KRAS, NRAS, or HRAS, such as G12C, G12D, G12R, G12S, G12V, G12W, G13D, Q61H, R68S, H95D, H95Q, H95R, or Y96C) or overexpression of a Ras protein. In some embodiments, the purified component of the biological sample is protein (*e.g.* total protein, cytoplasmic protein, or membrane protein). In some embodiments, the purified component of the sample is a nucleic acid, such as DNA (*e.g.* genomic DNA, cDNA, ctDNA, or cfDNA) or RNA (*e.g.* total RNA, mRNA, or microRNA).

[174] In practicing a subject method disclosed herein, administrating a SOS1 inhibitor or a pharmaceutical composition comprising an effective amount of a SOS1 inhibitor typically involves contacting a cell with a SOS1 inhibitor disclosed herein. The contacting, as disclosed herein, can occur *in vitro, ex vivo,* or *in vivo.*

[175] In some embodiments, the cell is contacted with (i) a SOS1 inhibitor disclosed herein and (ii) a KRAS inhibitor disclosed herein. Contacting with (i) and (ii) can take place conjunctively. For example, a SOS1 inhibitor can be administered prior to, subsequent to, or concurrently with the administration of a KRAS inhibitor disclosed herein. For simultaneous contacting, the SOS1 inhibitor and the KRAS inhibitor disclosed herein can be in the same composition (e.g., as a formulation or as a unit dosage) or in different compositions (e.g., subjecting the cell to two different compositions at the same time). For sequential contacting, SOS1 inhibitor and the KRAS inhibitor disclosed herein can be in the same composition (e.g., a single composition exhibiting different release profiles or in different compositions). For sequential contacting, a first contacting of the cell (e.g., with the SOS1 inhibitor or the KRAS inhibitor disclosed herein) and a second contacting of the cell (e.g., with the KRAS inhibitor disclosed herein or the SOS1 inhibitor) can be separated by at least about 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 60 minutes, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 12 hours, 16 hours, 24 hours, 1 day, 3 days, 5 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, or longer. The first contacting and the second contacting can be

separated by at most about 1 month, 1 week, 24 hours, 20 hours, 16 hours, 12 hours, 11 hours, 10 hours, 9 hours, 8 hours, 7 hours, 6 hours, 5 hours, 4 hours, 3 hours, 2 hours, 60 minutes, or less.

[176] Suitable agents that can be administered in combination with a subject SOS1 inhibitor and KRAS inhibitor disclosed herein include but are not limited to TKIs, other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, immunomodulatory agent, chemotherapeutic agent, and combinations thereof.

[177] Exemplary immunomodulatory agents include but are not limited to immunostimulatory agents, checkpoint immune blockade agents (e.g., blockade agents or inhibitors of immune checkpoint genes, such as, for example, PD-1, PD-L1, CTLA-4, IDO, TIM3, LAG3, TIGIT, BTLA, VISTA, ICOS, KIRs and CD39), radiation therapy agents, chemotherapy agents, and combinations thereof. In some embodiments, the immunostimulatory agents are selected from the group consisting of IL-12, an agonist costimulatory monoclonal antibody, and combinations thereof. In one embodiment, the immunostimulatory agent is IL-12. In some embodiments, the agonist costimulatory monoclonal antibody is selected from the group consisting of an anti-4-1BB antibody (e.g., urelumab, PF-05082566), an anti-OX40 antibody (pogalizumab, tavolixizumab, PF-04518600), an anti-ICOS antibody (BMS986226, MEDI-570, GSK3359609, JTX-2011), and combinations thereof. In one embodiment, the agonist costimulatory monoclonal antibody is an anti-4-1BB antibody. In some embodiments, the checkpoint immune blockade agents are selected from the group consisting of anti-PD-L1 antibodies (atezolizumab, avelumab, durvalumab, BMS-936559), anti-CTLA-4 antibodies (e.g., tremelimumab, ipilimumab), anti-PD-1 antibodies (e.g., pembrolizumab, nivolumab), anti-LAG3 antibodies (e.g., C9B7W, 410C9), anti-B7-H3 antibodies (e.g., DS-5573a), anti-TIM3 antibodies (e.g., F38-2E2), and combinations thereof. In one embodiment, the checkpoint immune blockade agent is an anti-PD-L1 antibody.

[178] In embodiments, an additional agent (e.g., in addition to a KRAS inhibitor and SOS1 inhibitor) may be included in a method, kit, or pharmaceutical composition described herein. In embodiments, an additional agent may be selected from other anti-cancer agents, chemotherapeutic agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, immunostimulants, and combinations thereof. In one embodiment, a subject treatment method includes a chemotherapeutic agent.

[179] Exemplary chemotherapeutic agents include an anthracycline (e.g., doxorubicin (e.g., liposomal doxorubicin)), a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine), an alkylating agent (e.g., cyclophosphamide, decarbazine, melphalan, ifosfamide, temozolomide), an immune cell antibody, an antimetabolite (including, e.g., folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors (e.g., fludarabine)), a TNFR glucocorticoid induced TNFR related protein (GITR) agonist, a proteasome inhibitor, an immunomodulator such as thalidomide or a thalidomide derivative. Additional chemotherapeutic agents contemplated for use in combination include busulfan (Myleran®), busulfan injection (Busulfex®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), mitoxantrone (Novantrone®), Gemtuzumab Ozogamicin (Mylotarg®), anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), dexamethasone, docetaxel (Taxotere®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase

(ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), pemetrexed (Alimta®), phoenix (Yttrium90/MX-DTPA), pentostatin, platinum-based chemotherapy, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®).

[180] In some embodiments, a method described herein that comprises administering (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, further comprises administering (c) an additional agent selected from (1) a SHP2 inhibitor (e.g., 6-(4-amino-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenyl)pyrazin-2-amine, RMC-4630, ERAS-601, TNO155, JAB-3068, IACS-13909/BBP-398, SHP099, RMC-4550), (2) an inhibitor of wildtype or mutant RAS, such as wildtype KRAS, wildtype HRAS, wildtype NRAS, mutant KRAS, mutant HRAS, mutant NRAS, KRAS G12C, KRAS G12D, KRAS G12S, KRAS G12V, KRAS G13D, KRAS G13C, KRAS G13V, or KRAS Q61H (e.g., LY3537982, JAB-21822, BBO-8520, D-1553, BI-1823911, RMC-9805, MRTX1133, MRTX849, AMG510, GDC-6036, AZD4625, JDQ443, RMC-6291, RMC-6236, BI-2493, MK-1084, RMC-8839, SHR1127, JAB-21822, GFH925, IBI351, BPI-421286, JMKX1899, HBI-2438, D3S-001, GFH375, VS-7375, RMC-7977, RMC-5127, FMC-376), and (3) a MET inhibitor (e.g., foretinib, AMG-458, tivantinib, crizotinib, cabozantinib, tepotinib, capmatinib, savolitinib, glesatinib).

[181] Anti-cancer agents of particular interest for use in the methods of the present disclosure include: anthracyclines; alkylating agents; antimetabolites; drugs that inhibit either the calcium dependent phosphatase calcineurin or the p70S6 kinase FK506 or inhibit the p70S6 kinase; mTOR inhibitors; immunomodulators; anthracyclines; vinca alkaloids; proteosome inhibitors; GITR agonists; protein tyrosine phosphatase inhibitors; a CDK4 kinase inhibitor; a BTK inhibitor; a MKN kinase inhibitor; a DGK kinase inhibitor; or an oncolytic virus.

[182] Exemplary antimetabolites include, without limitation, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors: methotrexate (Rheumatrex®, Trexall®), 5-fluorouracil (Adrucil®, Efudex®, Fluoroplex®), floxuridine (FUDF®), cytarabine (Cytosar-U®, Tarabine PFS), 6-mercaptopurine (Puri-Nethol®)), 6-thioguanine (Thioguanine Tabloid®), fludarabine phosphate (Fludara®), pentostatin (Nipent®), pemetrexed (Alimta®), raltitrexed (Tomudex®), cladribine (Leustatin®), clofarabine (Clofarex®, Clolar®), azacitidine (Vidaza®), decitabine and gemcitabine (Gemzar®). Preferred antimetabolites include, cytarabine, clofarabine and fludarabine.

[183] Exemplary alkylating agents include, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes: uracil mustard (Aminouracil Mustard®, Chlorethaminacil®, Demethyldopan®, Desmethyldopan®, Haemanthamine®, Nordopan®, Uracil nitrogen Mustard®, Uracillost®, Uracilmostaza®, Uramustin®, Uramustine®), chlormethine (Mustargen®), cyclophosphamide (Cytoxan®, Neosar®, Clafen®, Endoxan®, Procytox®, Revimmune™), ifosfamide (Mitoxana®), melphalan (Alkeran®), Chlorambucil (Leukeran®), pipobroman (Amedel®, Vercyte®), triethylenemelamine (Hemel®, Hexalen®, Hexastat®), triethylenethiophosphoramine, Temozolomide (Temodar®), thiotepa (Thioplex®), busulfan (Busilvex®, Myleran®), carmustine (BiCNU®), lomustine (CeeNU®), streptozocin (Zanosar®), and Dacarbazine (DTIC-Dome®). Additional exemplary alkylating agents include, without limitation, Oxaliplatin (Eloxatin®); Temozolomide (Temodar® and Temodal®); Dactinomycin (also known as actinomycin-D, Cosmegen®); Melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, Alkeran®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Carmustine (BiCNU®); Bendamustine (Treanda®); Busulfan (Busulfex® and Myleran®); Carboplatin (Paraplatin®); Lomustine (also known as CCNU, CeeNU®); Cisplatin (also known as CDDP, Platinol® and Platinol®-

AQ); Chlorambucil (Leukeran®); Cyclophosphamide (Cytoxan® and Neosar®); Dacarbazine (also known as DTIC, DIC and imidazole carboxamide, DTIC-Dome®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Ifosfamide (Ifex®); Prednumustine; Procarbazine (Matulane®); Mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, Mustargen®); Streptozocin (Zanosar®); Thiotepa (also known as thiophosphoamide, TESPA and TSPA, Thioplex®); Cyclophosphamide (Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®); and Bendamustine HCl (Treanda®).

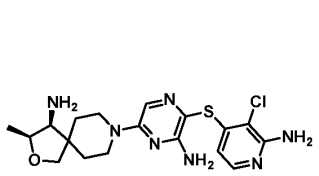
[184] In certain aspects, compositions provided herein can be administered in combination with radiotherapy, such as radiation. Whole body radiation may be administered at 12 Gy. A radiation dose may comprise a cumulative dose of 12 Gy to the whole body, including healthy tissues. A radiation dose may comprise from 5 Gy to 20 Gy. A radiation dose may be 5 Gy, 6 Gy, 7 Gy, 8 Gy, 9 Gy, 10 Gy, 11 Gy, 12, Gy, 13 Gy, 14 Gy, 15 Gy, 16 Gy, 17 Gy, 18 Gy, 19 Gy, or up to 20 Gy. Radiation may be whole body radiation or partial body radiation. In the case that radiation is whole body radiation it may be uniform or not uniform. For example, when radiation may not be uniform, narrower regions of a body such as the neck may receive a higher dose than broader regions such as the hips.

[185] Where desirable, an immunosuppressive agent can be used in conjunction with a subject treatment method. Exemplary immunosuppressive agents include but are not limited to cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, cytokines, and irradiation, peptide vaccine, and any combination thereof. In accordance with the presently disclosed subject matter, the above-described various methods can comprise administering at least one immunomodulatory agent. In certain embodiments, the at least one immunomodulatory agent is selected from the group consisting of immunostimulatory agents, checkpoint immune blockade agents (e.g., blockade agents or inhibitors of immune checkpoint genes, such as, for example, PD-1, PD-L1, CTLA-4, IDO, TIM3, LAG3, TIGIT, BTLA, VISTA, ICOS, KIRs and CD39), radiation therapy agents, chemotherapy agents, and combinations thereof. In some embodiments, the immunostimulatory agents are selected from the group consisting of IL-12, an agonist costimulatory monoclonal antibody, and combinations thereof. In one embodiment, the immunostimulatory agent is IL-12. In some embodiments, the agonist costimulatory monoclonal antibody is selected from the group consisting of an anti-4-lBB antibody, an anti-OX40 antibody, an anti-ICOS antibody, and combinations thereof. In one embodiment, the agonist costimulatory monoclonal antibody is an anti-4-l BB antibody. In some embodiments, the checkpoint immune blockade agents are selected from the group consisting of anti-PD-L1 antibodies, anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-LAG3 antibodies, anti-B7-H3 antibodies, anti-TIM3 antibodies, and combinations thereof. In one embodiment, the checkpoint immune blockade agent is an anti-PD-Ll antibody. In some embodiments, the method includes bone marrow transplantation, T cell ablative therapy using either chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or antibodies such as OKT3 or CAMPATH. In some cases, expanded cells can be administered before or following surgery. Alternatively, subject methods may include immunostimulants. Immunostimulants can be vaccines, colony stimulating agents, interferons, interleukins, viruses, antigens, co-stimulatory agents, immunogenicity agents, immunomodulators, or immunotherapeutic agents. An immunostimulant can be a cytokine such as an interleukin. One or more cytokines can be introduced with modified cells provided herein. Cytokines can be utilized to boost function of modified T lymphocytes (including adoptively transferred tumor-specific cytotoxic T lymphocytes) to expand within a tumor microenvironment. In some cases, IL-2 can be used to facilitate expansion of the modified cells described herein. Cytokines such as IL-15 can also be employed. Other relevant cytokines in the field of immunotherapy can also be utilized, such as IL-2, IL-7, IL-12, IL-15, IL-21, or any

combination thereof. An interleukin can be IL-2, or aldesleukin. Aldesleukin can be administered in low dose or high dose. A high dose aldesleukin regimen can involve administering aldesleukin intravenously every 8 hours, as tolerated, for up to about 14 doses at about 0.037 mg/kg (600,000 IU/kg). An immunostimulant (e.g., aldesleukin) can be administered within 24 hours after a cellular administration. An immunostimulant (e.g., aldesleukin) can be administered in as an infusion over about 15 minutes about every 8 hours for up to about 4 days after a cellular infusion. An immunostimulant (e.g., aldesleukin) can be administered at a dose from about 100,000 IU/kg, 200,000 IU/kg, 300,000 IU/kg, 400,000 IU/kg, 500,000 IU/kg, 600,000 IU/kg, 700,000 IU/kg, 800,000 IU/kg, 900,000 IU/kg, or up to about 1,000,000 IU/kg. In some cases, aldesleukin can be administered at a dose from about 100,000 IU/kg to 300,000 IU/kg, from 300,000 IU/kg to 500,000 IU/kg, from 500,000 IU/kg to 700,000 IU/kg, from 700,000 IU/kg to about 1,000,000 IU/kg.

[186] In embodiments, an additional agent (e.g., in addition to a KRAS inhibitor and SOS1 inhibitor) may be included in a method, kit, or pharmaceutical composition described herein. In some embodiments, an additional agent (e.g., in addition to a KRAS inhibitor and SOS1 inhibitor) included in a method, kit, or pharmaceutical composition described herein is selected from (1) an inhibitor of MEK (e.g., MEK1, MEK2) or of mutants thereof; (2) an inhibitor of epidermal growth factor receptor (EGFR) and/or of mutants thereof; (3) an immunotherapeutic agent (e.g., checkpoint immune blockade agents, as disclosed herein); (4) a taxane (e.g., paclitaxel, docetaxel); (5) an anti-metabolite (e.g. antifolates such as methotrexate, raltitrexed, pyrimidine analogues such as 5-fluorouracil (5-FU), ribonucleoside and deoxyribonucleoside analogues, capecitabine and gemcitabine, purine and adenosine analogues such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine (ara C), fludarabine); (6) an inhibitor of FGFR1 and/or FGFR2 and/or FGFR3 and/or FGFR4 and/or of mutants thereof; (7) a mitotic kinase inhibitor (e.g., a CDK4/6 inhibitor); (8) an anti-angiogenic drug (e.g., an anti-VEGF antibody); (9) a topoisomerase inhibitor; (10) a platinum-containing compound (e.g. cisplatin, oxaliplatin, carboplatin); (11) an inhibitor of ALK and/or of mutants thereof; (12) an inhibitor of c-MET and/or of mutants thereof; (13) an inhibitor of BCR-ABL and/or of mutants thereof; (14) an inhibitor of ErbB2 (Her2) and/or of mutants thereof; (15) an inhibitor of AXL and/or of mutants thereof; (16) an inhibitor of NTRK1 and/or of mutants thereof; (17) an inhibitor of RET and/or of mutants thereof; (18) an inhibitor of A-Raf and/or B-Raf and/or C-Raf and/or of mutants thereof; (19) an inhibitor of ERK and/or of mutants thereof; (20) an MDM2 inhibitor; (21) an inhibitor of mTOR; (22) an inhibitor of BET; (23) an inhibitor of IGF1/2 and/or of IGF1-R; (24) an inhibitor of CDK9; (25) an inhibitor of farnesyl transferase; (26) an inhibitor of SHIP pathway including SHIP2 inhibitor, as well as SHIP1 inhibitors; (27) an inhibitor of SRC; (28) an inhibitor of JAK; (29) a PARP inhibitor, (30) a BTK inhibitor, (31) a ROS1 inhibitor, (32) an inhibitor of Src, FLT3, HDAC, VEGFR, PDGFR, LCK, Bcr-Abl or AKT, (33) an inhibitor of KRAS G12C mutant (e.g., including but not limited to AMG510, MRTX849, and any covalent inhibitors binding to the cysteine residue 12 of KRAS, the structures of which are publicly known) (e.g., an inhibitor of Ras G12C as described in US20180334454, US20190144444, US20150239900, US10246424, US20180086753, WO2018143315, WO2018206539, WO20191107519, WO2019141250, WO2019150305, US9862701, US20170197945, US20180086753, US10144724, US20190055211, US20190092767, US20180127396, US20180273523, US10280172, US20180319775, US20180273515, US20180282307, US20180282308, WO2019051291, WO2019213526, WO2019213516, WO2019217691, WO2019241157, WO2019217307, WO2020047192, WO2017087528, WO2018218070, WO2018218069, WO2018218071, WO2020027083, WO2020027084, WO2019215203, WO2019155399, WO2020035031, WO2014160200, WO2018195349, WO2018112240, WO2019204442, WO2019204449, WO2019104505, WO2016179558, WO2016176338, or related patents and applications, each of which is incorporated by reference in its entirety), (34) an SHC inhibitor, (35) a GAB

inhibitor, (36) a GRB inhibitor, (37) a PI-3 kinase inhibitor, (38) a MARPK inhibitor, (39) a CDK4/6 inhibitor, (40) a MAPK inhibitor, or (41) a SHP pathway inhibitor, such as a SHP2 inhibitor (e.g., RMC-4630, ERAS-601,



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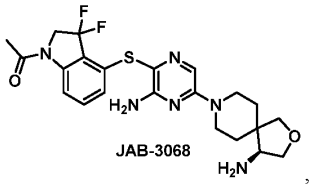

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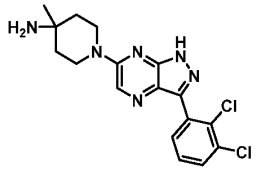

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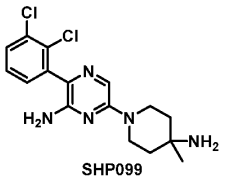

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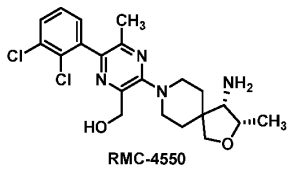


and) or a SHP1 inhibitor. In some embodiments, an additional agent is a checkpoint immune blockade agent (e.g., anti-PD-1 and/or anti-PD-L1 antibody, anti-CLTA-4 antibody). In some embodiments, an additional agent comprises an inhibitor against one or more targets selected from: MEK, epidermal growth factor receptor (EGFR), FGFR1, FGFR2, FGFR3, mitotic kinase, topoisomerase, ALK, ALK5, c-MET, ErbB2, AXL, NTRK1, RET, A-Raf, B-Raf, C-Raf, ERK, MDM2, mTOR, BET, IGF1/2, IGF1-R, CDK9, SHIP1, SHIP2, SHP2, SRC, JAK, PARP, BTK, FLT3, HDAC, VEGFR, PDGFR, LCK, Bcr-Abl, AKT, KRAS G12C mutant, and ROS1.

[187] In some embodiments, the agents of the method are administered either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two or more compounds in the body of the patient.

[188] In some embodiments, the agents of the method are administered sequentially in any order by a suitable route, such as infusion or orally. The dosing regimen may vary depending upon the stage of the disease, physical fitness of the patient, safety profiles of the individual drugs, and tolerance of the individual drugs, as well as other criteria known to the attending physician and medical practitioner(s) administering the combination. In embodiments, the agents of the method are administered within minutes of each other, hours, days, or even weeks apart depending upon the particular cycle being used for treatment. In addition, the cycle could include administration of one drug more often than the other during the treatment cycle and at different doses per administration of the drug.

[189] In some cases, a treatment regime may be dosed according to a body weight of a subject. In subjects who are determined obese (BMI > 35) a practical weight may need to be utilized. BMI is calculated by: BMI = weight (kg)/[height (m)]^2. Body weight may be calculated for men as 50 kg + 2.3*(number of inches over 60 inches) or for women 45.5 kg + 2.3*(number of inches over 60 inches). An adjusted body weight may be calculated for subjects who are more than 20% of their ideal body weight. An adjusted body weight may be the sum of an ideal body weight + (0.4*(Actual body weight – ideal body weight)). In some cases, a body surface area may be utilized to calculate a dosage. A body surface area (BSA) may be calculated by: BSA (m^2) = $\sqrt{}$Height (cm) ∗Weight (kg)/3600.

[190] A reduction in Ras signaling can be evidenced by one or more of the following: (i) an increase in steady state level of GDP-bound modified protein; (ii) a reduction in steady state level of GTP-bound Ras protein; (iii) a reduction of phosphorylated AKTs473, (iv) a reduction of phosphorylated ERKT202/y204, (v) a reduction of phosphorylated S6S235/236, (vi) a reduction of cell growth of a tumor cell expressing a Ras mutant (e.g., G12S, G12C, G12D, G12V, G13C, and/or G13D) protein, (vii) a reduction in Ras interaction with a Ras-pathway signaling protein, and (viii) a reduction in expression level of Ras protein. Non-limiting examples of Ras-pathway signaling proteins include SOS (including SOS1 and SOS2), RAF, SHC, SHP (including SHP1 and SHP2), MEK, MAPK, ERK, GRB, RASA1, and

GNAQ. In some embodiments, the reduction in Ras signaling output can be evidenced by two, three, four, five, six, seven, or all of (i)-(viii) above. In some embodiments, the reduction of any one or more of (i)-(viii) can be 0.1-fold, 0.2-fold, 0.3-fold, 0.4-fold, 0.5-fold, 0.6-fold, 0.7-fold, 0.8-fold, 0.9-fold, 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, or more as compared to a control not treated with a method or composition described herein. A reduction in cell growth can be demonstrated with the use of tumor cells or cell lines. A tumor cell line can be derived from a tumor in one or more tissues, e.g., pancreas, lung, ovary, biliary tract, intestine (e.g., small intestine, large intestine, colon), endometrium, stomach, hematopoietic tissue (e.g., lymphoid tissue), etc. Examples of tumor cell lines comprising a K-Ras mutation include, but are not limited to, A549 (e.g., K-Ras G12S), AGS (e.g., K-Ras G12D), ASPC1 (e.g., K-Ras G12D), Calu-6 (e.g., K-Ras Q61K), CFPAC-1 (e.g., K-Ras G12V), CL40 (e.g., K-Ras G12D), COLO678 (e.g., K-Ras G12D), COR-L23 (e.g., K-Ras G12V), DAN-G (e.g., K-Ras G12V), GP2D (e.g., K-Ras G12D), GSU (e.g., K-Ras G12F), HCT116 (e.g., K-Ras G13D), HEC1A (e.g., K-Ras G12D), HEC1B (e.g., K-Ras G12F), HEC50B (e.g., K-Ras G12F), HEYA8 (e.g., K-Ras G12D or G13D), HPAC (e.g., K-Ras G12D), HPAFII (e.g., K-Ras G12D), HUCCT1 (e.g., K-Ras G12D), KARPAS620 (e.g., K-Ras G13D), KOPN8 (e.g., K-Ras G13D), KP-3 (e.g., K-Ras G12V), KP-4 (e.g., K-Ras G12D), L3.3 (e.g., K-Ras G12D), LoVo (e.g., K-Ras G13D), LS180 (e.g., K-Ras G12D), LS513 (e.g., K-Ras G12D), MCAS (e.g., K-Ras G12D), NB4 (e.g., K-Ras A18D), NCI-H1355 (e.g., K-Ras G13C), NCI-H1573 (e.g., K-Ras G12A), NCI-H1944 (e.g., K-Ras G13D), NCI-H2009 (e.g., K-Ras G12A), NCI-H441 (e.g., K-Ras G12V), NCI-H747 (e.g., K-Ras G13D), NOMO-1 (e.g., K-Ras G12D), OV7 (e.g., K-Ras G12D), PANC0203 (e.g., K-Ras G12D), PANC0403 (e.g., K-Ras G12D), PANC0504 (e.g., K-Ras G12D), PANC0813 (e.g., K-Ras G12D), PANC1 (e.g., K-Ras G12D), Panc-10.05 (e.g., K-Ras G12D), PaTu-8902 (e.g., K-Ras G12V), PK1 (e.g., K-Ras G12D), PK45H (e.g., K-Ras G12D), PK59 (e.g., K-Ras G12D), SK-CO-1 (e.g., K-Ras G12V), SKLU1 (e.g., K-Ras G12D), SKM-1 (e.g., K-Ras K117N), SNU1 (e.g., K-Ras G12D), SNU1033 (e.g., K-Ras G12D), SNU1197 (e.g., K-Ras G12D), SNU407 (e.g., K-Ras G12D), SNU410 (e.g., K-Ras G12D), SNU601 (e.g., K-Ras G12D), SNU61 (e.g., K-Ras G12D), SNU8 (e.g., K-Ras G12D), SNU869 (e.g., K-Ras G12D), SNU-C2A (e.g., K-Ras G12D), SU.86.86 (e.g., K-Ras G12D), SUIT2 (e.g., K-Ras G12D), SW1990 (e.g., K-Ras G12D), SW403 (e.g., K-Ras G12V), SW480 (e.g., K-Ras G12V), SW620 (e.g., K-Ras G12V), SW948 (e.g., K-Ras Q61L), T3M10 (e.g., K-Ras G12D), TCC-PAN2 (e.g., K-Ras G12R), TGBC11TKB (e.g., K-Ras G12D), and MIA Pa-Ca (e.g., MIA Pa-Ca 2 (e.g., K-Ras G12C)).

[191] A reduction of signaling output can be ascertained by a wide variety of methods known in the art. For example, phosphorylation of a substrate or a specific amino acid residue thereof can be detected and/or quantified using one or more techniques, such as kinase activity assays, phospho-specific antibodies, Western blot, enzyme-linked immunosorbent assays (ELISA), cell-based ELISA, intracellular flow cytometry, mass spectrometry, and multi-analyte profiling. A host of readout can evidence a reduction of Ras signaling output, including without limitation: (i) an increase in steady state level of GDP-bound modified protein; (ii) a reduction in steady state level of GTP-bound Ras protein; (iii) a reduction of phosphorylated AKTs473, (iv) a reduction of phosphorylated ERKT202/y204, (v) a reduction of phosphorylated S6S235/236, (vi) a reduction of cell growth of a tumor cell expressing a Ras mutant (e.g., G12S, G12C, G12D, G12V, G13C, and/or G13D) protein, (vii) a reduction in Ras interaction with a Ras-pathway signaling protein, and (viii) a reduction in expression level of Ras protein. In some embodiments, a reduction is evidenced by 2, 3, 4 or more of items (i)-(viii). In some embodiments, the reduction in Ras signaling output can be evidenced by any one of (i)-(viii) as compared to control corresponding Ras protein in the absence of a compound disclosed herein. For example, a control Ras protein, as described herein, can be a Ras protein (e.g., wildtype or

mutated) that is not bound to any subject compound of the present disclosure. The increase in item (i) or reduction in items (ii) through (vi) can be at least about 0.1-fold, 0.2-fold, 0.3-fold, 0.4-fold, 0.5-fold, 0.6-fold, 0.7-fold, 0.8-fold, 0.9-fold, 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, or more as compared to the control Ras protein. In some embodiments, a reduction in Ras interaction with a Ras-pathway signaling protein is established by a reduced interaction with SOS (including SOS1 and SOS2), RAF, SHC, SHP (including SHP1 and SHP2), MEK, MAPK, ERK, GRB, RASA1, or GNAQ.

[192] In some embodiments, additional therapies, can be administered to the subject for other purposes. For example, anti-inflammatory agents or other agents that treat symptoms associated with cancer, but not the underlying cancer itself, including, e.g., inflammation, pain, nausea, weight loss, and general malaise can be administered to a subject with cancer during the period of monotherapy treatment. A subject being treated by the present methods can have completed any prior treatment (e.g., surgery, chemotherapy, bone marrow transplant, or being treated with some other anti-cancer agents) before the monotherapy treatment or receive additional therapies after the monotherapy treatment.

[193] A synergistic effect of a combination treatment comprising a plurality of agents, as disclosed herein, can be characterized by a synergistic value as ascertained by an "excess over Bliss independence" or "BLISS" independence criterion. The BLISS independence criterion can be used to screen for candidate drug combinations. The criterion can compare the observed combination response with the predicted combination response, which predicted combination response is obtained based on the assumption that there is no effect from drug-drug interactions. The combination effect can be determined to be synergistic when the observed combination response is greater than the predicted combination response (e.g., greater by a threshold value). To determine a synergistic value of a combination treatment comprising inhibitor (a) (e.g., a SOS1 inhibitor) and inhibitor (b) (e.g., a KRAS inhibitor disclosed or exemplified herein) for inducing growth inhibition of target cells (e.g., cells including a KRAS mutant or cells overexpressing KRAS), the BLISS independence criterion can utilize the following equation:

$$Y_{AB,O} - Y_{AB,P} \quad (1)$$

wherein:

$Y_{AB,O}$ is observed percentage growth inhibition of the target cells by the combination comprising (a) at dose A and (b) at dose B; and

$Y_{AB,P}$ is predicted percentage growth inhibition of the target cells by the combination comprising (a) at the dose A, and (b) at the dose B, wherein:

$$Y_{AB,P} = Y_A + Y_B - Y_A Y_B \quad (2)$$

wherein further:

Y_A is observed percentage growth inhibition of the target cells by (a) alone at the dose A;

Y_B is observed percentage growth inhibition of the target cells by (b) alone at the dose B; and

$Y_A Y_B$ is product of Y_A and Y_B.

The observed combined percentage inhibition $Y_{AB,O}$ is compared with the predicted percentage growth inhibition $Y_{AB,P}$ in accordance with equation (1). The comparison can determine whether the combination treatment promotes a synergistic effect, an additive effect, or an antagonistic effect, as summarized in equation (3). When $Y_{AB,O} > Y_{AB,P}$, the combination treatment can be determined to be more efficacious than expected (e.g., a synergistic effect). When $Y_{AB,O} < Y_{AB,P}$, the combination treatment can be determined to be worse than expected (e.g., an antagonistic effect). When $Y_{AB,O} = Y_{AB,P}$, the combination treatment can be determined to be substantially the same as a simple addition of

two separate drugs (e.g., independent effects, or an additive effect).

$$Y_{AB,P}\begin{cases} > Y_{AB,P} & \text{Synergy} \\ = Y_{AB,P} & \text{Independent} \\ < Y_{AB,P} & \text{Antagonism} \end{cases} \quad (3)$$

[194] When using the BLISS independence criterion, the percentage growth inhibition of the target cells can be provided based on a percentage scale (e.g., between about 0% to about 100%) or a fractional scale (e.g., between about 0 to 1). For example, a 75% growth inhibition of the target cells can be expressed as 0.75 for purposes of analysis in accordance with the BLISS independence criterion. For example, with the fractional scale is used, the difference between the observed combined percentage inhibition $Y_{AB,O}$ and the predicted percentage growth inhibition $Y_{AB,P}$, in accordance with equation (1) (e.g., based on one or more *in vitro* experiments), can be determined to be additive (or antagonistic) when the difference is less than or equal to zero. Such difference can be determined to be synergistic when the difference is greater than zero. Here, the synergistic effect can be divided into a plurality of sub-ranges, e.g., a first synergistic sub-range having the difference between about 0.05 and about 0.1 (e.g., mild synergy), a second synergistic sub-range having the difference between about 0.1 and about 0.2 (e.g., moderate synergy), and a third synergistic sub-range having the difference greater than or equal to 0.2 (e.g., robust synergy).

[195] In some embodiments, the combination treatment comprising a plurality of agents (e.g., a SOS1 inhibitor and a KRAS inhibitor disclosed herein), can be utilized to reduce growth or proliferation of target cells, *in vitro* or *in vivo*. The therapeutic efficacy of the combination treatment can be characterized by a synergistic value of above 0.1 as ascertained by the Bliss independence criterion. The therapeutic efficacy of the combination treatment can be characterized by a synergistic value of at least about 0.1, 0.2, 0.3, 0.4, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 13, 14, 15, or above as ascertained by the Bliss independence criterion. The therapeutic efficacy of the combination treatment can be characterized by a synergistic value of about 0.1 to about 1, about 1.0-5, about 5 to about 10, or about 10-15.

[196] The subject combination therapy comprising a plurality of different therapeutic agents (e.g. a SOS1 inhibitor and a KRAS inhibitor disclosed herein) can synergistically achieve one or more desired therapeutic actions or outcomes. In some embodiments, the reduced progression of a cancer is evidenced by an improvement of a response such as a molecular response or cytogenetic response in a subject being treated. A subject treated according to a method of the present disclosure may exhibit one or more desired therapeutic outcomes described herein, any of which may persist for at least 1 month, such as at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, at least 24 months, at least 30 months, at least 36 months, or longer. For example, a subject treated according to a method of the present disclosure may exhibit one or more of (i) disease stabilization, (ii) disease regression, and (iii) improvement of one or more symptoms of the cancer, any one or more of which may persist for at least 1 month, such as at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, at least 24 months, at least 30 months, at least 36 months, or longer.

[197] The subject combination treatment disclosed herein can achieve such desired actions or outcomes, while synergistically providing one or more superior advantages including, but not limited to, (i) decreased amount (e.g., dosage regimen, number of doses, etc.) of one, more, or all of the therapeutic agents utilized in the combination therapy; (ii) avoiding, limiting, or reducing one or more undesirable side-effects associated with the use of any one of the plurality of different therapeutic agents when used in the therapeutically effective amount or clinically approved amount; (iii) allowing for the use of a KRAS inhibitor disclosed herein that would otherwise be intolerable to the

subject.

[198] Through the administration of a combination therapy disclosed herein, a range of undesirable side-effects associated may be reduced, including diarrhea, rash, nausea, vomiting, decreased appetite, fatigue, musculoskeletal pain, dyspnea, and acute kidney injury. In some embodiments, other side effects of a KRAS inhibitor disclosed herein including diarrhea, rash, nausea, vomiting, decreased appetite, fatigue, musculoskeletal pain, dyspnea, and acute kidney injury can be reduced. The combination treatment with a SOS1 inhibitor disclosed herein may allow administration of a KRAS inhibitor disclosed herein that is otherwise not tolerable to the subject. The combination treatment with a subject SOS1 inhibitor may allow a more frequent dosage regimen of KRAS inhibitor disclosed herein that is otherwise too toxic or not tolerable to a subject in need of such treatment.

[199] The combination treatment as disclosed herein can utilize a KRAS inhibitor disclosed herein that can be therapeutically sub-optimal when used alone, but in combination with a SOS1 inhibitor disclosed herein yields an overall therapeutic efficacy (e.g., promoting one or more desired therapeutic outcomes and/or reducing undesirable side-effects). In some embodiments, the combination therapy utilizes a sub-therapeutic dose of a KRAS inhibitor disclosed herein approved for treating a human subject for a given indication. In some embodiments, the sub-therapeutic dose is less than 95% of the approved dose of the KRAS inhibitor, such as less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, or less than 10% of the approved dose of the KRAS inhibitor.

[200] In practicing any of the subject methods, the SOS1 inhibitor may be administered at a dose of at least 5 mg daily, such as 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 120 mg, 140 mg, 160 mg, 180 mg, 200 mg, 220 mg, 240 mg, 260 mg, 280 mg, 300 mg, 320 mg, 340 mg, 360 mg, 380 mg, 400 mg, 420 mg, 440 mg, 460 mg, 480 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg daily in combination with a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof,. In some embodiments, the SOS1 inhibitor is administered at a dose of 5 to 1000 mg, such as about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, about 360 mg, about 380 mg, about 400 mg, about 420 mg, about 440 mg, about 460 mg, about 480 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg in combination with a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof.

[201] In another aspect, the present disclosure provides a method of treating cancer in a subject in need thereof. The method comprises administering a pharmaceutical composition that comprises an effective amount of a small molecule SOS1 inhibitor to the subject, wherein said SOS1 inhibitor inhibits growth of a cancer cell line with an IC50 less than about 100 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, 0.1 nM or even less, as ascertained in a growth inhibition assay utilizing the cancer cell line. In some embodiments, the SOS1 inhibitor inhibits growth of a cancer cell line with an IC50 at least 100 times less than that of BI3406 or that of MRTX0902. In some embodiments, the SOS1 inhibitor synergistically inhibits growth of a cancer cell line in combination with a KRAS inhibitor disclosed herein. In some embodiments, the SOS1 inhibitor is characterized in that it synergistically increases percent of cell growth inhibition from about 10% to at least about 50%, when less than about

100 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM of the SOS1 inhibitor is applied in combination with the KRAS inhibitor disclosed herein applied at its IC10 molarity, as ascertained in an in vitro growth inhibition assay using cancer cells.

[202] In yet another aspect, the present disclosure provides a method of reducing proliferation of a cancer cell. The method comprises administering to the cell (a) a small molecule SOS1 inhibitor disclosed herein, and (b) a KRAS inhibitor disclosed herein, wherein the administration of (a) and (b) synergistically inhibits growth of cancer cells as evidenced by achieving a comparable or higher degree of growth inhibition when either (1) less than 90% of the SOS1 inhibitor is administered as compared to the amount required for the SOS1 inhibitor when administered alone; or (2) less than 90% of the KRAS inhibitor disclosed herein is administered as compared to the amount required for the KRAS inhibitor disclosed herein when administered alone. In some embodiments, the KRAS inhibitor disclosed herein administered is less than about 80%, 70%, 60%, 50%, 40%, 30%, 25%, 20%, 15%, or 10% of the amount required to achieve a comparable or higher degree of growth inhibition.

[203] In some embodiments, the subject is a naïve subject that has not been treated for the cancer. In some embodiments, the naïve subject has not been treated with a KRAS inhibitor prior to administering (a) and (b). In some embodiments, the subject has been treated with chemotherapy. In some embodiments, the subject has received surgery to treat the cancer. In some embodiments, the subject has not been treated with chemotherapy. In some embodiments, the subject has not received surgery. In some embodiments, the subject has been treated with a KRAS inhibitor prior to administering (a) and (b). In some embodiments, the subject has not been treated with a KRAS inhibitor prior to administering (a) and (b).

[204] In some embodiments, a subject suitable for a treatment method of the present disclosure has previously been treated with one or more KRAS inhibitors prior to administering (a) and (b). In some embodiments, a subject suitable for a treatment method of the present disclosure has previously been treated with platinum-based chemotherapy prior to administering (a) and (b). In some embodiments, the disease of the subject has progressed on or after platinum-based chemotherapy. In some embodiments, the subject has undergone tumor resection. In some embodiments, the disease of the subject has progressed on or after platinum-based chemotherapy in the locally advanced metastatic setting or recurred in the adjuvant setting. In some embodiments, the disease of the subject has progressed on or after KRAS inhibitor treatment. In some embodiments, the disease of the subject has progressed on or after KRAS inhibitor treatment in the locally advanced metastatic setting or recurred in the adjuvant setting.

[205] Drug resistance and/or intolerance to the certain KRAS inhibitors may severely limit treatment options for subjects who exhibit resistance or intolerance to one or more KRAS inhibitors, or relapse following treatment with one or more KRAS inhibitors. Resistance to a KRAS inhibitor may be characterized by one or more changes selected from (1) progression of the cancer, (2) mutation of KRAS that was not present prior to the earlier treatment, including point mutation, (3) *KRAS* gene amplification, (4) RAS-MAPK pathway activation, (5) histologic transformation, and (6) phenotypic transformation. In some embodiments, resistance to a KRAS inhibitor is characterized by a new mutation at the amino acid corresponding to the 12 position of KRAS.

[206] In some embodiments, a subject suitable for a treatment method of the present disclosure exhibits intolerance to a KRAS inhibitor. In some embodiments, the subject suffers from one or more side effects selected from fluid retention, headache, diarrhea, fatigue, cough, dyspnea, musculoskeletal pain, nausea, skin rash, myalgia, arthralgia, infection, abdominal pain, hemorrhage, pruritis, pain, constipation, myelosuppression, bleeding-related events, cardiovascular toxicity, pulmonary arterial hypertension, QT prolongation, dermatologic reactions, Stevens-Johnson syndrome, erythema multiforme, tumor lysis syndrome, musculoskeletal disorder, decreased appetite, hepatic enzyme increase (e.g., AST, ALK, alkaline phosphatase), and hepatotoxicity.

[207] A subject resistant to treatment with a KRAS inhibitor may exhibit progression of the disease or condition, such as cancer (e.g., NSCLC, lung cancer, colorectal cancer, pancreatic cancer), despite treatment with the KRAS inhibitor.

[208] Progression may be established by a lack of reduction in any or some of the symptoms disclosed herein or known in the art that are associated with a KRAS-mediated cancer, such as NSCLC, lung cancer, colorectal cancer, or pancreatic cancer. In some embodiments, progression is established for a lack of reduction in one or more symptoms after, for example, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more months from the initial treatment of KRAS inhibitor.

[209] In some embodiments, a subject suitable for a treatment method of the present disclosure suffers from a relapse of a KRAS-mediated cancer, such as NSCLC, lung cancer, colorectal cancer, or pancreatic cancer. A relapse can be established by a renewed onset of any of the symptoms associated with the cancer with which the subject has previously been diagnosed, or by the detection of the cancer via a suitable method, such as a CT scan, a PET scan, an MRI, a bronchoscopy, or a lung biopsy. A relapse may occur, e.g., 3, 5, 7, 8, 9, 10, 11, 12, 15, 18, 24, 25, 26, 27, 28, 29, 30, 36, or more months after the initial treatment with KRAS inhibitor.

Kits

[210] In an aspect is provided a kit for use in reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS overexpression, the kit comprising: (1) a composition comprising a small molecule SOS1 inhibitor of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SI-1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or any embodiment of the preceding formulae; (2) a composition comprising a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae; and (3) instructions for using the composition(s) of (1) and (2).

[211] In an aspect is provided a kit for use in reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS overexpression, the kit comprising: (1) a composition comprising a small molecule SOS1 inhibitor of Formula (SI-1); (2) a composition comprising a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae; and (3) instructions for using the composition(s) of (1) and (2).

[212] In embodiments of the kit, the SOS1 inhibitor and the KRAS inhibitor are formulated in the same unit dosage form. In embodiments of the kit, the SOS1 inhibitor and the KRAS inhibitor are formulated in different unit dosage forms.

[213] In embodiments, the small molecule SOS1 inhibitor is a small molecule SOS1 inhibitor of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SI-1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1). In some embodiments, instructions for contacting the cells in vitro, ex vivo, or in vivo are provided. In some embodiments, the kit can comprise a multi-day supply, including instructions directing the multi-day administration.

Pharmaceutical Compositions

[214] In an aspect is provided a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SI-1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2),

(II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, and (iii) a pharmaceutically acceptable excipient.

[215] In an aspect is provided a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SI-1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), or any embodiment of the preceding formulae, or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, and (iii) a pharmaceutically acceptable excipient.

[216] In an aspect is provided a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae, and (iii) a pharmaceutically acceptable excipient.

[217] Compounds described herein, or pharmaceutically acceptable salts or solvates thereof, may be administered to a subject in biologically compatible forms suitable for administration to treat or prevent a disease, disorder or condition. Compounds described herein may be administered in any pharmacological form including a therapeutically effective amount administered separately or in combination. Compounds described herein may be administered in any pharmacological form including therapeutically effective amounts of the compounds alone or in combination with pharmaceutically acceptable carriers. In some embodiments, the present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and compounds described herein, or pharmaceutically acceptable salts or solvates thereof.

[218] In some embodiments, a compound described herein is administered as a pure chemical. In some embodiments, a compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[219] Accordingly, provided herein is a pharmaceutical composition comprising compounds described herein, or pharmaceutically acceptable salts, together with one or more pharmaceutically acceptable excipients. The excipient(s) (or carrier(s)) is acceptable or suitable if the excipient is compatible with the other ingredients of the composition and not deleterious to the recipient of the composition.

[220] In practicing any of the subject methods, the compounds described herein may be administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition. Administration of the compounds and compositions described herein can be affected by any method that enables delivery of the compounds to the site of action. These methods include, though are not limited to delivery via enteral routes (including oral, gastric or duodenal feeding tube, rectal suppository and rectal enema), parenteral routes (injection or infusion, including intraarterial, intracardiac, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration, although the most suitable route may depend upon, for example, the condition and disorder of the recipient. By way of example only, a compound described herein can be administered locally to the area in need of treatment, by for example, local infusion during surgery, topical application such as

creams or ointments, injection, catheter, or implant. The administration can also be by direct injection at the site of a diseased tissue or organ. In some embodiments, a compound described herein is administered orally.

[221] In practicing any of the subject methods, a pharmaceutical composition suitable for oral administration may be presented as a discrete unit such as a capsule, cachet or tablet, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In some embodiments, the active ingredient is presented as a bolus, electuary or paste.

[222] Pharmaceutical compositions which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. In some embodiments, the tablets are coated or scored and are formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

[223] In some embodiments, a pharmaceutical composition is formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

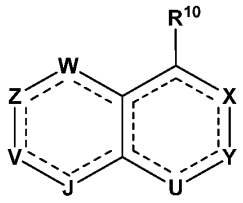
[224] Pharmaceutical compositions for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[225] Pharmaceutical compositions may also be formulated as a depot preparation. Such long-acting formulations

may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Compounds

[226] In an aspect is provided a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein

W is a N, C(R^{18}), N(R^{18b}), C(R^{18})(R^{18a}), C(O), S(O), or S($O)_2$;

Z is N, C(R^8), N(R^{8b}), C(R^8)(R^{8a}), C(O), S(O), or S($O)_2$; wherein W and Z are not both selected from C(O), S(O), and S($O)_2$;

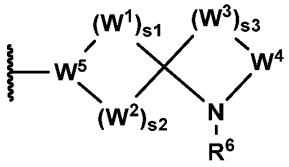
V and J are each independently selected from C(R^{17}), C(R^{17})(R^{16a}), C(R^{16}), C(R^{16})(R^{16a}), N, N(R^{17b}), and N(R^{16b}); wherein exactly one of V and J is C(R^{17}), C(R^{17})(R^{16a}), or N(R^{17b});

Y is N, C(R^2), C(R^2)(R^{2c}), N(R^{2b}), S(O), or S($O)_2$;

U is N, C(R^{2c}), C(R^{2c})(R^{2c}), N(R^{2b}), S(O), S($O)_2$, or C(O);

R^{10} is -L^7-R^7;

L^7 is a bond, -O-, -N(R^{14})-, -C(O)-, -S-, -S($O)_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is 

;

W^1 and W^3 are independently selected from N(R^1), N(R^4), C(R^1)(R^1), C(R^1)(R^4), C(R^4)(R^4), C(O), S, O, S(O), and S($O)_2$;

W^2 is independently selected from a N(R^1), N(R^4), C(R^1)(R^1), C(R^1)(R^4), C(R^4)(R^4), C(O), S, O, S(O), and S($O)_2$;

W^4 is selected from C(R^1)(R^1), C(R^1)(R^4), C(R^4)(R^4), S(O), and S($O)_2$;

W^5 is selected from N, C(R^1), and C(R^4);

a) s1 is 1 and s2 is 0, 2, or 3; s1 is 2 and s2 is 0, 1, or 3; s1 is 3 and s2 is 0 to 3; s1 is 4 and s2 is 0 to 3; s1 is 5 and s2 is 0 to 3; or s1 is 6 and s2 is 0 to 3; or

b) s1 is an integer from 1 to 6; s2 is an integer from 0 to 3; s1 and s2 are not both 1; and s1 and s2 are not both 2;

s3 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -

CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, =$C(R^{21b})_2$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is -L^2-R^5, wherein R^6 is optionally capable of forming a covalent bond with a RAS amino acid;

L^2 is a bond, -O-, -$N(R^{4d})$-, -C(O)-, -S-, -$S(O)_2$-, -S(O)-, -$P(O)R^{4d}$-, $CR^{4c}R^{4c}$, -$OCR^{4c}R^{4c}$-, -$N(R^{4d})CR^{4c}R^{4c}$-, -$C(O)CR^{4c}R^{4c}$-, -$SCR^{4c}R^{4c}$-, -$S(O)_2CR^{4c}R^{4c}$-, -$S(O)CR^{4c}R^{4c}$-, -$P(O)R^{4d}CR^{4c}R^{4c}$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}$, -$CR^{4c}R^{4c}O$-, -$CR^{4c}R^{4c}N(R^{4d})$-, -$CR^{4c}R^{4c}C(O)$-, -$CR^{4c}R^{4c}S$-, -$CR^{4c}R^{4c}S(O)_2$-, -$CR^{4c}R^{4c}S(O)$-, -$CR^{4c}R^{4c}P(O)R^{4d}$-, -$N(R^{4d})C(O)$-, -$N(R^{4d})S(O)_2$-, -$N(R^{4d})S(O)$-, -$N(R^{4d})P(O)R^{4d}$-, -$C(O)N(R^{4d})$-, -$S(O)_2N(R^{4d})$-, -$S(O)N(R^{4d})$-, -$P(O)R^{4d}N(R^{4d})$-, -OC(O)-, -$OS(O)_2$-, -OS(O)-, -$OP(O)R^{4d}$-, -C(O)O-, -$S(O)_2O$-, -S(O)O-, -$P(O)R^{4d}O$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}$-, -$OCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$SCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$CR^{4c}R^{4c}CR^{4c}R^{4c}O$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)$-, or -$CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}$-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, -$OC(O)R^{14a}$, -$N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14a}$, and -$N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, and -$OC(O)R^{14a}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl,

-OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is -L^1-R^{19};

R^{17b} is -L^{1b}-R^{19};

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, -$N(R^{14})$-, -C(O)-, -$N(R^{14})C(O)$-, -$C(O)N(R^{14})$-, -S-, -$S(O)_2$-, -S(O)-, -$S(O)_2N(R^{14})$-, -$S(O)N(R^{14})$-, -$N(R^{14})S(O)$-, -$N(R^{14})S(O)_2$-, -$OCON(R^{14})$-, -$N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, -$C(O)N(R^{14})$-, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl,

and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12''})(R^{13})$, $-N=(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{4-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, and $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one,

two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -$C(O)OR^{12'}$, -$OC(O)N(R^{12'})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12'})(R^{13})$, -$C(O)C(O)N(R^{12'})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, -$CH_2C(O)N(R^{12'})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12'})(R^{13})$, –($C_{1-6}$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, C_{1-9}heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $=C(R^{21b})_2$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{21}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{21}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

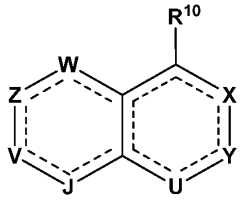
each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

~~~ indicates the location of attachment of the depicted chemical formula or atom to a substituent, a further component of a molecule, or an atom; and

====== indicates a single or double bond such that all valences are satisfied.

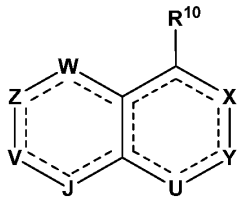
[227] In an aspect is provided a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I); wherein s1 is an integer from 1 to 6 and s2 is an integer from 1 to 3; and all other variables are as described for the aspect immediately above.

[228] In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, s1 is 1 and s2 is 0, 2, or 3; s1 is 2 and s2 is 0, 1, or 3; s1 is 3 and s2 is 0 to 3; s1 is 4 and s2 is 0 to 3; s1 is 5 and s2 is 0 to 3; or s1 is 6 and s2 is 0 to 3. In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, s1 is an integer from 1 to 6; s2 is an integer from 0 to 3; s1 and s2 are not both 1; and s1 and s2 are not both 2.

[229] In an aspect is provided a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

Z is N, $C(R^{8})$, $N(R^{8b})$, $C(R^{8})(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

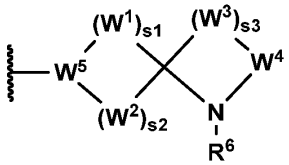
V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

Y is N, $C(R^{2})$, $C(R^{2})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$;

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^{7}-R^{7}$;

L^{7} is a bond, -O-, $-N(R^{14})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^{7} is 

;

W^{1} and W^{3} are independently selected from $N(R^{1})$, $N(R^{4})$, $C(R^{1})(R^{1})$, $C(R^{1})(R^{4})$, $C(R^{4})(R^{4})$, C(O), S, O, S(O), and $S(O)_2$;

W^{2} is independently selected from a $N(R^{1})$, $N(R^{4})$, $C(R^{1})(R^{1})$, $C(R^{1})(R^{4})$, $C(R^{4})(R^{4})$, C(O), S, O, S(O), and $S(O)_2$;
~~~

W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is 1 and s2 is 0, 2, or 3; s1 is 2 and s2 is 0, 1, or 3; s1 is 3 and s2 is 0 to 3; s1 is 4 and s2 is 0 to 3; s1 is 5 and s2 is 0 to 3; or s1 is 6 and s2 is 0 to 3;

s3 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $=C(R^{21b})_2$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl$)-S(O)_2R^{15}$, $-(C_{1-6}$alkyl$)-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl$)-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is $-L^2-R^5$, wherein R^6 is optionally capable of forming a covalent bond with a RAS amino acid;

L^2 is a bond, -O-, $-N(R^{4d})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{4d}$-, $CR^{4c}R^{4c}$, $-OCR^{4c}R^{4c}$-, $-N(R^{4d})CR^{4c}R^{4c}$-, $-C(O)CR^{4c}R^{4c}$-, $-SCR^{4c}R^{4c}$-, $-S(O)_2CR^{4c}R^{4c}$-, $-S(O)CR^{4c}R^{4c}$-, $-P(O)R^{4d}CR^{4c}R^{4c}$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}$, $-CR^{4c}R^{4c}O$-, $-CR^{4c}R^{4c}N(R^{4d})$-, $-CR^{4c}R^{4c}C(O)$-, $-CR^{4c}R^{4c}S$-, $-CR^{4c}R^{4c}S(O)_2$-, $-CR^{4c}R^{4c}S(O)$-, $-CR^{4c}R^{4c}P(O)R^{4d}$-, $-N(R^{4d})C(O)$-, $-N(R^{4d})S(O)_2$-, $-N(R^{4d})S(O)$-, $-N(R^{4d})P(O)R^{4d}$-, $-C(O)N(R^{4d})$-, $-S(O)_2N(R^{4d})$-, $-S(O)N(R^{4d})$-, $-P(O)R^{4d}N(R^{4d})$-, -OC(O)-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{4d}$-, -C(O)O-, $-S(O)_2O$-, -S(O)O-, $-P(O)R^{4d}O$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}$-, $-OCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-SCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-CR^{4c}R^{4c}CR^{4c}R^{4c}O$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)$-, or $-CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}$-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, $-OCH_2C(O)OR^{14}$, $-OC(O)R^{14a}$, $-N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14a}$, and $-N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, and $-CH_2-C_{2-9}$heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{14}$, $-SR^{14}$, $-N(R^{14})(R^{14})$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14}$, $-N(R^{14})S(O)_2R^{14}$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, and $-OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, -

$C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, $-OCH_2C(O)OR^{14}$, and $-OC(O)R^{14a}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, and $-CH_2-C_{2-9}$heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{14}$, $-SR^{14}$, $-N(R^{14})(R^{14})$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14}$, $-N(R^{14})S(O)_2R^{14}$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, and $-OC(O)R^{14a}$;

R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, C_{1-11}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl$)-S(O)_2R^{15}$, $-(C_{1-6}$alkyl$)-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl$)-S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is $-L^1-R^{19}$;

R^{17b} is $-L^{1b}-R^{19}$;

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, $-N(R^{14})$-, -C(O)-, $-N(R^{14})C(O)$-, $-C(O)N(R^{14})$-, -S-, $-S(O)_2$-, -S(O)-, $-S(O)_2N(R^{14})$-, $-S(O)N(R^{14})$-, $-N(R^{14})S(O)$-, $-N(R^{14})S(O)_2$-, $-OCON(R^{14})$-, $-N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, $-C(O)N(R^{14})$-, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, -

$S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12''})(R^{13})$, $-N{=}(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{4-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, and $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2$-C_{6-10}aryl, $-C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2$-C_{6-10}aryl, $-C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2$-C_{6-10}aryl, $-C(R^{12c})_2$-C_{1-}

$_{9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH$_2$-C_{6-10}aryl, -CH$_2$-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -N(R^{22})(R^{23}), =C(R^{21b})$_2$, -C(O)OR^{22}, -C(O)N(R^{22})(R^{23}), -C(O)C(O)N(R^{22})(R^{23}), -OC(O)N(R^{22})(R^{23}), -N(R^{24})C(O)N(R^{22})(R^{23}), -N(R^{24})C(O)OR^{25}, -N(R^{24})C(O)R^{21}, -N(R^{24})S(O)$_2$$R^{25}$, -C(O)$R^{21}$, -S(O)$_2$$R^{25}$, -S(O)$_2$N($R^{22}$)($R^{23}$), -OCH$_2$C(O)O$R^{22}$, and -OC(O)$R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH$_2$-C_{6-10}aryl, -CH$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -N(R^{22})(R^{23}), -C(O)OR^{22}, -C(O)N(R^{22})(R^{23}), -C(O)C(O)N(R^{22})(R^{23}), -OC(O)N(R^{22})(R^{23}), -N(R^{24})C(O)N(R^{22})(R^{23}), -N(R^{24})C(O)OR^{25}, -N(R^{24})C(O)R^{25}, -N(R^{24})S(O)$_2$$R^{25}$, -C(O)$R^{25}$, -S(O)$_2$$R^{25}$, -S(O)$_2$N($R^{22}$)($R^{23}$), and -OC(O)$R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-}

$_{6}$alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

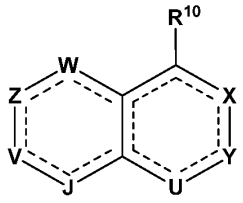
each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

〰 indicates the location of attachment of the depicted chemical formula or atom to a substituent, a further component of a molecule, or an atom; and

┅┅ indicates a single or double bond such that all valences are satisfied.

[230] In embodiments of the methods described herein, the KRAS inhibitor is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

Z is N, $C(R^{8})$, $N(R^{8b})$, $C(R^{8})(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

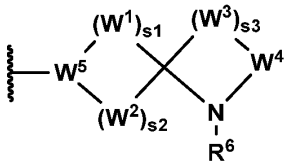
V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

Y is N, $C(R^{2})$, $C(R^{2})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$;

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^{7}-R^{7}$;

L^{7} is a bond, -O-, $-N(R^{14})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^{7} is 

;

W^{1} and W^{3} are independently selected from $N(R^{1})$, $N(R^{4})$, $C(R^{1})(R^{1})$, $C(R^{1})(R^{4})$, $C(R^{4})(R^{4})$, C(O), S, O, S(O), and $S(O)_2$;

W^{2} is independently selected from a $N(R^{1})$, $N(R^{4})$, $C(R^{1})(R^{1})$, $C(R^{1})(R^{4})$, $C(R^{4})(R^{4})$, C(O), S, O, S(O), and $S(O)_2$;

W^{4} is selected from $C(R^{1})(R^{1})$, $C(R^{1})(R^{4})$, $C(R^{4})(R^{4})$, S(O), and $S(O)_2$;

W^{5} is selected from N, $C(R^{1})$, and $C(R^{4})$;

s1 is 1 and s2 is 0, 2, or 3; s1 is 2 and s2 is 0, 1, or 3; s1 is 3 and s2 is 0 to 3; s1 is 4 and s2 is 0 to 3; s1 is 5 and s2 is 0 to 3; or s1 is 6 and s2 is 0 to 3;

s3 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, =$C(R^{21b})_2$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is -L^2-R^5, wherein R^6 is optionally capable of forming a covalent bond with a Ras amino acid;

L^2 is a bond, -O-, -$N(R^{4d})$-, -C(O)-, -S-, -$S(O)_2$-, -S(O)-, -$P(O)R^{4d}$-, $CR^{4c}R^{4c}$, -$OCR^{4c}R^{4c}$-, -$N(R^{4d})CR^{4c}R^{4c}$-, -$C(O)CR^{4c}R^{4c}$-, -$SCR^{4c}R^{4c}$-, -$S(O)_2CR^{4c}R^{4c}$-, -$S(O)CR^{4c}R^{4c}$-, -$P(O)R^{4d}CR^{4c}R^{4c}$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}$, -$CR^{4c}R^{4c}CR^{4c}R^{4c}$-, -$CR^{4c}R^{4c}O$-, -$CR^{4c}R^{4c}N(R^{4d})$-, -$CR^{4c}R^{4c}C(O)$-, -$CR^{4c}R^{4c}S$-, -$CR^{4c}R^{4c}S(O)_2$-, -$CR^{4c}R^{4c}S(O)$-, -$CR^{4c}R^{4c}P(O)R^{4d}$-, -$N(R^{4d})C(O)$-, -$N(R^{4d})S(O)_2$-, -$N(R^{4d})S(O)$-, -$N(R^{4d})P(O)R^{4d}$-, -$C(O)N(R^{4d})$-, -$S(O)_2N(R^{4d})$-, -$S(O)N(R^{4d})$-, -$P(O)R^{4d}N(R^{4d})$-, -OC(O)-, -$OS(O)_2$-, -OS(O)-, -$OP(O)R^{4d}$-, -C(O)O-, -$S(O)_2O$-, -S(O)O-, -$P(O)R^{4d}O$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}$-, -$OCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$SCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$CR^{4c}R^{4c}CR^{4c}R^{4c}O$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)$-, or -$CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}$-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, -$OC(O)R^{14a}$, -$N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14a}$, and -$N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, and -$OC(O)R^{14a}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are

optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{14}$, $-SR^{14}$, $-N(R^{14})(R^{14})$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14}$, $-N(R^{14})S(O)_2R^{14}$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, and $-OC(O)R^{14a}$;

R^5 is a 5 or 6 membered partially unsaturated heterocycloalkyl or a 5 or 6 membered heteroaryl, each optionally substituted with one, two or three R^{20k}, wherein the partially unsaturated 5 or 6 membered heterocycloalkyl or 5 or 6 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and the 5 or 6 membered partially unsaturated heterocycloalkyl or 5 or 6 membered heteroaryl is each bonded to L^2 through a ring nitrogen;

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is $-L^1-R^{19}$;

R^{17b} is $-L^{1b}-R^{19}$;

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, $-N(R^{14})$-, -C(O)-, $-N(R^{14})C(O)$-, $-C(O)N(R^{14})$-, -S-, $-S(O)_2$-, -S(O)-, $-S(O)_2N(R^{14})$-, $-S(O)N(R^{14})$-, $-N(R^{14})S(O)$-, $-N(R^{14})S(O)_2$-, $-OCON(R^{14})$-, $-N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, $-C(O)N(R^{14})$-, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12''})(R^{13})$, $-N{=}(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{4-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, and $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-}$

$_9$heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -$C(O)OR^{12'}$, -$OC(O)N(R^{12'})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12'})(R^{13})$, -$C(O)C(O)N(R^{12'})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, -$CH_2C(O)N(R^{12'})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12'})(R^{13})$, –($C_{1-6}$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or

three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, C_{1-9}heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $=C(R^{21b})_2$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{21}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{21}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

------ indicates a single or double bond such that all valences are satisfied.

[231] In embodiments of the methods described herein, wherein the KRAS inhibitor is a compound of Formula (I) as recited above, or a pharmaceutically acceptable salt or solvate thereof;

W is a $C(R^{18})$ or C(O); Z is N, $C(R^{8})$, or $N(R^{8b})$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^{2})$; U is N; X is N;

L^1 is a bond;

L^7 is a bond;

W^1, W^2, and W^3 are independently selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, and O; W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$; W^5 is selected from N and CH;

L^2 is -C(O)-; R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N ring atom of R^5;

R^2 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12'}$, $-SR^{12'}$, and $-N(R^{12''})(R^{13})$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20d};

R^8 is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12}$, $-SR^{12}$, and $-N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20e};

R^{8b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20e};

R^{16} is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12}$, $-SR^{12}$, and $-N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20g};

R^{18} is hydrogen; and

all other variables are as described for a compound of Formula (I) as recited in the method above.

[232] In embodiments of the methods described herein, wherein the KRAS inhibitor is a compound of Formula (I) as recited above, or a pharmaceutically acceptable salt or solvate thereof;

W^1, W^2, and W^3 are independently selected from CH_2 and O; W^4 is CH_2; W^5 is selected from N and CH;

R^2 is $-OR^{12'}$;

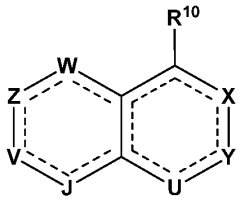
R^8 is independently selected halogen and C_{1-6}haloalkyl;

R^{8b} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20e};

R^{16} is halogen; and

all other variables are as described for a compound of Formula (I), as recited in the method or embodiment thereof, of the two paragraphs immediately above.

[233] In an aspect is provided a compound of Formula (I-1), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I-1);

wherein

Y is N, C(R^2), C(R^2)(R^{2c}), N(R^{2b}), S(O), S($O)_2$, or C(O);

W^4 is selected from C(R^1)(R^1), C(R^1)(R^4), and C(R^4)(R^4);

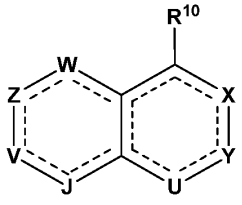
R^2 is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -N($R^{12''}$)(R^{13}), -N=(R^{15}), -C(O)$OR^{12'}$, -OC(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S($O)_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N($R^{12'}$)(R^{13}), -C(O)C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)R^{15}, -S($O)_2R^{15}$, -S($O)_2$N($R^{12'}$)(R^{13})-, S(=O)(=NH)N($R^{12'}$)(R^{13}), -CH_2C(O)N($R^{12'}$)(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S($O)_2R^{15}$, -CH_2S($O)_2$N($R^{12'}$)(R^{13}), –(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, and –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{19} is selected from C_{2-11}heterocycloalkyl and C_{2-12}heteroaryl, wherein the C_{2-11}heterocycloalkyl and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

all other variables are as described for compounds of Formula (I), or embodiments thereof; and

------ indicates a single or double bond such that all valences are satisfied.

[234] In an aspect is provided a compound of Formula (I-2), or a pharmaceutically acceptable salt or solvate thereof:

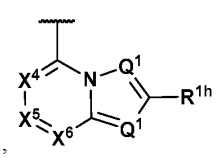
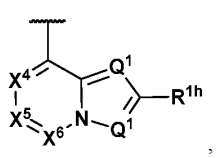
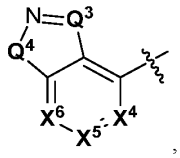
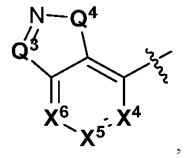
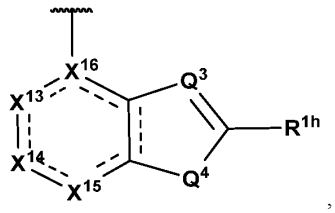
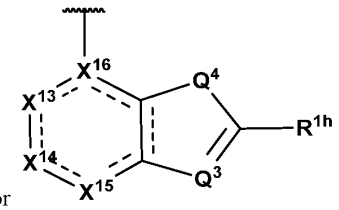


Formula (I-2);

wherein

Y is N, C(R^2), C(R^2)(R^{2c}), N(R^{2b}), S(O), S($O)_2$, or C(O);

R^2 is hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -N($R^{12''}$)(R^{13}), -N=(R^{15}), -C(O)$OR^{12'}$, -OC(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S($O)_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N($R^{12'}$)(R^{13}), -C(O)C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)R^{15}, -S($O)_2R^{15}$, -S($O)_2$N($R^{12'}$)(R^{13})-, S(=O)(=NH)N($R^{12'}$)(R^{13}), -CH_2C(O)N($R^{12'}$)(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S($O)_2R^{15}$, -CH_2S($O)_2$N($R^{12'}$)(R^{13}), –(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{19} is:,  ,  ,  ,  ,  , or  ;

Q^1, Q^3, and Q^5 are independently selected from N and $C(R^{1d})$;

Q^4 and Q^6 are independently selected from O, S, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

X^4, X^5, X^6, X^9, X^{10} are independently selected from $C(R^{1a})$ and N;

X^{13} is selected from a bond, $C(R^{1a})$, N, C(O), $C(R^{1a})(R^{1b})$, $C(O)C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})N(R^{1c})$, and $N(R^{1c})$;

X^{14}, X^{15}, X^{17}, X^{18} are independently selected from a C(O), $C(R^{1a})$, N, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

X^{16} are independently selected from C, N, and $C(R^{1a})$;

each R^{1a}, R^{1b}, R^{1d}, and R^{1h} are each independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1a} and R^{1b} bonded to the same carbon are joined to form a 3-10 membered heterocycloalkyl ring or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or two R^{1a} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, C_{6-10}aryl ring, 5-12 membered heteroaryl ring, or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or R^{1h} and one of R^{1a}, R^{1b}, R^{1c}, and R^{1d} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, and C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

each R^{1c} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

all other variables are as described for compounds of Formula (I), or embodiments thereof; and

------ indicates a single or double bond such that all valences are satisfied.

[235] In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof,

W is a $C(R^{18})$ or C(O); Z is N, $C(R^8)$, or $N(R^{8b})$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^2)$; U is N; X is N;

L^7 is a bond;

W^1, W^2, and W^3 are independently selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, and O;

W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$;

W^5 is selected from N and CH;

L^2 is selected from -C(O)-;

R^5 is a 5-6 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5-6 membered heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N ring atom of R^5;

R^8 is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12}$, $-SR^{12}$, and $-N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20c};

R^{8b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20c};

L^1 is a bond;

R^{16} is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12}$, $-SR^{12}$, and $-N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20g};

R^2 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12'}$, $-SR^{12'}$, and $-N(R^{12''})(R^{13})$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20d};

R^{18} is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20h};

all other variables are as described for compounds of Formula (I), or embodiments thereof; and

------ indicates a single or double bond such that all valences are satisfied.

[236] In further embodiments of the embodiment immediately above, or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof, R^{8b} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20c}.

[237] In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof:

W is a CH; Z is N or $C(R^8)$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^2)$; U is N; X is N;

L^7 is a bond;

W^1, W^2, and W^3 are independently selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, and O; W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$; W^5 is selected from N and CH;

L^2 is -C(O)-; R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N ring atom of R^5;

R^8 is independently selected from hydrogen and halogen;

L^1 is a bond; R^{19} is selected from a C_{6-12}aryl and C_{2-12}heteroaryl, wherein the C_{6-12}aryl and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}; each R^{1i} is independently selected from halogen, oxo, -

CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -OR^{12}, -$N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted with one, two, or three R^{20i};

R^{16} is independently selected from hydrogen and halogen; R^2 is -$OR^{12'}$; each $R^{12'}$ is independently selected from -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, wherein -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl is optionally substituted with one, two, or three R^{20d};

all other variables are as described for compounds of Formula (I), or embodiments thereof; and

------ indicates a single or double bond such that all valences are satisfied.

[238] In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof:

W is a CH; Z is N or $C(R^8)$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^2)$; U is N; X is N;

L^7 is a bond;

W^1, W^2, and W^3 are independently selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, and O; W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$; W^5 is selected from N and CH;

L^2 is -C(O)-; R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N ring atom of R^5;

R^8 is independently selected from hydrogen and halogen;

L^1 is a bond; R^{19} is selected from a C_{6-12}aryl and C_{2-12}heteroaryl, wherein the C_{6-12}aryl and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}; each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -OR^{12}, -$N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted with one, two, or three R^{20i};

R^{16} is independently selected from hydrogen and halogen; R^2 is -$OR^{12'}$; each $R^{12'}$ is independently selected from -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, wherein -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl is optionally substituted with one, two, or three R^{20d};

each R^{20k} is independently selected from halogen, -CN, -CH_2-CN, C_{1-6}alkyl, and C_{3-10}cycloalkyl, wherein C_{1-6}alkyl and C_{3-10}cycloalkyl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$;

all other variables are as described for compounds of Formula (I), or embodiments thereof; and

------ indicates a single or double bond such that all valences are satisfied.

[239] In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof:

W is a CH; Z is N or $C(R^8)$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^2)$; U is N; X is N;

L^7 is a bond;

W^1, W^2, and W^3 are independently selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, and O; W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$; W^5 is selected from N and CH;

L^2 is -C(O)-; R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N ring atom of R^5;

R^8 is independently selected from hydrogen and halogen;

L^1 is a bond; R^{19} is selected from a C_{6-12}aryl and C_{2-12}heteroaryl, wherein the C_{6-12}aryl and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}; each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted with one, two, or three R^{20i};

R^{16} is independently selected from hydrogen and halogen; R^2 is $-OR^{12'}$; each $R^{12'}$ is independently selected from $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl, wherein $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl is optionally substituted with one, two, or three R^{20d};

each R^{20k} is independently selected from halogen, -CN, $-CH_2$-CN, C_{1-3}alkyl, and C_{3-4}cycloalkyl, wherein C_{1-3}alkyl and C_{3-4}cycloalkyl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

all other variables are as described for compounds of Formula (I), or embodiments thereof; and

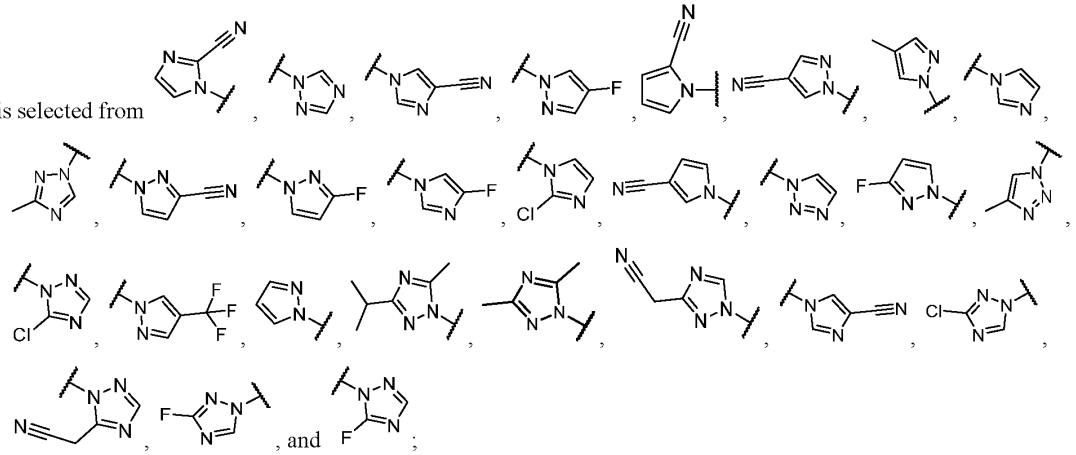
------ indicates a single or double bond such that all valences are satisfied.

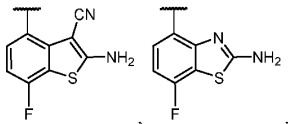
[240] In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof:

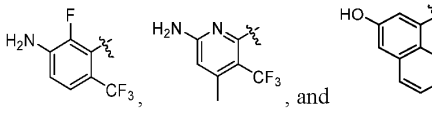
W is a CH; Z is N or $C(R^8)$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^2)$; U is N; X is N;

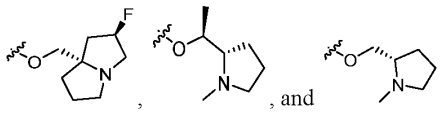
L^7 is a bond;

W^1, W^2, and W^3 are independently selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, and O; W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$; W^5 is selected from N and CH; L^2 is -C(O)-;

R^5 is selected from 

R^8 is independently selected from hydrogen and halogen; R^{17} is selected from 



; R^{16} is independently selected from hydrogen and halogen; R^2 is selected from 

all other variables are as described for compounds of Formula (I), or embodiments thereof; and

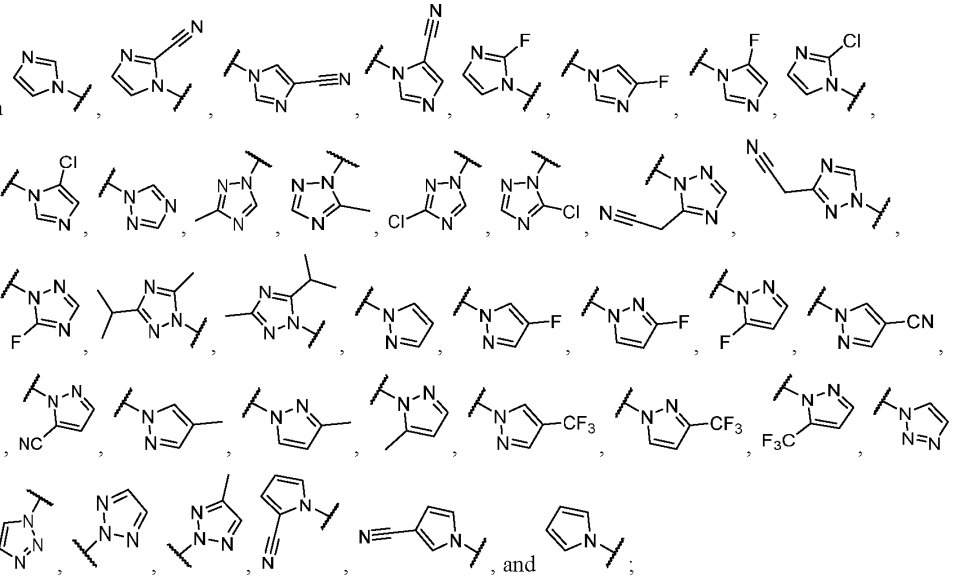
------ indicates a single or double bond such that all valences are satisfied.

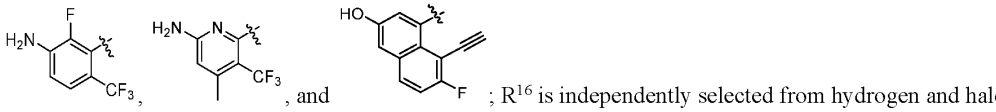
[241] In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof:

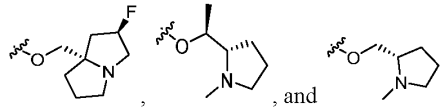
W is a CH; Z is N or C(R^8); V is C(R^{17}); J is C(R^{16}); Y is C(R^2); U is N; X is N;

L^7 is a bond;

W^1, W^2, and W^3 are independently selected from C(R^1)(R^1), C(R^1)(R^4), C(R^4)(R^4), and O; W^4 is selected from C(R^1)(R^1), C(R^1)(R^4), and C(R^4)(R^4); W^5 is selected from N and CH; L^2 is -C(O)-;

R^5 is selected from 

R^8 is independently selected from hydrogen and halogen; R^{17} is selected from 

; R^{16} is independently selected from hydrogen and halogen; R^2 is selected from 

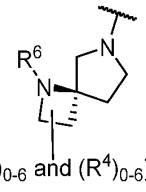
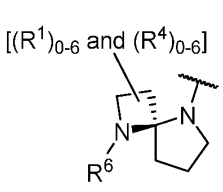
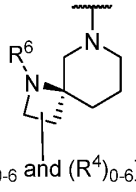
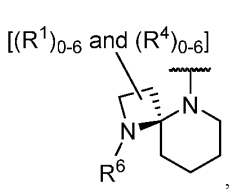
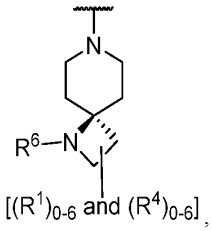
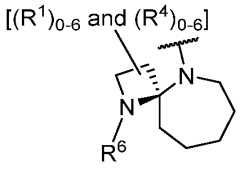
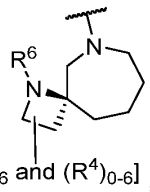
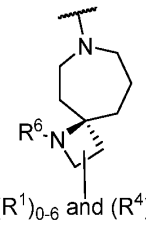
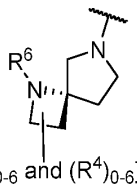
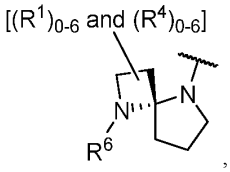
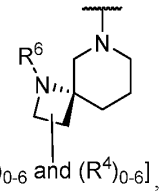
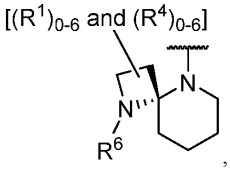
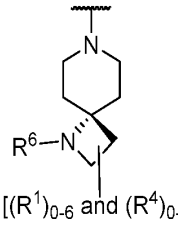
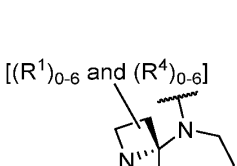
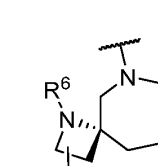
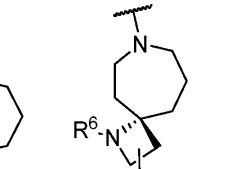
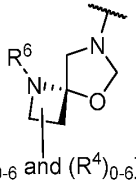
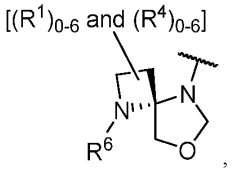
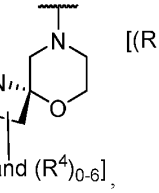
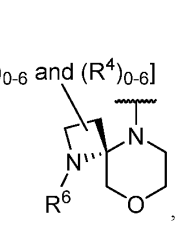
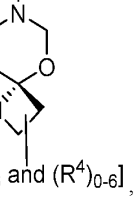
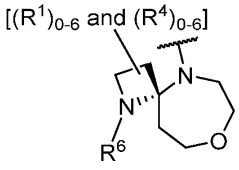
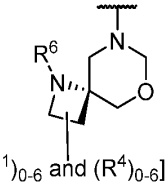
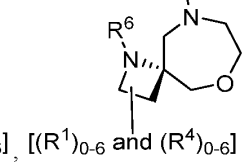
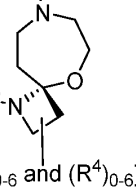
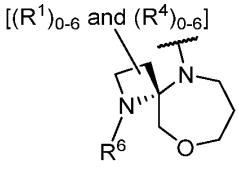
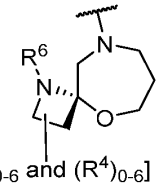
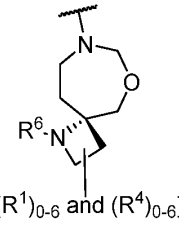
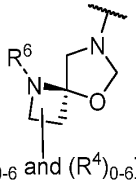
all other variables are as described for compounds of Formula (I), or embodiments thereof; and

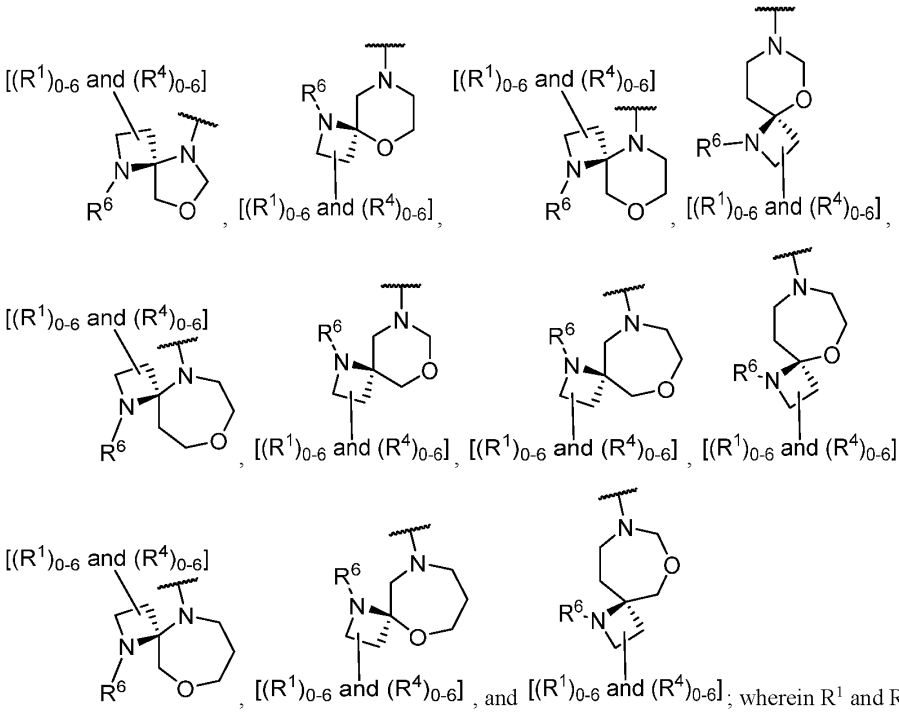
------ indicates a single or double bond such that all valences are satisfied.

[242] In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof:

W is a CH or C(O); Z is N, C(R^8), or N(R^{8b}); V is C(R^{17}); J is C(R^{16}); Y is C(R^2); U is N; X is N;

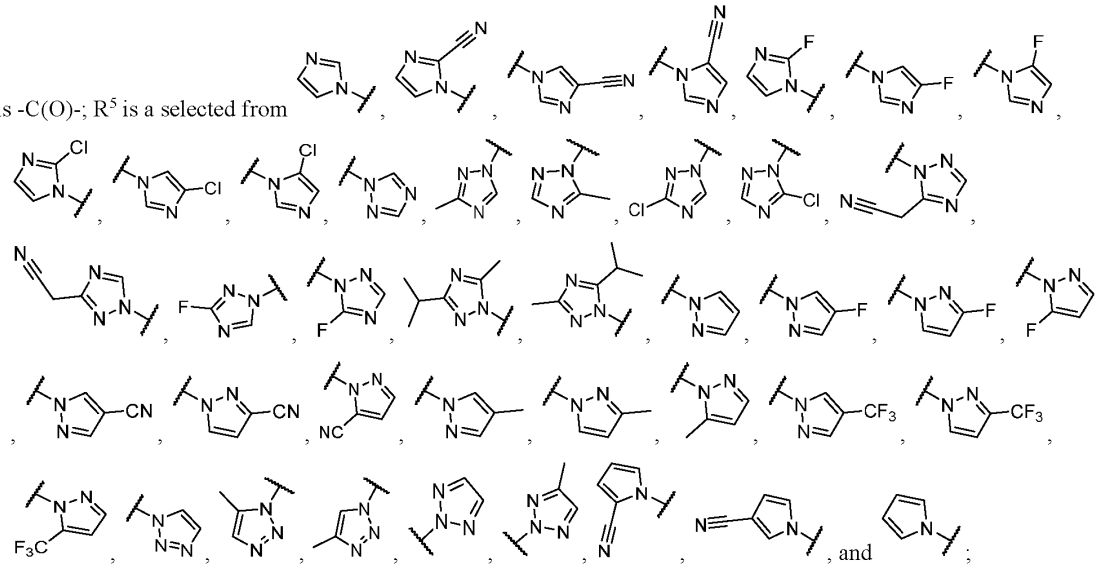
L^7 is a bond;

R^7 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .



; wherein R^1 and R^4 substituents may be bonded to either spirocyclic ring;

L^2 is -C(O)-; R^5 is a selected from

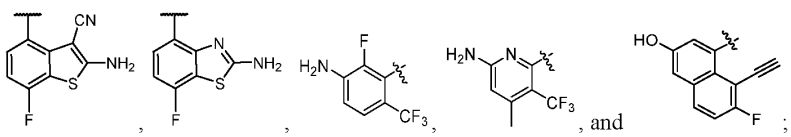


;

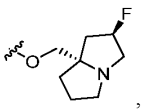
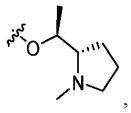
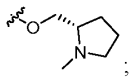
R^8 is independently selected from hydrogen or halogen;

R^{8b} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20c};

R^{17} is selected from



; R^{16} is

independently selected from hydrogen and halogen; R^2 is selected from  ,  , and  ;

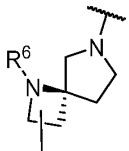
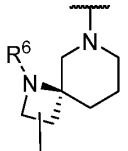
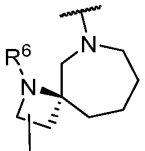
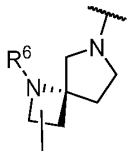
all other variables are as described for compounds of Formula (I), or embodiments thereof; and

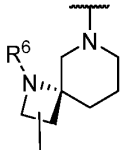
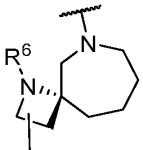
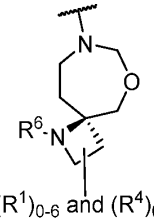
indicates a single or double bond such that all valences are satisfied. In embodiments, $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$ is equal to R^4, and R^4 is selected from halogen, methyl, and $-CH_2CN$. In embodiments, $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$ is equal to $[(R^1)_0$ and $(R^4)_0]$ (i.e., no R^1 or R^4 substituent). In embodiments, $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$ is equal to two R^4, and each R^4 is independently selected from halogen, methyl, and $-CH_2CN$.

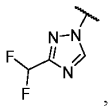
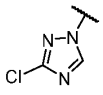
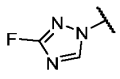
[243] In embodiments of a compound of Formula (I), (I-1), or (I-2), or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof:

W is a CH or C(O); Z is N, $C(R^8)$, or $N(R^{8b})$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^2)$; U is N; X is N;

L^7 is a bond;

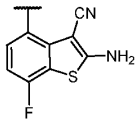
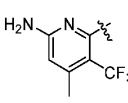
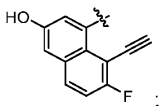
R^7 is selected from  $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$,  $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$,  $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$,  $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$,

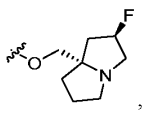
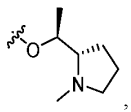
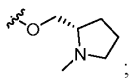
 $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$,  $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$, and  $[(R^1)_{0\text{-}6}$ and $(R^4)_{0\text{-}6}]$; wherein R^1 and R^4 substituents may be bonded to either spirocyclic ring;

L^2 is -C(O)-; R^5 is a selected from  ,  , and  ;

R^8 is independently selected from hydrogen or halogen;

R^{8b} is selected from $C_{1\text{-}2}$alkyl and $C_{3\text{-}4}$cycloalkyl, wherein $C_{1\text{-}2}$alkyl and $C_{3\text{-}4}$cycloalkyl are optionally substituted with one, two, or three R^{20c} selected from halogen and CN;

R^{17} is selected from  ,  , and  ;

R^{16} is independently selected from hydrogen and halogen; R^2 is selected from  ,  , and  ;

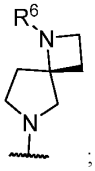
all other variables are as described for compounds of Formula (I), or embodiments thereof; and

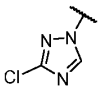
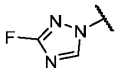
indicates a single or double bond such that all valences are satisfied.

[244] In embodiments of a compounds of Formula (I), (I-1), (I-2), or embodiments thereof, or a pharmaceutically acceptable salt or solvate thereof:

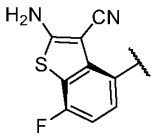
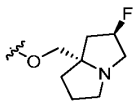
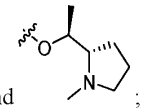
W is a CH or C(O); Z is N, C(R^8), or N(R^{8b}); V is C(R^{17}); J is C(R^{16}); Y is C(R^2); U is N; X is N;

R^{10} is -L^7-R^7; L^7 is a bond;

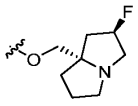
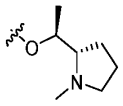
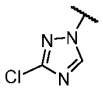
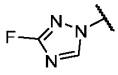
R^7 is  ;

L^2 is -C(O)-; R^5 is a selected from  , and  ;

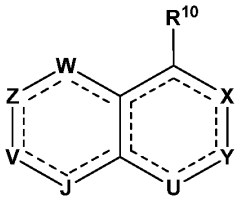
R^8 is independently -Cl; R^{8b} is cyclopropyl;

R^{17} is  ; R^{16} is -F; R^2 is selected from  and  ;

all other variables are as described for compounds of Formula (I), or embodiments thereof; and

indicates a single or double bond such that all valences are satisfied. In embodiments, R^2 is  . In embodiments, R^2 is  . In embodiments, R^5 is  . In embodiments, R^5 is  . In embodiments, W is a CH. In embodiments, W is C(O) and Z is N(R^{8b}). In embodiments, Z is N. In embodiments, Z is C(R^8).

[245] In an aspect is provided a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:

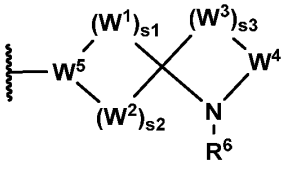
 Formula (I);

wherein

W is a C(R^{18}) or C(O); Z is N, C(R^8), or N(R^{8b}); V is C(R^{17}); J is C(R^{16}); Y is C(R^2); U is N; X is N;

R^{10} is -L^7-R^7;

L^7 is a bond;

R^7 is  ;

W^1, W^2, and W^3 are independently selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, and O;

W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$;

W^5 is selected from N and CH;

s1 is an integer from 1 to 6;

s2 is an integer from 1 to 3;

s3 is an integer from 1 to 3;

R^6 is $-L^2-R^5$ and wherein R^6 is optionally capable of forming a covalent bond with a Ras amino acid;

L^2 is selected from -C(O)-;

R^5 is a 5-6 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5-6 membered heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N atom of R^5;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $=C(R^{21b})_2$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl)$-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl)$-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl)$-S(O)_2R^{15}$, $-(C_{1-6}$alkyl)$-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl)$-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^8 is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-OR^{12}$, $-SR^{12}$, and $-N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20c};

R^{8b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20c};

R^{17} is $-L^1-R^{19}$;

L^1 is a bond;

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$,

-C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -$CH_2$C(O)N($R^{12}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, and -$CH_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -OR^{12}, -SR^{12}, and -N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20g};

R^2 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$OR^{12'}$, -$SR^{12'}$, and -N($R^{12''}$)(R^{13}), wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20d};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} is selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -N(R^{22})(R^{23}), =C(R^{21b})$_2$, -C(O)OR^{22}, -C(O)N(R^{22})(R^{23}), -C(O)C(O)N(R^{22})(R^{23}), -OC(O)N(R^{22})(R^{23}), -N(R^{24})C(O)N(R^{22})(R^{23}), -

$N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{21}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{21}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, $-CH_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

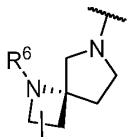
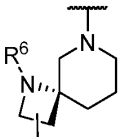
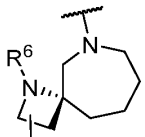
each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

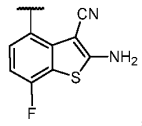
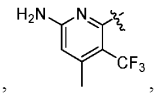
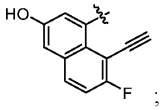
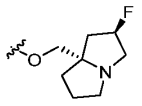
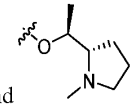
each R^{23} is independently selected from H and C_{1-6}alkyl;

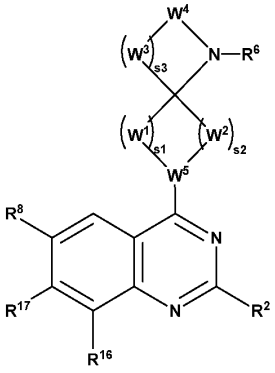
each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

------ indicates a single or double bond such that all valences are satisfied. In embodiments, R^7 is selected from

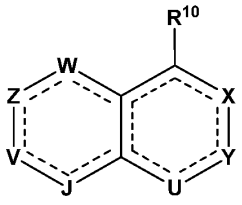




$[(R^1)_{0-6}$ and $(R^4)_{0-6}]$, $[(R^1)_{0-6}$ and $(R^4)_{0-6}]$, and $[(R^1)_{0-6}$ and $(R^4)_{0-6}]$ wherein R^1 and R^4 substituents may be bonded to either spirocyclic ring; R^{17} is selected from  ,  , and  ; and R^2 is selected from  and  . In embodiments, the compound, or a pharmaceutically acceptable



salt or solvate thereof, has the formula .

[246] In an aspect is provided a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II);

wherein

W is a N, C(R^{18}), N(R^{18b}), C(R^{18})(R^{18a}), C(O), S(O), or S(O)$_2$;

Z is N, C(R^{8}), N(R^{8b}), C(R^{8})(R^{8a}), C(O), S(O), or S(O)$_2$; wherein W and Z are not both selected from C(O), S(O), and S(O)$_2$;

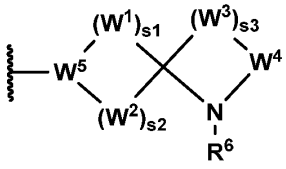
V and J are each independently selected from C(R^{17}), C(R^{17})(R^{16a}), C(R^{16}), C(R^{16})(R^{16a}), N, N(R^{17b}), and N(R^{16b}); wherein exactly one of V and J is C(R^{17}), C(R^{17})(R^{16a}), or N(R^{17b});

Y is N, C(R^{2}), C(R^{2})(R^{2c}), N(R^{2b}), S(O), S(O)$_2$, or C(O);

U is N, C(R^{2c}), C(R^{2c})(R^{2c}), N(R^{2b}), S(O), S(O)$_2$, or C(O);

R^{10} is -L^{7}-R^{7};

L^{7} is a bond, -O-, -N(R^{14})-, -C(O)-, -S-, -S(O)$_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^{7} is  ;

W^{1} and W^{3} are independently selected from N(R^{1}), N(R^{4}), C(R^{1})(R^{1}), C(R^{1})(R^{4}), C(R^{4})(R^{4}), C(O), S, O, S(O), and S(O)$_2$;

W^{2} is independently selected from a bond, N(R^{1}), N(R^{4}), C(R^{1})(R^{1}), C(R^{1})(R^{4}), C(R^{4})(R^{4}), C(O), S, O, S(O), and S(O)$_2$;

W^{4} is selected from C(R^{1})(R^{1}), C(R^{1})(R^{4}), C(R^{4})(R^{4}), C(O), S(O), and S(O)$_2$;

W^{5} is selected from N, C(R^{1}), and C(R^{4});

s1 is an integer from 1 to 6;

s2 is an integer from 1 to 3;

s3 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, =$C(R^{21b})_2$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is -L^2-R^5, wherein R^6 is optionally capable of forming a covalent bond with a RAS amino acid;

L^2 is -C(O)-;

R^5 is selected from C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, C_{6-12}aryl, and C_{1-11}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, C_{6-12}aryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is -L^1-R^{19};

R^{17b} is -L^{1b}-R^{19};

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, -$N(R^{14})$-, -C(O)-, -$N(R^{14})C(O)$-, -$C(O)N(R^{14})$-, -S-, -$S(O)_2$-, -S(O)-, -$S(O)_2N(R^{14})$-, -$S(O)N(R^{14})$-, -$N(R^{14})S(O)$-, -$N(R^{14})S(O)_2$-, -$OCON(R^{14})$-, -$N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, -$C(O)N(R^{14})$-, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)N(R^{12})(R^{13})-, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)N(R^{12})(R^{13}), $-(C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl)-$S(O)_2R^{15}$, $-(C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)N(R^{12})(R^{13}), $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)N(R^{12})(R^{13}), $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)N(R^{12})(R^{13}), $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$, $-N=(R^{15})$, $-C(O)OR^{12'}$, -

$OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3\text{-}10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2\text{-}9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6\text{-}10}\text{aryl})\text{-}R^{12b}$, and $-(C_{1\text{-}9}\text{heteroaryl})\text{-}R^{12b}$, wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}9}$heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3\text{-}10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2\text{-}9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6\text{-}10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1\text{-}9}\text{heteroaryl})\text{-}R^{12b}$, wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}9}$heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3\text{-}10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2\text{-}9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6\text{-}10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1\text{-}9}\text{heteroaryl})\text{-}R^{12b}$, wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-CH_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-CH_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}9}$heteroaryl, wherein $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-CH_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-CH_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}9}$heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-CH_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-CH_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}9}$heteroaryl, wherein $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-CH_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-CH_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -C(O)OR^{12}, -OC(O)$N(R^{12})(R^{13})$, -$N(R^{14})$C(O)$N(R^{12})(R^{13})$, -$N(R^{14})$C(O)OR^{15}, -$N(R^{14})S(O)_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)$N(R^{12})(R^{13})$, -C(O)C(O)$N(R^{12})(R^{13})$, -$N(R^{14})$C(O)R^{15}, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -CH_2C(O)$N(R^{12})(R^{13})$, -$CH_2N(R^{14})$C(O)R^{15}, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -C(O)OR^{12}, -OC(O)$N(R^{12})(R^{13})$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)$N(R^{12})(R^{13})$, -C(O)C(O)$N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -CH_2C(O)$N(R^{12})(R^{13})$, -$CH_2N(R^{14})$C(O)R^{15}, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, $=C(R^{21b})_2$, -C(O)OR^{22}, -C(O)$N(R^{22})(R^{23})$, -C(O)C(O)$N(R^{22})(R^{23})$, -OC(O)$N(R^{22})(R^{23})$, -$N(R^{24})$C(O)$N(R^{22})(R^{23})$, -$N(R^{24})$C(O)OR^{25}, -$N(R^{24})$C(O)R^{21}, -$N(R^{24})S(O)_2R^{25}$, -C(O)R^{21}, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -OCH_2C(O)OR^{22}, and -OC(O)R^{25}; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted

with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

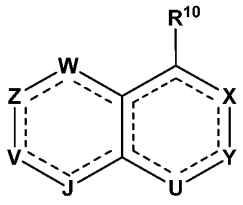
each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

~~~~ indicates the location of attachment of the depicted chemical formula or atom to a substituent, a further component of a molecule, or an atom; and

------ indicates a single or double bond such that all valences are satisfied.

[247] In an aspect is provided a compound of Formula (II-1), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-1);

wherein

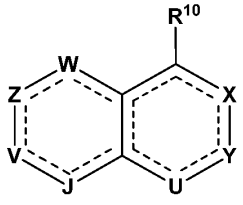
R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

R^2 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -$N(R^{12'})(R^{13})$, -$N{=}(R^{15})$, -$C(O)OR^{12'}$, -$OC(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12'})(R^{13})$, -$C(O)C(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, -$CH_2C(O)N(R^{12'})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12'})(R^{13})$,
~~~~

–(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, and –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d}; and

all other variables are as described for a compound of Formula (II), or embodiments thereof.

[248] In an aspect is provided a compound of Formula (II-2), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-2);

Wherein

W^2 is independently selected from a $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S(O), and $S(O)_2$;

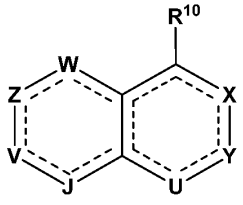
s1 is an integer from 1 to 6;

s2 is an integer from 0 to 3;

s3 is an integer from 1 to 3; and

all other variables are as described for a compound of Formula (II), or embodiments thereof.

[249] In an aspect is provided a compound of Formula (II-3), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-3);

Wherein

W^2 is independently selected from a $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S(O), and $S(O)_2$;

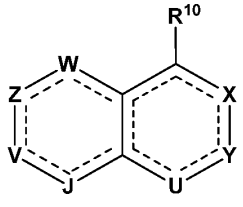
s1 is an integer from 1 to 6;

s2 is an integer from 0 to 3;

s3 is an integer from 1 to 3; and

all other variables are as described for a compound of Formula (II-1), or embodiments thereof.

[250] In an aspect is provided a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV);

wherein

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

Z is N, $C(R^8)$, $N(R^{8b})$, $C(R^8)(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

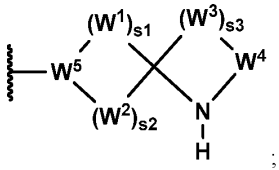
V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^7-R^7$;

L^7 is a bond, -O-, $-N(R^{14})-$, -C(O)-, -S-, $-S(O)_2-$, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is 

;

W^1 and W^3 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^2 is independently selected from a bond, $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, or $C(R^4)(R^4)$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is an integer from 1 to 6 and s2 is an integer selected from 2 and 3; or s1 is an integer from 2 to 6 and s2 is an integer from 1 to 3;

s3 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-}

$_{10}$aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is $-L^1$-R^{19};

R^{17b} is $-L^{1b}$-R^{19};

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, $-N(R^{14})$-, -C(O)-, $-N(R^{14})C(O)$-, $-C(O)N(R^{14})$-, -S-, $-S(O)_2$-, -S(O)-, $-S(O)_2N(R^{14})$-, $-S(O)N(R^{14})$-, $-N(R^{14})S(O)$-, $-N(R^{14})S(O)_2$-, $-OCON(R^{14})$-, $-N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, $-C(O)N(R^{14})$-, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, -

$OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'''}$, $-SR^{12'}$, $-N(R^{12'''})(R^{13})$, $-N{=}(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})-$, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{4-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})-$, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2\text{-}C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2\text{-}C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2\text{-}C_{6-10}$aryl, $-CH_2\text{-}C_{1-9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2\text{-}C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2\text{-}C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2\text{-}C_{6-10}$aryl, $-CH_2\text{-}C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, $-CH_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, $-CH_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{3-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{3-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d}; and ------ indicates a single or double bond such that all valences are satisfied.

each $R^{12'''}$ is independently selected from hydrogen, C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{4-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{4-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d}; and

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl,

C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, C_{1-9}heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $=C(R^{21b})_2$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{21}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{21}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

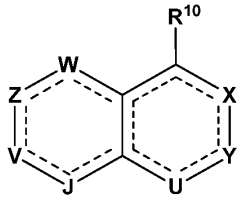
each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

indicates the location of attachment of the depicted chemical formula or atom to a substituent, a further component of a molecule, or an atom; and

indicates a single or double bond such that all valences are satisfied.

[251] In embodiments of Formula (IV), s1, s2, and s3 are not all 2.

[252] In an aspect is provided a compound of Formula (IV-1), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV-1);

wherein

R^{10} is $-L^7-R^7$;

W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S(O), and $S(O)_2$;

s1 is an integer from 1 to 6;

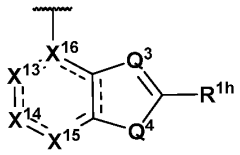
s2 is an integer from 1 to 3;

s3 is an integer from 1 to 3;

R^2 is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'''}$, $-SR^{12'}$, $-N(R^{12''''})(R^{13})$, $-N{=}(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, and $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'''}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2\text{-}C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2\text{-}C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2\text{-}C_{6-10}$aryl, $-C(R^{12c})_2\text{-}C_{1-9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2\text{-}C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2\text{-}C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2\text{-}C_{6-10}$aryl, $-C(R^{12c})_2\text{-}C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''''}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2\text{-}C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2\text{-}C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2\text{-}C_{6-10}$aryl, $-C(R^{12c})_2\text{-}C_{1-9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2\text{-}C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2\text{-}C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2\text{-}C_{6-10}$aryl, $-C(R^{12c})_2\text{-}C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{19} is: 

;

Q^3 is $C(R^{1d})$; Q^4 is S;

X^{13} is $C(R^{1a})$; X^{14} and X^{15} are independently $C(R^{1a})$; X^{16} is C;

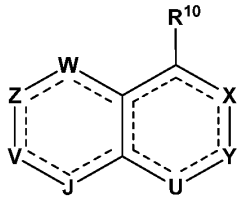
each R^{1a}, R^{1d}, and R^{1h} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

all other variables are as described for a compound of Formula (IV), or embodiments thereof; and

------ indicates a single or double bond such that all valences are satisfied.

[253] In embodiments of a compound of Formula (IV-1), s1, s2, and s3 are not all 2.

[254] In an aspect is provided a compound of Formula (IV-2), or a pharmaceutically acceptable salt or solvate thereof,



Formula (IV-2); wherein

W^2 is independently selected from a $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$;

s1 is an integer from 1 to 6;

s2 is an integer from 0 to 3;

s1 + s2 is not equal to 2 or 4;

R^{19} is selected from a C_{2-11}heterocycloalkyl and C_{2-12}heteroaryl, wherein the C_{2-11}heterocycloalkyl and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

R^2 is hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$, $-N=(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

all other variables are as described for a compound of Formula (IV), or embodiments thereof; and

------ indicates a single or double bond such that all valences are satisfied.

[255] The individual embodiments herein below, or combinations thereof, are applicable to compounds of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), and (IV-2), or embodiments of any of the preceding formulae, a pharmaceutically acceptable salt, or solvate thereof.

[256] In embodiments of the formulae above, R^{12} is independently C_{1-6}alkyl. In embodiments of the formulae above, R^{12} is independently C_{2-6}alkenyl. In embodiments of the formulae above, R^{12} is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^{12} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{12}

is independently -CH_2-C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{12} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{12} is independently C_{6-10}aryl. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{6-10}aryl. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{1-9}heteroaryl. In embodiments of the formulae above, R^{12} is independently C_{1-9}heteroaryl

[257] In embodiments of the formulae above, R^{12} is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently C_{1-9}heteroaryl. In additional embodiments, R^{12} is independently hydrogen.

[258] In embodiments of the formulae above, R^{12} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}.

[259] In embodiments of the formulae above, R^{12} is independently methyl optionally substituted with one or two R^{20d}. In embodiments of the formulae above, R^{12} is independently methyl. In embodiments of the formulae above, R^{12} is independently ethyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently ethyl. In embodiments of the formulae above, R^{12} is independently propyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently propyl. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}.

[260] In embodiments of the formulae above, $R^{12'}$ is independently hydrogen. In embodiments of the formulae above, $R^{12'}$ is independently C_{1-6}alkyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-6}alkenyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-6}alkynyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{6-10}aryl. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl. In embodiments of the formulae above, $R^{12'}$ is independently and C_{1-9}heteroaryl.

[261] In embodiments of the formulae above, $R^{12'}$ is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}.

[262] In select embodiments, R^{12b} is independently C_{1-6}alkyl. In select embodiments, R^{12b} is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently methylene optionally substituted with one or two R^{20d}. In embodiments of the formulae above, R^{12b} is independently methylene. In embodiments of the formulae above, R^{12b} is independently ethylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently ethylene. In embodiments of the formulae above, R^{12b} is independently propylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently propylene. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}.

[263] In embodiments of the formulae above, R^{12b} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is

independently (monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}.

[264] In embodiments of the formulae above, R^{12b} is independently C_{2-6}alkenyl. In embodiments of the formulae above, R^{12b} is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^{12b} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{12b} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{12b} is independently C_{6-10}aryl. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{6-10}aryl. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{1-9}heteroaryl. In embodiments of the formulae above, R^{12b} is independently C_{1-9}heteroaryl

[265] In embodiments of the formulae above, R^{12b} is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently C_{1-9}heteroaryl. In additional embodiments, R^{12b} is independently hydrogen.

[266] In embodiments of the formulae above, each R^{12c} is independently hydrogen. In embodiments of the formulae above, each R^{12c} is independently halogen. In embodiments of the formulae above, each R^{12c} is independently oxo. In embodiments of the formulae above, each R^{12c} is independently -CN. In embodiments of the formulae above, each R^{12c} is independently C_{1-6}alkyl. In embodiments of the formulae above, each R^{12c} is independently C_{2-6}alkenyl. In embodiments of the formulae above, each R^{12c} is independently C_{2-6}alkynyl. In embodiments of the formulae above, each R^{12c} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{3-10}cycloalkyl. In embodiments of the formulae above, each R^{12c} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, each R^{12c} is independently C_{6-10}aryl. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{6-10}aryl. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{1-9}heteroaryl. In embodiments of the formulae above, each R^{12c} is independently C_{1-9}heteroaryl. In embodiments of the formulae above, each R^{12c} is independently -OR^{21}. In embodiments of the formulae above, each R^{12c} is independently -SR^{21}. In embodiments of the formulae above, each R^{12c} is independently -$N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$C(O)OR^{22}$. In embodiments of the formulae above, each R^{12c} is independently -$C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$C(O)C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$OC(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is

independently -$N(R^{24})C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$N(R^{24})C(O)OR^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$N(R^{24})S(O)_2R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$C(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$S(O)_2R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$S(O)_2N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$OCH_2C(O)OR^{22}$. In embodiments of the formulae above, each R^{12c} is independently -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{1-6}alkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{2-6}alkenyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{2-6}alkynyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{3-10}cycloalkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{3-10}cycloalkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{2-9}heterocycloalkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{2-9}heterocycloalkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{6-10}aryl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{6-10}aryl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -

$C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently $-CH_2$-C_{1-9}heteroaryl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{1-9}heteroaryl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently methyl. In embodiments of the formulae above, each R^{12c} is independently ethyl. In embodiments of the formulae above, each R^{12c} is independently propyl.

[267] In embodiments of the formulae above, $R^{12''}$ is independently C_{1-6}alkyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{3-6}alkyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkenyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkynyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12''}$ is independently $-C(R^{12c})_2$-C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12''}$ is independently $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{6-10}aryl. In embodiments of the formulae above, $R^{12''}$ is independently $-C(R^{12c})_2$-C_{6-10}aryl. In embodiments of the formulae above, $R^{12''}$ is independently $-C(R^{12c})_2$-C_{1-9}heteroaryl. In embodiments of the formulae above, $R^{12''}$ is independently and C_{1-9}heteroaryl.

[268] In embodiments of the formulae above, $R^{12''}$ is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{3-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently $-C(R^{12c})_2$-C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently $-C(R^{12c})_2$-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently $-C(R^{12c})_2$-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}.

[269] In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{3-6}alkyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkenyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkynyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12'''}$ is independently $-C(R^{12c})_2$- C_{4-10}cycloalkyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12'''}$ is independently $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12'''}$

is independently C_{6-10}aryl. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl. In embodiments of the formulae above, $R^{12'''}$ is independently and C_{1-9}heteroaryl.

[270] In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{3-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{4-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}.

[271] In embodiments of the formulae above, $R^{12''''}$ is independently C_{1-6}alkyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{3-6}alkyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-6}alkenyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-6}alkynyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{6-10}aryl. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl. In embodiments of the formulae above, $R^{12''''}$ is independently and C_{1-9}heteroaryl.

[272] In embodiments of the formulae above, $R^{12''''}$ is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{3-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}.

[273] In select embodiments, R^{2c} is independently C_{1-6}alkyl. In embodiments of the formulae above, R^{2c} is

independently C_{2-6}alkenyl. In embodiments of the formulae above, R^{2c} is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^{2c} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{2c} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{2c} is independently C_{6-10}aryl. In embodiments of the formulae above, R^{2c} is independently C_{1-9}heteroaryl.

[274] In select embodiments, R^{2c} is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently methyl optionally substituted with one or two R^{20d}. In embodiments of the formulae above, R^{2c} is independently methyl. In embodiments of the formulae above, R^{2c} is independently ethyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently ethyl. In embodiments of the formulae above, R^{2c} is independently propyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently propyl. In embodiments of the formulae above, R^{2c} is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In additional embodiments, R^{2c} is independently hydrogen.

[275] In additional embodiments, R^{2b} is independently -CN. In embodiments of the formulae above, R^{2b} is $-OR^{12'}$. In embodiments of the formulae above, R^{2b} is $-SR^{12'}$. In embodiments of the formulae above, R^{2b} is $-C(O)OR^{12'}$. In embodiments of the formulae above, R^{2b} is $-OC(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-C(O)R^{15}$. In embodiments of the formulae above, R^{2b} is $-S(O)R^{15}$. In embodiments of the formulae above, R^{2b} is $-OC(O)R^{15}$. In embodiments of the formulae above, R^{2b} is $-C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-C(O)C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-S(O)_2R^{15}$. In embodiments of the formulae above, R^2 is $-S(O)_2N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $S(=O)(=NH)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-CH_2C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-CH_2N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^{2b} is $-CH_2S(O)_2R^{15}$. In embodiments of the formulae above, R^{2b} is $-CH_2S(O)_2N(R^{12'})(R^{13})$.

[276] In select embodiments, R^{2b} is independently C_{1-6}alkyl. In embodiments of the formulae above, R^{2b} is independently C_{2-6}alkenyl. In embodiments of the formulae above, R^{2b} is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^{2b} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{2b} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{2b} is independently C_{6-10}aryl. In embodiments of the formulae above, R^{2b} is independently and C_{1-9}heteroaryl.

[277] In select embodiments, R^{2b} is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently methyl optionally substituted with one or two R^{20d}. In embodiments of the formulae above, R^{2b} is independently methyl. In embodiments of the formulae above, R^{2b} is independently ethyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently ethyl. In embodiments of the formulae above, R^{2b} is independently propyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently propyl. In embodiments of the formulae above, R^{2b} is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three

R^{20d}. In embodiments of the formulae above, R^{2b} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently and C_{1-9}heteroaryl. In additional embodiments, R^{2b} is independently hydrogen.

[278] In embodiments of the formulae above, R^{2b} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently $-(C_1$-C_6alkyl)-R^{12b}. In embodiments of the formulae above, R^{2b} is independently, $-(C_{2-6}$alkenyl)-R^{12b}. In embodiments of the formulae above, R^{2b} is independently, $-(C_{2-6}$alkynyl)-R^{12b}. In embodiments of the formulae above, R^{2b} is independently, -(C_{3-10}cycloalkyl)-R^{12b}. In embodiments of the formulae above, R^{2b} is independently, -(C_{2-9}heterocycloalkyl)-R^{12b}. In embodiments of the formulae above, R^{2b} is independently, -(C_{6-10}aryl)-R^{12b}. In embodiments of the formulae above, R^{2b} is independently, or $-(C_{1-9}$heteroaryl)-R^{12b}. In embodiments of the formulae above, R^{2b} is independently $-(C_1$-C_6alkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, $-(C_{2-6}$alkenyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, $-(C_{2-6}$alkynyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, -(C_{3-10}cycloalkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, -(C_{2-9}heterocycloalkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, -(C_{6-10}aryl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, $-(C_{1-9}$heteroaryl)-R^{12b} optionally substituted with one, two, or three R^{20d}.

[279] In embodiments of the formulae above, W^1 is $N(R^1)$. In embodiments of the formulae above, W^1 is $N(R^4)$. In embodiments of the formulae above, W^1 is $C(R^1)(R^1)$. In embodiments of the formulae above, W^1 is $C(R^1)(R^4)$. In embodiments of the formulae above, W^1 is $C(R^4)(R^4)$. In embodiments of the formulae above, W^1 is C(O). In embodiments of the formulae above, W^1 is S. In embodiments of the formulae above, W^1 is O. In embodiments of the formulae above, W^1 is S(O). In embodiments of the formulae above, W^1 is $S(O)_2$. In embodiments of the formulae above, W^1 is NH. In embodiments of the formulae above, W^1 is CH_2.

[280] In embodiments of the formulae above, W^3 is $N(R^1)$. In embodiments of the formulae above, W^3 is $N(R^4)$. In embodiments of the formulae above, W^3 is $C(R^1)(R^1)$. In embodiments of the formulae above, W^3 is $C(R^1)(R^4)$. In embodiments of the formulae above, W^3 is $C(R^4)(R^4)$. In embodiments of the formulae above, W^3 is C(O). In embodiments of the formulae above, W^3 is S. In embodiments of the formulae above, W^3 is O. In embodiments of the formulae above, W^3 is S(O). In embodiments of the formulae above, W^3 is $S(O)_2$. In embodiments of the formulae above, W^3 is NH. In embodiments of the formulae above, W^3 is CH_2.

[281] In embodiments of the formulae above, W^1 and W^3 are independently CH_2.

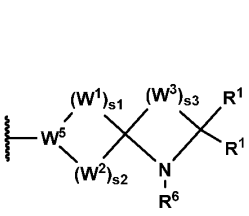
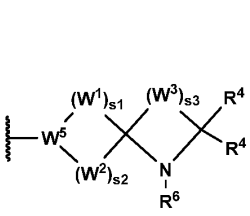
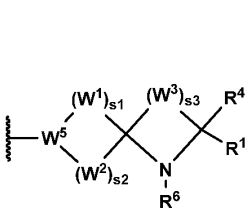
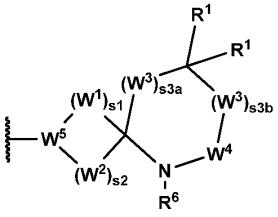
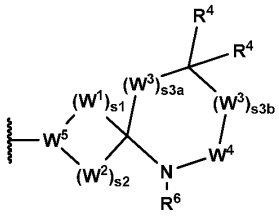
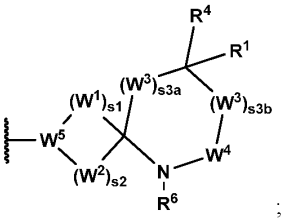
[282] In embodiments of the formulae above, W^2 is a bond. In embodiments of the formulae above, W^2 is $N(R^1)$. In embodiments of the formulae above, W^2 is $N(R^4)$. In embodiments of the formulae above, W^2 is $C(R^1)(R^1)$. In

embodiments of the formulae above, W^2 is $C(R^1)(R^4)$. In embodiments of the formulae above, W^3 is $C(R^4)(R^4)$. In embodiments of the formulae above, W^2 is C(O). In embodiments of the formulae above, W^2 is S. In embodiments of the formulae above, W^2 is O. In embodiments of the formulae above, W^2 is S(O). In embodiments of the formulae above, W^2 is $S(O)_2$. In embodiments of the formulae above, W^2 is NH. In embodiments of the formulae above, W^2 is CH_2. In embodiments of the formulae above, W^4 is $C(R^1)(R^1)$. In embodiments of the formulae above, W^4 is $C(R^1)(R^4)$. In embodiments of the formulae above, W^4 is $C(R^4)(R^4)$. In embodiments of the formulae above, W^4 is CH_2. In embodiments of the formulae above, W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, and $C(R^4)(R^4)$. In embodiments of the formulae above, W^5 is N. In embodiments of the formulae above, W^5 is $C(R^1)$. In embodiments of the formulae above, W^5 is $C(R^4)$. In embodiments of the formulae above, W^5 is CH. In embodiments of the formulae above, W^4 is C(O). In embodiments of the formulae above, W^4 is S(O). In embodiments of the formulae above, W^4 is $S(O)_2$. In embodiments of the formulae above, W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, S(O), and $S(O)_2$.

[283] In embodiments of the formulae above, s1 is 1. In embodiments of the formulae above, s1 is 2. In embodiments of the formulae above, s1 is 3. In embodiments of the formulae above, s1 is 4. In embodiments of the formulae above, s1 is 5. In embodiments of the formulae above, s1 is 6. In embodiments of the formulae above, s2 is 1. In embodiments of the formulae above, s2 is 2. In embodiments of the formulae above, s2 is 3. In embodiments of the formulae above, s3 is 1. In embodiments of the formulae above, s3 is 2. In embodiments of the formulae above, s3 is 3. In embodiments of the formulae above, s2 is 0 (i.e., W^2 is a bond). In embodiments of the formulae above, s1 is 1 and s2 is 3. In embodiments of the formulae above, s1 is 2 and s2 is 1. In embodiments of the formulae above, s1 is 2 and s2 is 2. In embodiments of the formulae above, s1 is 2 and s2 is 3. In embodiments of the formulae above, s1 is 3 and s2 is 1. In embodiments of the formulae above, s1 is 3 and s2 is 2. In embodiments of the formulae above, s1 is 3 and s2 is 3. In embodiments of the formulae above, s1 is an integer from 2 to 6 and s2 is an integer from 1 to 3. In embodiments of the formulae above, s1 is an integer from 1 to 6 and s2 is an integer from 2 to 3.

[284] In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); or embodiments of any formula thereof; at least one W^3 and/or W^4 is $C(R^1)(R^1)$, $C(R^1)(R^4)$, or $C(R^4)(R^4)$; R^1 and R^4 are as described for a Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); or embodiments of any formula thereof; and at least one i) R^1 of W^3 or W^4 is not hydrogen or ii) one R^4 of W^3 or W^4 is not hydrogen. In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); or embodiments of any formula thereof; at least one W^3 and/or W^4 is $C(R^1)(R^1)$, $C(R^1)(R^4)$, or $C(R^4)(R^4)$; R^1 and R^4 are as described for a Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); or embodiments of any formula thereof. In embodiments, R^1 and R^4 are hydrogen.

[285] In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); or embodiments of any formula thereof;

R^7 is  ,  ,  ,  ,  , or  ;

at least one R^1 or R^4 shown in the formulae immediately above is not hydrogen; and

s3a is 0, 1, or 2; s3b is 0, 1, or 2; the sum of s3a and s3b is 0, 1, or 2; and

R^1 and R^4 are as described for Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); or embodiments of any formula thereof.

[286] In embodiments of Formula (IV), (IV-1), or (IV-2); or embodiments of any formula thereof;

at least one W^3 and/or W^4 is $C(R^1)(R^1)$, $C(R^1)(R^4)$, or $C(R^4)(R^4)$;

at least one i) R^1 of W^3 or W^4 is not hydrogen or ii) one R^4 of W^3 or W^4 is not hydrogen; and

R^1 and R^4 are as described for Formula IV, IV-1, or IV-2; or embodiments of any formula thereof.

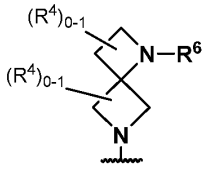
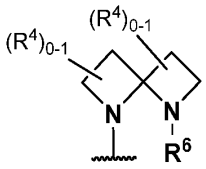
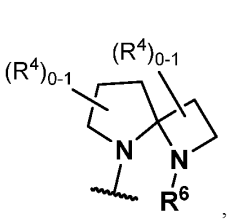
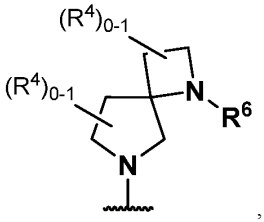
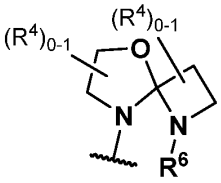
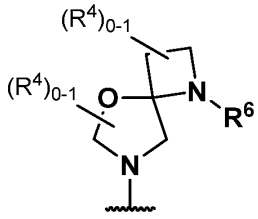
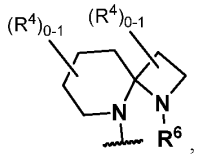
[287] In embodiments of Formula (IV), (IV-1), or (IV-2); or embodiments of any formula thereof;

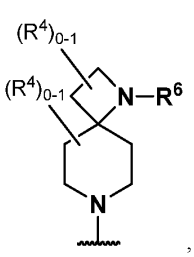
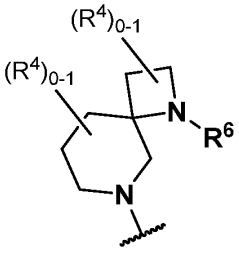
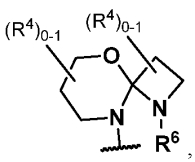
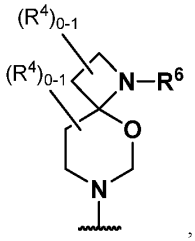
at least one W^3 and/or W^4 is $C(R^1)(R^1)$, $C(R^1)(R^4)$, or $C(R^4)(R^4)$;

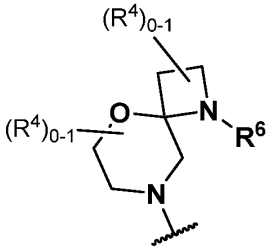
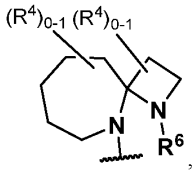
R^1 and R^4 are as described for Formula IV, IV-1, or IV-2; or embodiments of any formula thereof.

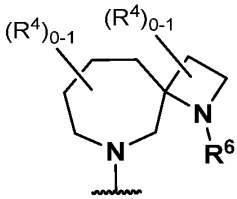
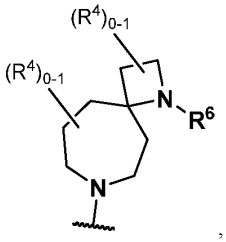
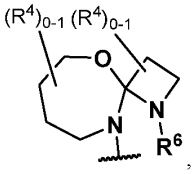
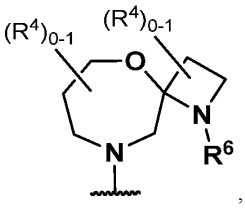
[288] In embodiments, R^1 and R^4 are hydrogen.

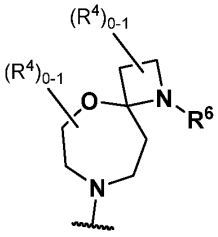
[289] The individual embodiments herein below, or combinations thereof, are applicable to compounds of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); or embodiments of any of the preceding formulae, a pharmaceutically acceptable salt, or solvate thereof.

[290] In embodiments, R^7 is  or  ; wherein each R^4 substituent is attached to an atom of only the ring on which the R^4 substituent is floating; and wherein R^7 is substituted with one or two R^4; and each R^4 is independently selected from halogen, -CN, C_{1-4}alkyl, and C_{3-4}cycloalkyl, wherein C_{1-4}alkyl and C_{3-4}cycloalkyl are optionally substituted with one, two, or three R^{20a} selected from halogen, -CN, -OH, and $-NH_2$. In embodiments, R^7 is  ,  ,  , or  ; wherein each R^4 substituent is attached to an atom of only the ring on which the R^4 substituent is floating; and wherein R^7 is substituted with one or two R^4; and each R^4 is independently selected from halogen, -CN, C_{1-4}alkyl, and C_{3-4}cycloalkyl, wherein C_{1-4}alkyl and C_{3-4}cycloalkyl are optionally substituted with one, two, or three R^{20a} selected from halogen, -CN, -OH, and $-NH_2$. In embodiments, R^7 is  ,

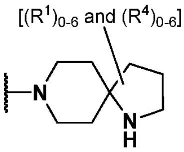
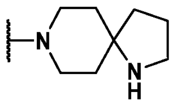
 ,  ,  ,  , or

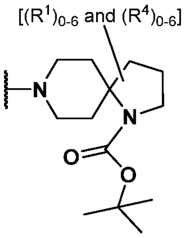
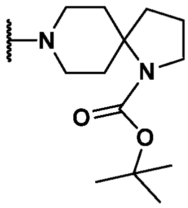
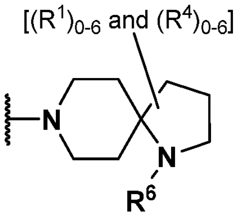
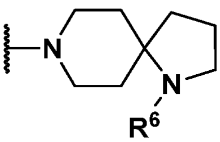
 ; wherein each R^4 substituent is attached to an atom of only the ring on which the R^4 substituent is floating; and wherein R^7 is substituted with one or two R^4; and each R^4 is independently selected from halogen, -CN, C_{1-4}alkyl, and C_{3-4}cycloalkyl, wherein C_{1-4}alkyl and C_{3-4}cycloalkyl are optionally substituted with one, two, or three R^{20a} selected from halogen, -CN, -OH, and $-NH_2$. In embodiments, R^7 is  ,

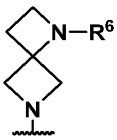
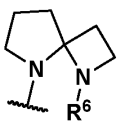
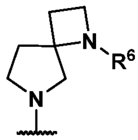
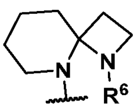
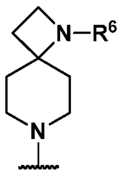
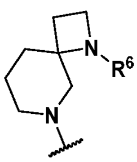
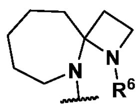
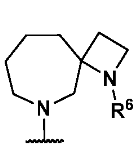
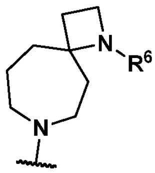
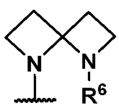
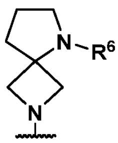
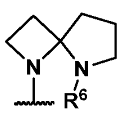
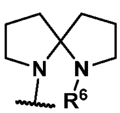
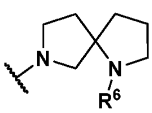
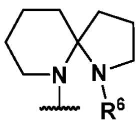
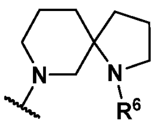
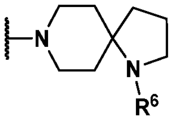
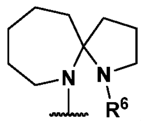
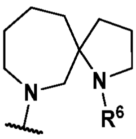
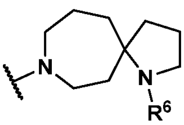
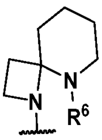
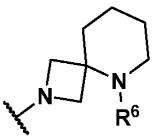
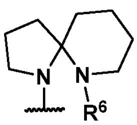
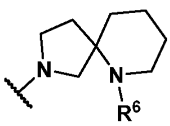
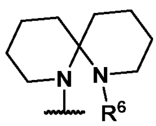
 ,  ,  ,  , or

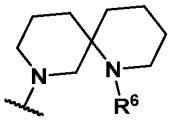
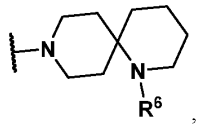
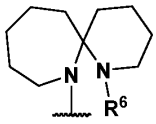
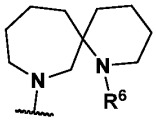
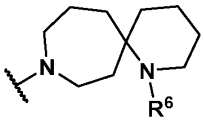
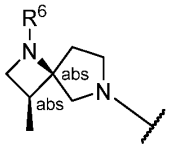
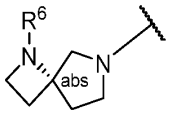
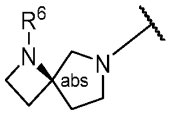
 ; wherein each R^4 substituent is attached to an atom of only the ring on which the R^4 substituent is floating; and wherein R^7 is substituted with one or two R^4; and each R^4 is independently selected from halogen, -CN, C_{1-4}alkyl, and C_{3-4}cycloalkyl, wherein C_{1-4}alkyl and C_{3-4}cycloalkyl are optionally substituted with one, two, or three R^{20a} selected from halogen, -CN, -OH, and $-NH_2$. In embodiments, R^7 is a single spirocyclic R stereoisomer. In embodiments, R^7 is a single spirocyclic S stereoisomer. In embodiments, R^7 is substituted with one R^4 substituent wherein the carbon atom attached to the R^4 substituent is an R isomer. In embodiments, R^7 is substituted with one R^4 substituent wherein the carbon atom attached to the R^4 substituent is an S isomer. In embodiments, R^7 is substituted with two optionally different R^4 substituents wherein the carbon atoms attached to the R^4 substituents are both R isomers. In embodiments, R^7 is substituted with two optionally different R^4 substituents wherein the carbon atoms

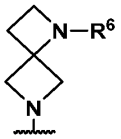
attached to the R^4 substituents are both S isomers. In embodiments, R^7 is substituted with two optionally different R^4 substituents wherein the carbon atom attached to the R^4 substituent in the ring bonded directly to R^6 is an R isomer and the carbon atom attached to the R^4 substituent in the other ring is an S isomer. In embodiments, R^7 is substituted with two optionally different R^4 substituents wherein the carbon atom attached to the R^4 substituent in the ring bonded directly to R^6 is an S isomer and the carbon atom attached to the R^4 substituent in the other ring is an R isomer. In embodiments, each R^4 is independently selected from F, -CN, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, $-CHF_2$, CF_3, and $-CH_2CN$.

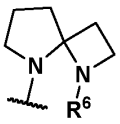
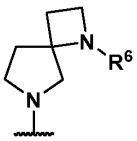
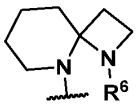
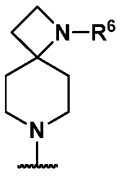
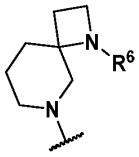
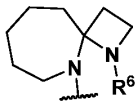
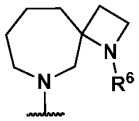
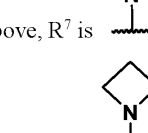
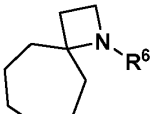
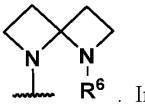
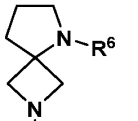
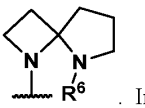
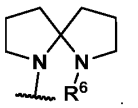
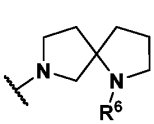
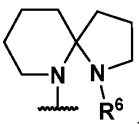
[291] In embodiments, R^7 is not  . In embodiments, R^7 is not  .

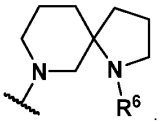
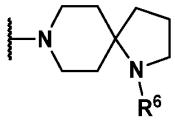
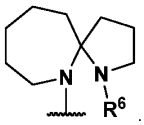
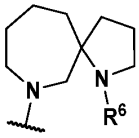
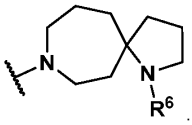
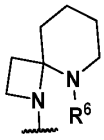
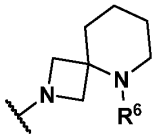
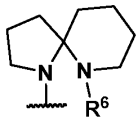
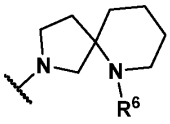
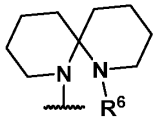
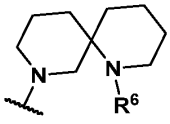
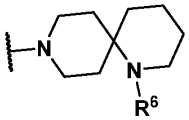
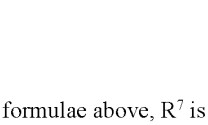
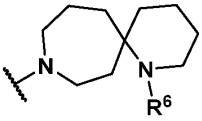
[292] In embodiments, R^7 is not  . In embodiments, R^7 is not  . In embodiments, R^7 is not  . In embodiments, R^7 is not  .

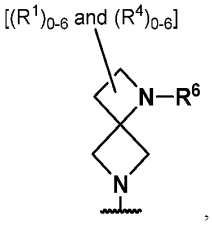
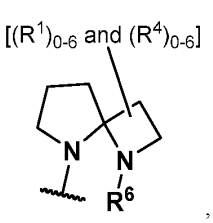
[293] In embodiments of the formulae above, R^7 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,

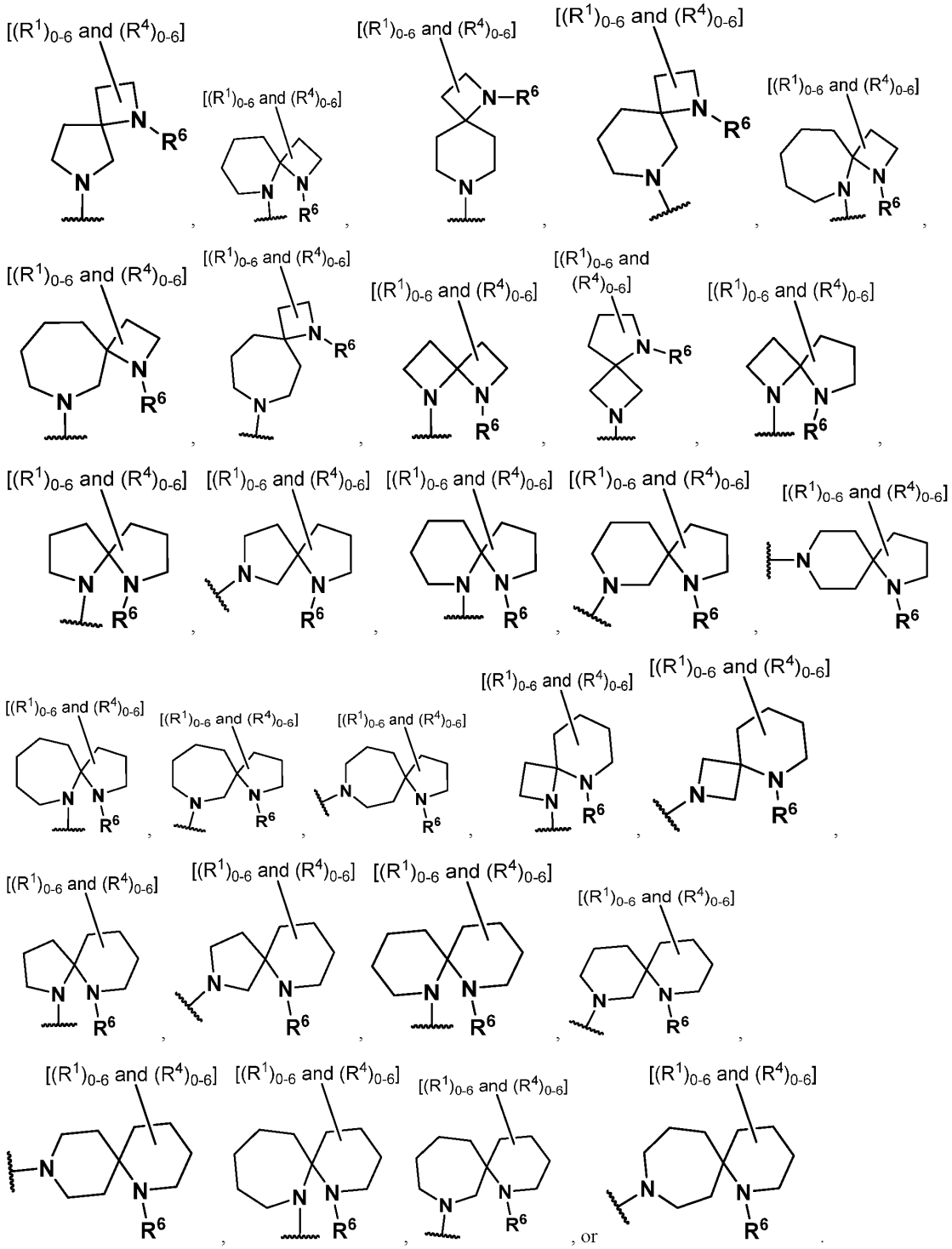




, or  . In embodiments of the formulae above, R^7 is selected from  ,  , and  .



[294] In embodiments of the formulae above, R^7 is . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments

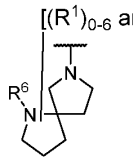
of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  . In embodiments of the formulae above, R^7 is  .

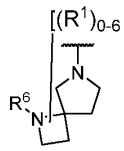
[295] In embodiments of the formulae above, R^7 is  ,  ,

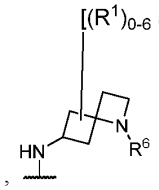


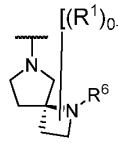
[296] It will be understood that when one or more floating substituent(s) is/are shown extending from one ring in a polycyclic ring system (e.g., fused ring system, bridged ring system, or spirocyclic ring system), the one or more floating substituent(s), may be bonded to the ring from which the one or more floating substituents are shown extending or may be bonded to any other ring in the polycyclic ring system (e.g., fused ring system, spirocyclic ring system, or bridged ring system) and when multiple substituents are represented by the floating substituents, each substituent may

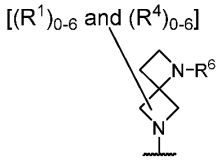
be bonded to the same or different rings in the polycyclic ring system, unless indicated otherwise.

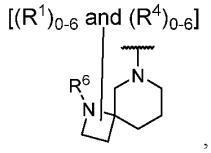
[297] In embodiments of the formulae above, R^7 is selected from 

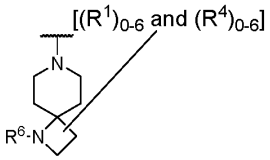
, 

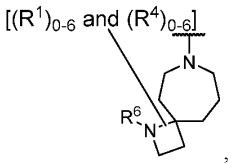
, 

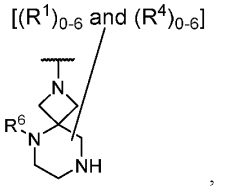
, 

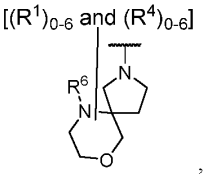
, 

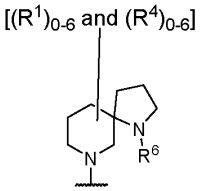
, 

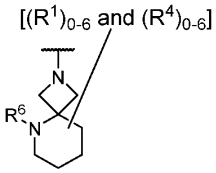
, 

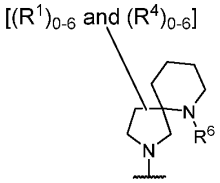
, 

, 

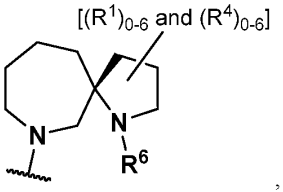
, 

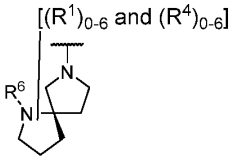
, 

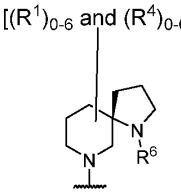
, 

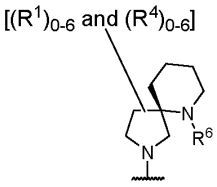
, 

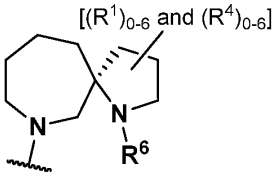
, and .

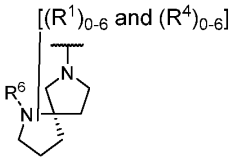
[298] In embodiments of the formulae above, R^7 is selected from 

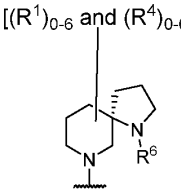
, 

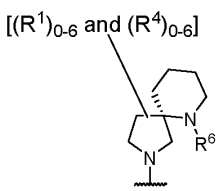
, 

, 

, 

, 

, 

, and 

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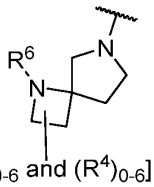
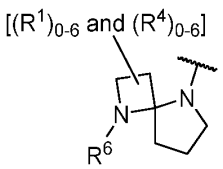
[299] In embodiments of the formulae above, R^7 is selected from 

, 

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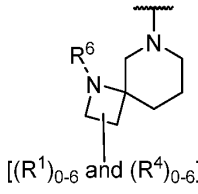

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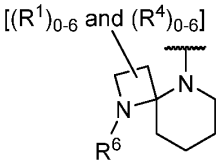

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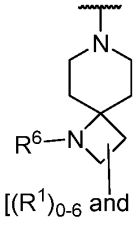

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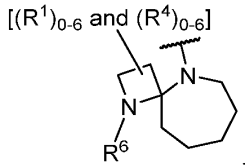

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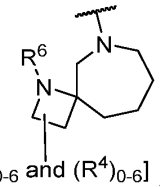

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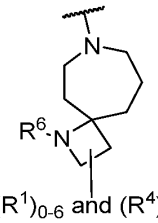

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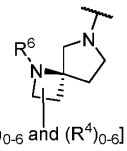
[300] In embodiments of the formulae above, R^7 is selected from


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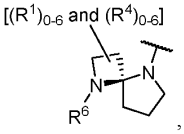

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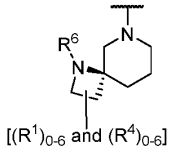

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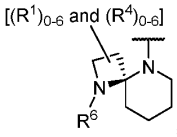

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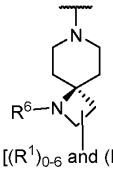

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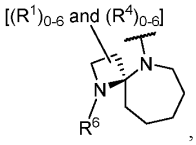

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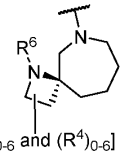

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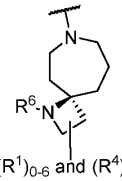

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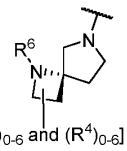
[301] In embodiments of the formulae above, R^7 is selected from


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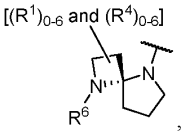

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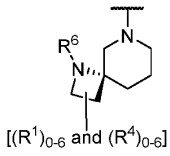

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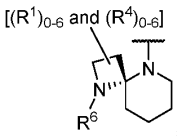

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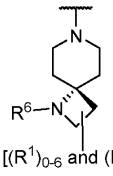

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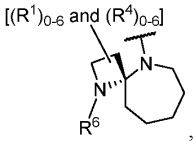

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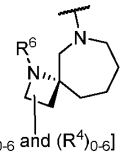

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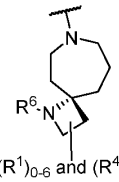
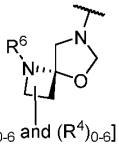
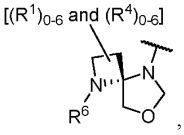
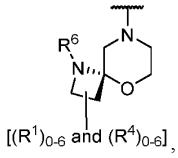
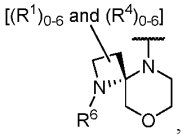
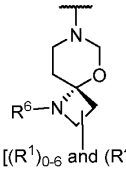
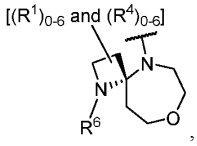
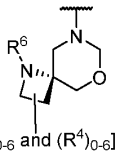
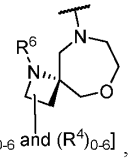
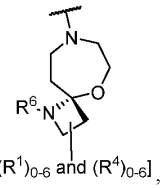
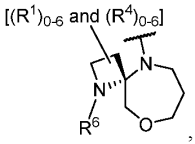
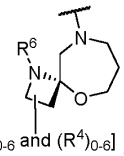
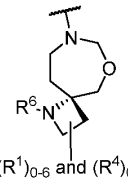
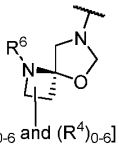
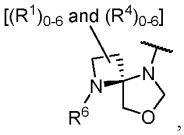
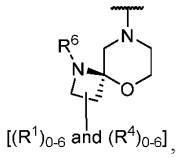
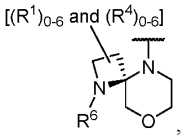
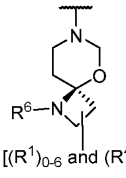
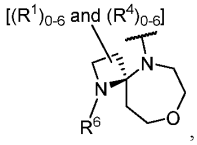
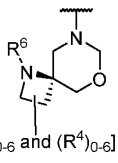
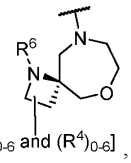
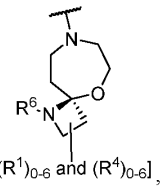
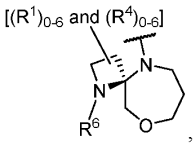
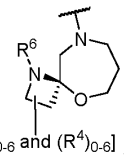
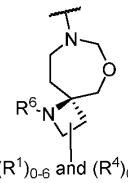


.

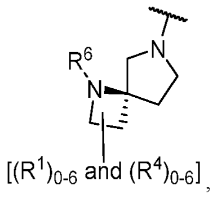
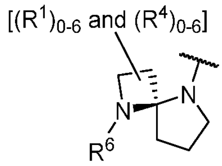
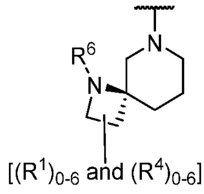
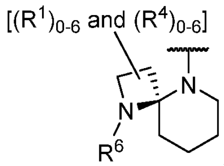
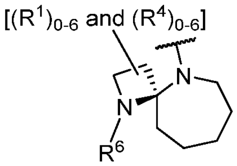
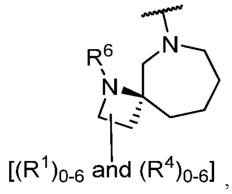
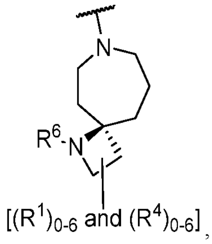
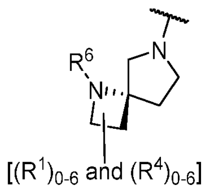
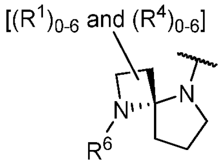
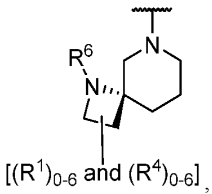
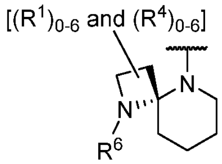
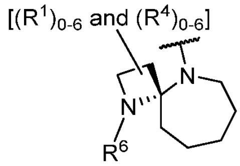
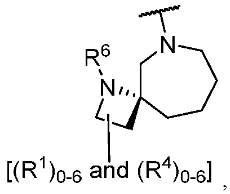
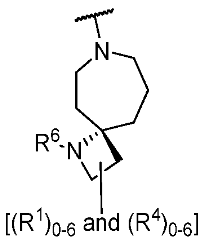
[302] In embodiments of the formulae above, R^7 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

[303] In embodiments of the formulae above, R^7 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

[304] It will be understood that when one or more floating substituent(s) is/are shown extending from one ring in a polycyclic ring system (e.g., fused ring system, bridged ring system, or spirocyclic ring system), the one or more floating substituent(s), may be bonded to the ring from which the one or more floating substituents are shown extending or may be bonded to any other ring in the polycyclic ring system (e.g., fused ring system, spirocyclic ring system, or bridged ring system) and when multiple substituents are represented by the floating substituents, each substituent may be bonded to the same or different rings in the polycyclic ring system, unless indicated otherwise.

[305] In embodiments, L^7 is a bond.

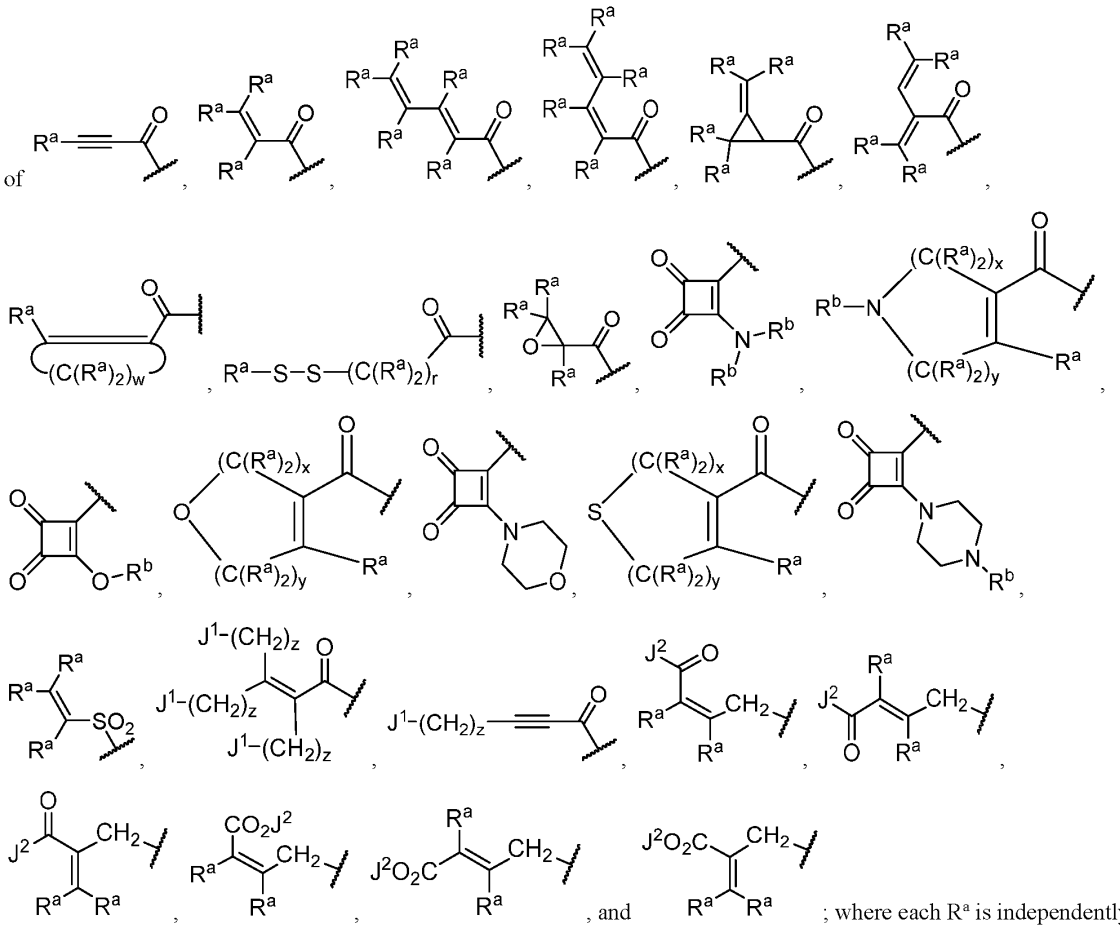
[306] In embodiments, s1 is 2 and s2 is 0, 1, or 3.

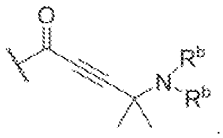
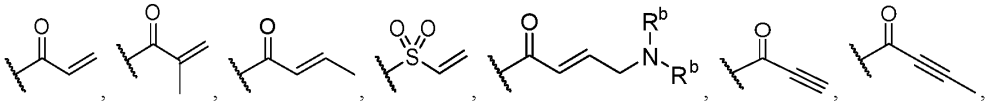
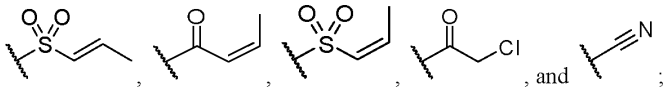
[307] In embodiments, R^7 is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; wherein R^1 and R^4 substituents may be bonded to either spirocyclic ring.

[308] In embodiments, R^{17} is $-L^1-R^{19}$ or $-L^{1b}-R^{19}$; L^1 is a bond, and L^{1b} is a bond.

[309] The individual embodiments herein below, or combinations thereof, (e.g., embodiments of R^6) are applicable to compounds of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); or a pharmaceutically acceptable salt or solvate thereof. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with a Ras amino acid sidechain. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with a KRAS amino acid. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 12th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 12th amino acid of a mutant KRAS protein selected from KRAS G12D, KRAS G12C, and KRAS G12S. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 13th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 13th amino acid of a mutant KRAS protein selected from KRAS G13D, KRAS G13C, and KRAS G13S. In embodiments of the formulae above, R^6 is incapable of forming a covalent bond with a Ras amino acid sidechain. In embodiments of the formulae above, R^6 is incapable of forming a covalent bond with a KRAS amino acid. In embodiments of the formulae above, R^6 is incapable of forming a covalent bond with the 12th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is incapable of forming a covalent bond with the 12th amino acid of a mutant KRAS protein selected from KRAS G12D, KRAS G12C, and KRAS G12S. In embodiments of the formulae above, R^6 is incapable of forming a covalent bond with the 13th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is incapable of

forming a covalent bond with the 13th amino acid of a mutant KRAS protein selected from KRAS G13D, KRAS G13C, and KRAS G13S. In embodiments of the formulae above, R^6 is incapable of forming a covalent bond with the 12th amino acid of a human KRAS protein selected from KRAS wildtype, KRAS G12D, KRAS G12C, KRAS G12S, KRAS G12V, KRAS G13D, KRAS G13C, KRAS G13S, and KRAS G13V. In embodiments of the formulae above, R^6 is incapable of forming a covalent bond with the 13th amino acid of human KRAS protein selected from KRAS wildtype, KRAS G12D, KRAS G12C, KRAS G12S, KRAS G12V, KRAS G13D, KRAS G13C, KRAS G13S, and KRAS G13V.

[310] In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^6 is selected from the group consisting of  , and ; where each R^a is independently hydrogen, $C_{1\text{-}6}$alkyl, carboxy, $C_{1\text{-}6}$carboalkoxy, phenyl, $C_{2\text{-}7}$carboalkyl, R^c-$(C(R^b)_2)_z$-, R^c-$(C(R^b)_2)_w$-M-$(C(R^b)_2)_r$-, $(R^d)(R^e)$CH-M-$(C(R^b)_2)_r$-, or Het-J^3-$(C(R^b)_2)_r$-; each R^b is independently hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}6}$cycloalkyl, $C_{2\text{-}7}$carboalkyl, $C_{2\text{-}7}$carboxyalkyl, phenyl, or phenyl optionally substituted with one or more halogen, $C_{1\text{-}6}$alkoxy, trifluoromethyl, amino, $C_{1\text{-}3}$alkylamino, $C_{2\text{-}6}$dialkylamino, nitro, azido, halomethyl, $C_{2\text{-}7}$alkoxymethyl, $C_{2\text{-}7}$alkanoyloxymethyl, $C_{1\text{-}6}$alkylthio, hydroxy, carboxyl, $C_{2\text{-}7}$carboalkoxy, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, $C_{1\text{-}6}$alkanoylamino, or $C_{1\text{-}6}$alkyl; each R^c is independently -NR^bR^b or -OR^b; R^d and R^e are each, independently, -$(C(R^b)_2)_r$-NR^bR^b, or -$(C(R^b)_2)_r$-OR^b; each J^1 is independently hydrogen, chlorine, fluorine, or bromine; J^2 is $C_{1\text{-}6}$alkyl or hydrogen; each M is independently -$N(R^b)$-, -O-, -$N[(C(R^b)_2)_w$-$NR^bR^b]$-, or -$N[(C(R^b)_2)_w$-$OR^b]$-; each J^3 is independently -$N(R^b)$-, -O-, or a bond; each Het is independently a heterocycle, optionally mono- or di-substituted on carbon or nitrogen with R^b and optionally mono-substituted on carbon with -CH_2OR^b; wherein the heterocycle is selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide,

thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, piperazine, tetrahydrofuran, and tetrahydropyran; each r is independently 1-4; each w is independently 2-4; x is 0-1; y is 0-4, and each z is independently 1-6; wherein the sum of x+y is 2-4. In embodiments of Formula (I), (I-1), or (I-2), R^6 is  . In embodiments of embodiments of Formula (I), (I-1), or (I-2), R^6 is selected from the group consisting of  ,  , and ; where each R^b is independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_6 alkoxy, and C_1-C_6 alkyl, or two R^b optionally join to form heterocycle having 3-12 ring atoms or C_3-C_6 cycloalkyl.

[311] In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is a 5 or 6 membered partially unsaturated heterocycloalkyl or a 5 or 6 membered heteroaryl optionally substituted with one, two or three R^{20k}, wherein the partially unsaturated 5 or 6 membered heterocycloalkyl or 5 or 6 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and is bonded to L^2 through a ring nitrogen.

[312] In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is not a 5 or 6 membered partially unsaturated heterocycloalkyl or a 5 or 6 membered heteroaryl optionally substituted with one, two or three R^{20k}, wherein the partially unsaturated 5 or 6 membered heterocycloalkyl or 5 or 6 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and is bonded to L^2 through a ring nitrogen.

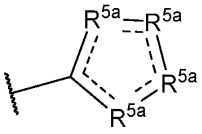
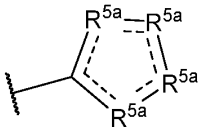
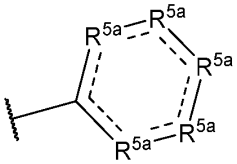
[313] In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is a 5 or 6 membered partially unsaturated heterocycloalkyl or a 5 or 6 membered heteroaryl optionally substituted with one, two or three R^{20k}, wherein the partially unsaturated 5 or 6 membered heterocycloalkyl or 5 or 6 membered heteroaryl comprises one, two, three, or four ring nitrogen atoms; and is bonded to L^2 through a ring nitrogen.

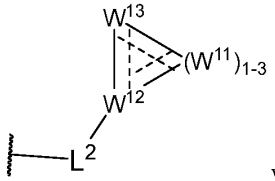
[314] In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is not a 5 or 6 membered partially unsaturated heterocycloalkyl or a 5 or 6 membered heteroaryl optionally substituted with one, two or three R^{20k}, wherein the partially unsaturated 5 or 6 membered heterocycloalkyl or 5 or 6 membered heteroaryl comprises one, two, three, or four ring nitrogen atoms; and is bonded to L^2 through a ring nitrogen.

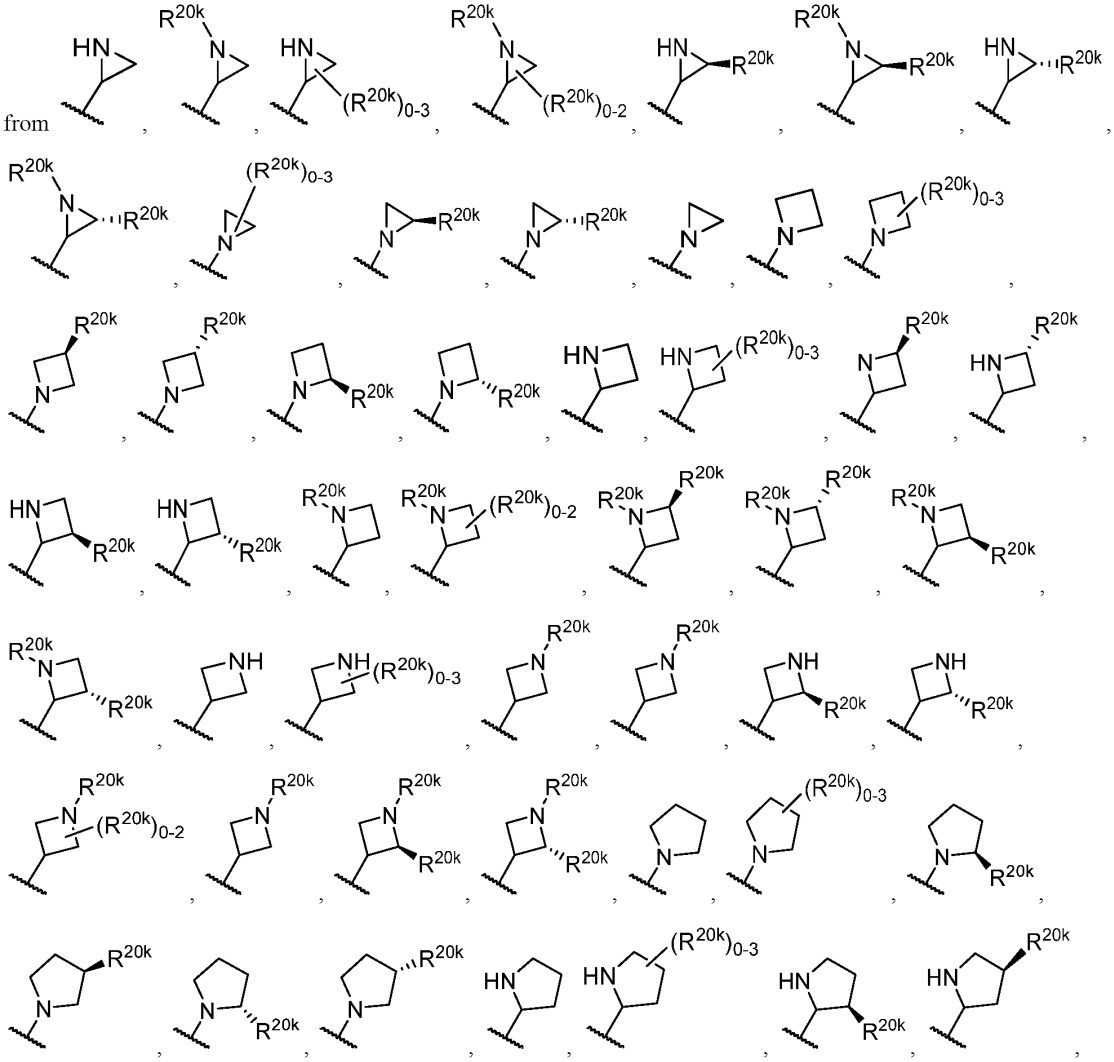
[315] In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is a 5 membered heteroaryl optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, three, or four ring nitrogen atoms; and is bonded to L^2 through a ring nitrogen.

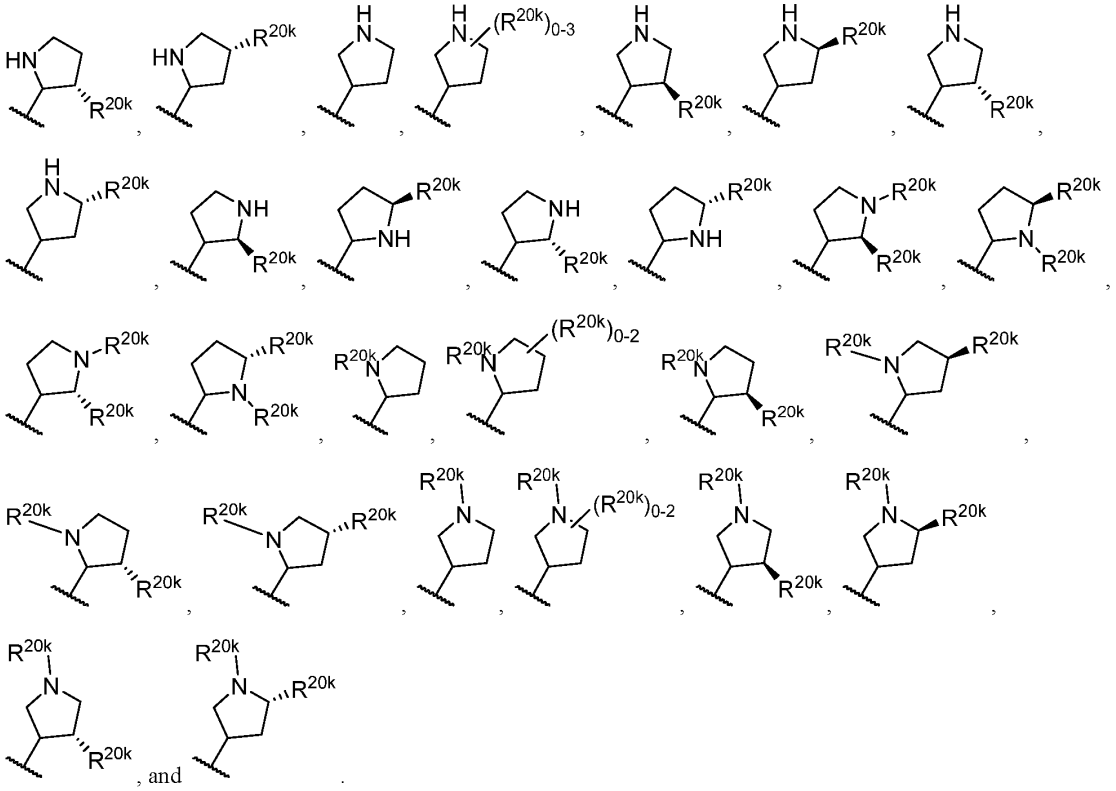
[316] In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}. In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is a 5-6 membered partially unsaturated heterocycloalkyl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}, wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is $-C(O)N(R^{4d})-$. In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5

ring carbon to the N(R^{4d}) of L^2 when L^2 is -C(O)N(R^{4d})-. In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is a 5-6 membered heteroaryl comprising one, two, three, or four ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the N(R^{4d}) of L^2 when L^2 is -C(O)N(R^{4d})-. In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is a 5-10 membered spirocyclic bicyclic heterocycloalkyl comprising at least one nitrogen ring atom and optionally substituted with one, two, three, or four R^{20k}. In embodiments of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is a 3 membered heterocycloalkyl comprising one nitrogen ring atom optionally substituted with one, two, or three R^{20k}.

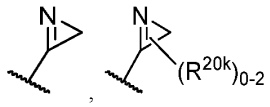
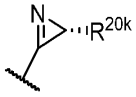
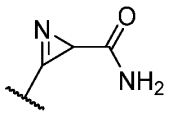
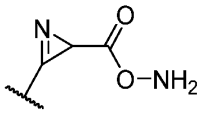
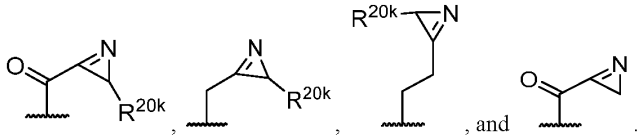
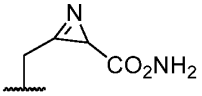
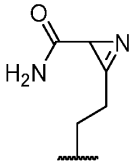
[317] In some embodiments of a compound of Formula (I), (I-1), or (I-2), L^2 is a bond, -C(O)NH-, -NHC(O)-, or -C(O)-; L^2 is bonded to a carbon atom of R^5; and R^5 is selected from -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, C_{6-12}aryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, C_{6-12}aryl, and C_{1-11}heteroaryl, are optionally substituted with one, two, or three R^{20k}. In some embodiments of a compound of Formula (I), (I-1), or (I-2), L^2 is -C(O)-; L^2 is bonded to a carbon atom of R^5; and R^5 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and C_{1-11}heteroaryl, are optionally substituted with one, two, or three R^{20k}. In some embodiments of a compound of Formula (I), (I-1), or (I-2), L^2 is -C(O)-; L^2 is bonded to a carbon atom of R^5; and R^5 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and 5-6 membered heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and 5-6 membered heteroaryl are optionally substituted with one, two, or three R^{20k}. In some embodiments of a compound of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); L^2 is -C(O)-; R^5 is a heteroaryl having the formula:  ; R^{5a} is independently O, S, CH, C(R^{20k}), N, NH, or N(R^{20k}); R^5 comprises 0-3 independent R^{20k}; and 0-4 R^{5a} are independently N, NH, or N(R^{20k}). In some embodiments of a compound of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); L^2 is -C(O)-; and R^5 is a heteroaryl having the formula:  ; R^{5a} is independently CH, C(R^{20k}), N, NH, or N(R^{20k}); R^5 comprises 0-3 independent R^{20k}; and 0-4 R^{5a} are independently N, NH, or N(R^{20k}). In some embodiments of a compound of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); L^2 is -C(O)-; R^5 is  ; R^{5a} is independently CH, C(R^{20k}), CH(R^{20k}), CH_2, C(R^{20k})$_2$, N, NH, or N(R^{20k}); R^5 comprises 0-3 independent R^{20k}; and 0-4 R^{5a} are independently N, NH, or N(R^{20k}). R^{5a} is independently CH, C(R^{20k}), CH(R^{20k}), CH_2, C(R^{20k})$_2$, N, NH, or N(R^{20k}); R^5 comprises 0-3 independent R^{20k}; and 0-4 R^{5a} are N, NH, or N(R^{20k}). In some embodiments of a compound of Formula (I), (I-1), or (I-2), L^2 is -C(O)-; and R^5 is selected from C_{2-6}alkenyl and C_{2-6}alkynyl, wherein C_{2-6}alkenyl and C_{2-6}alkynyl are optionally substituted with one, two, or three R^{20k}. In some embodiments of a compound of Formula (I),

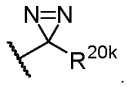
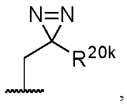
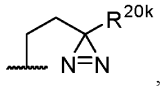
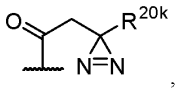
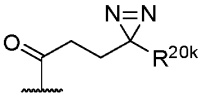
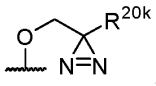
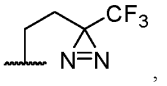
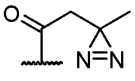
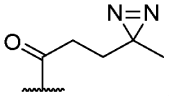
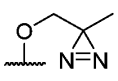
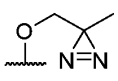
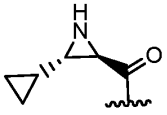
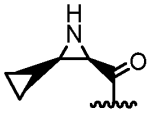
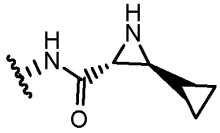
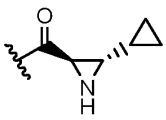
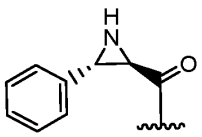
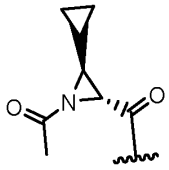
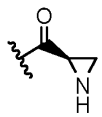
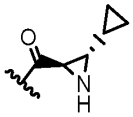
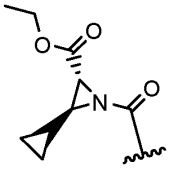
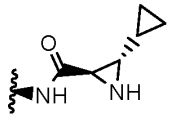
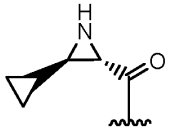
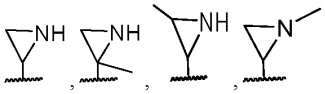
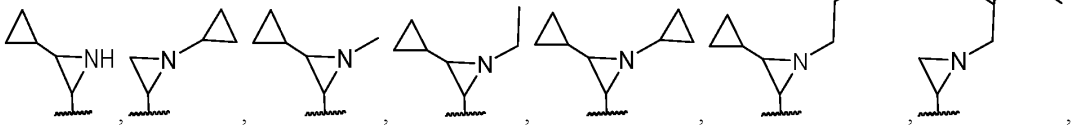
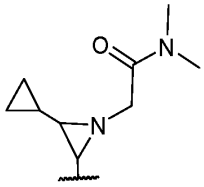
(I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^6 is  wherein each W^{11} and W^{13} are independently selected from O, S, CH, CR^{20k}, CH_2, CHR^{20k}, $C(R^{20k})_2$, N, NH, and NR^{20k} and W^{12} is independently selected from C, CH, CR^{20k}, and N, wherein at least one of W^{11} and W^{13} is N, NH, or NR^{20k} or W^{12} is N, and wherein the ring including W^{11}, W^{12}, and W^{13} is not an aromatic ring. ------ indicates a single or double bond such that all valences are satisfied. It will be understood that when W^{11} is N, NH, or NR^{20k}, then only one, two or three W^{11} may be N, NH, or NR^{20k} and each W^{11} may optionally be different and may each be independently selected from O, S, CH, CR^{20k}, CH_2, CHR^{20k}, $C(R^{20k})_2$, N, NH, and NR^{20k} with the requirement that at least one of W^{11} and W^{13} is N, NH, or NR^{20k} or W^{12} is N. For example, when R^6 includes three W^{11}, one W^{11} may be N, a second W^{11} may be CR^{20k}, and a third W^{11} may be CH_2.

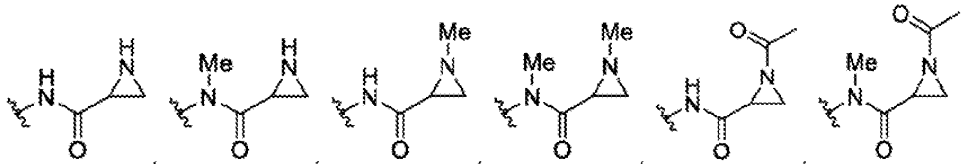
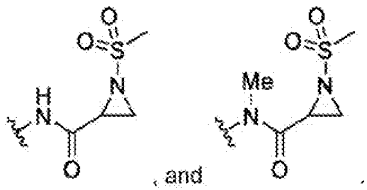
[318] In some embodiments of a compound of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3); R^5 is selected from 



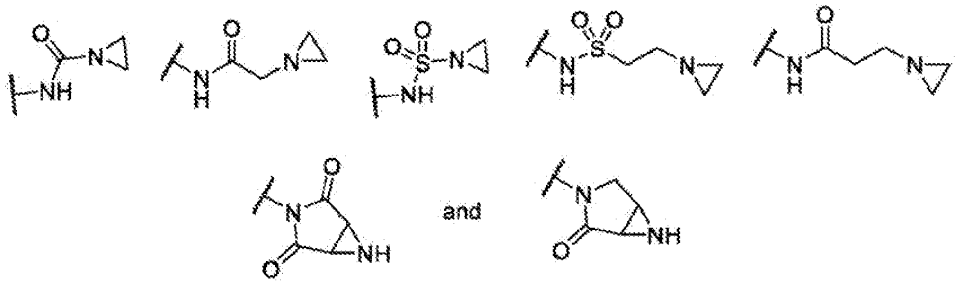
, and .

[319] The individual embodiments herein below, or combinations thereof, (e.g., embodiments of R^5 or R^6) are applicable to compounds of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3), or a pharmaceutically acceptable salt or solvate thereof. In embodiments of the formulae above,, R^5 is selected from  , and  . In embodiments of the formulae above, R^5 is  . In embodiments of the formulae above, R^5 is  . In embodiments of the formulae above, R^6 is independently selected from  , and . In embodiments of the formulae above, R^6 is  . In embodiments of the formulae above, R^6 is  . In embodiments of the formulae

above, R^5 is  . In embodiments of the formulae above , R^6 is selected from  ,  ,  ,  , and  . In embodiments of the formulae above, R^6 is selected from ,  ,  ,  ,  , and  . In embodiments of the formulae above, R^6 is selected from:  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In embodiments of the formulae above, R^5 is selected from:  ,  , and  . In embodiments of the formulae above, R^6 is selected from:

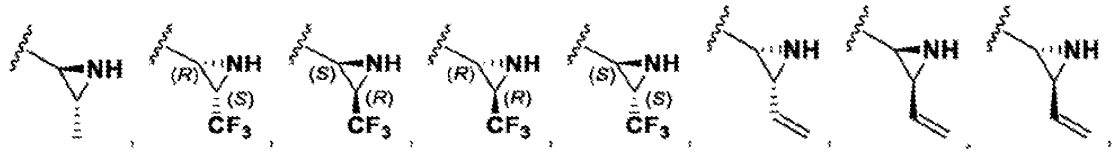
 , and  . In

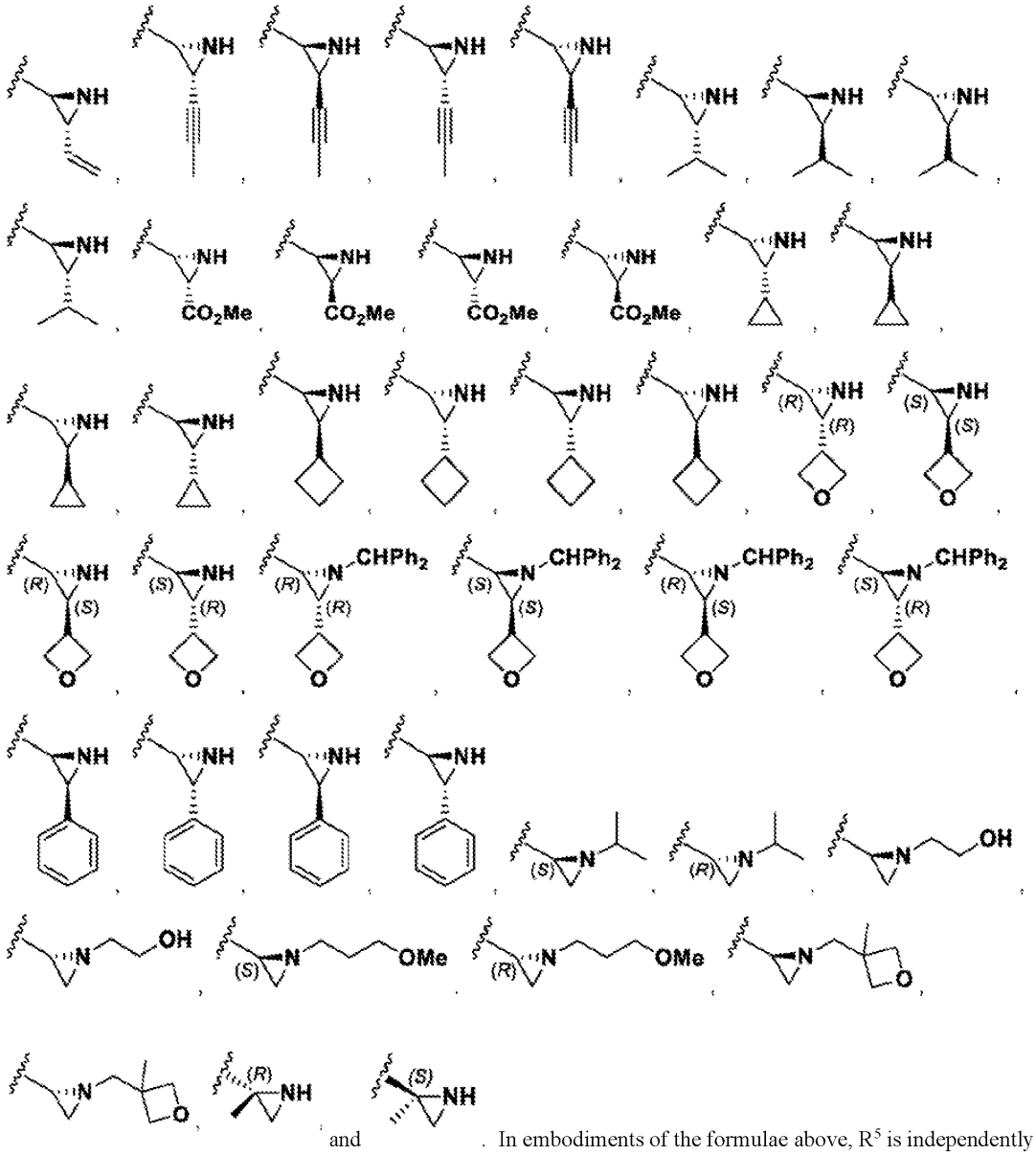
embodiments of the formulae above, R^6 is selected from:



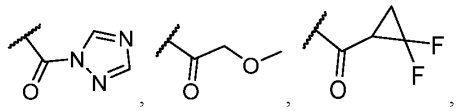
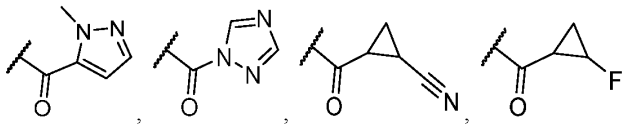
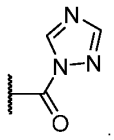
In

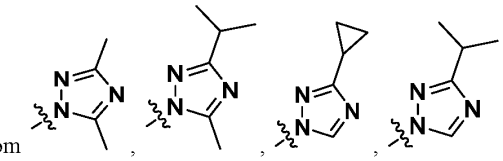
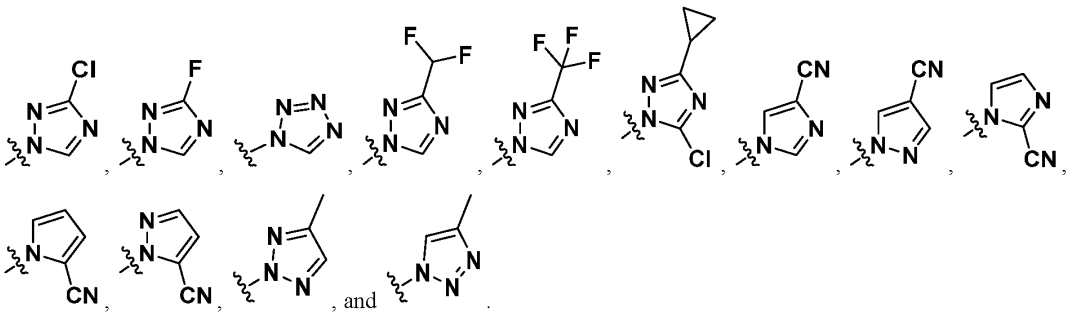
embodiments of the formulae above, R^5 is selected from:

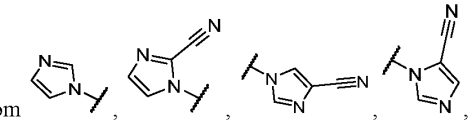
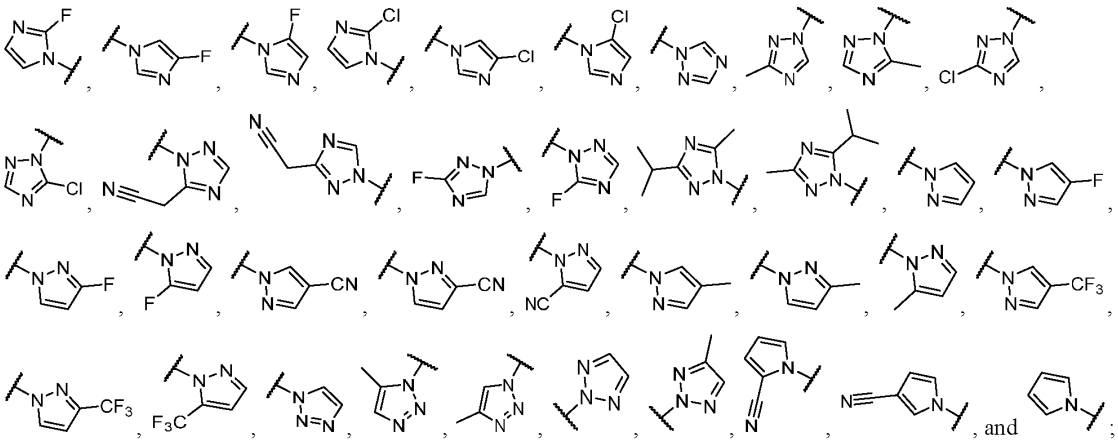
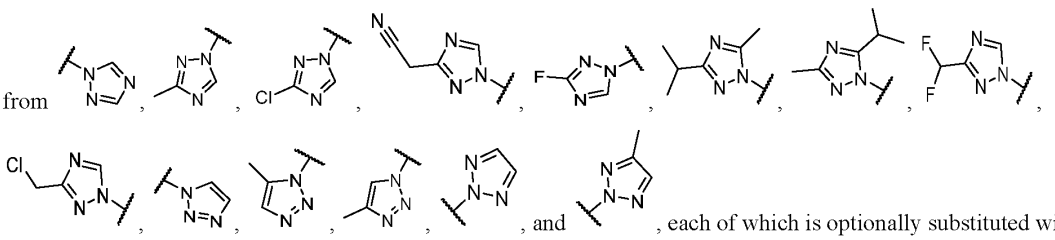




and . In embodiments of the formulae above, R^5 is independently a 5 membered spirocyclic bicyclic heterocycloalkyl comprising at least one nitrogen ring atom and optionally substituted with one, two, three, or four R^{20k}. In embodiments of the formulae above, R^5 is independently a 6 membered spirocyclic bicyclic heterocycloalkyl comprising at least one nitrogen ring atom and optionally substituted with one, two, three, or four R^{20k}. In embodiments of the formulae above, R^5 is independently a 7 membered spirocyclic bicyclic heterocycloalkyl comprising at least one nitrogen ring atom and optionally substituted with one, two, three, or four R^{20k}. In embodiments of the formulae above, R^5 is independently a 8 membered spirocyclic bicyclic heterocycloalkyl comprising at least one nitrogen ring atom and optionally substituted with one, two, three, or four R^{20k}. In embodiments of the formulae above, R^5 is independently a 9 membered spirocyclic bicyclic heterocycloalkyl comprising at least one nitrogen ring atom and optionally substituted with one, two, three, or four R^{20k}. In embodiments of the formulae above, R^5 is independently a 10 membered spirocyclic bicyclic heterocycloalkyl comprising at least one nitrogen ring atom and optionally substituted with one, two, three, or four R^{20k}.

[320] In embodiments of the formulae above,R^6 is selected from  ,  , and  .

[321] In embodiments of the formulae above, R^5 is selected from  ,  , and .

[322] In embodiments of the formulae above, R^5 is selected from  ,  , and ; each of which is optionally substituted with one or more R^{20k}. In embodiments of the formulae above, R^5 is selected from  , and , each of which is optionally substituted with one or more R^{20k}.

[323] In embodiments of the formulae above, R^5 is a 5 membered heteroaryl optionally substituted with one, two or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and the 5 membered heteroaryl is bonded to L^2 through a ring nitrogen. In embodiments of the formulae above, L^2 is -C(O)-; and R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and L^2 is directly bonded to an N ring atom of R^5.

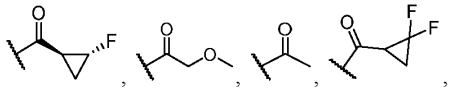
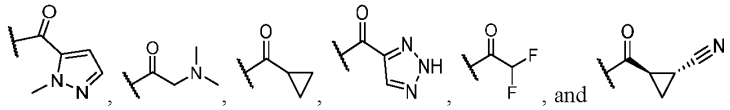
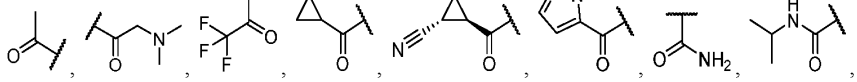
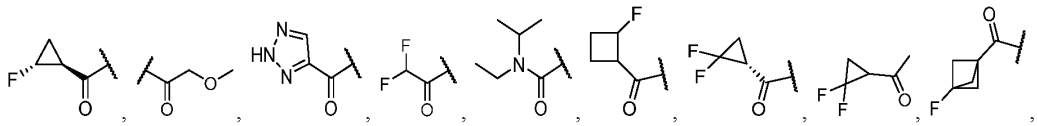
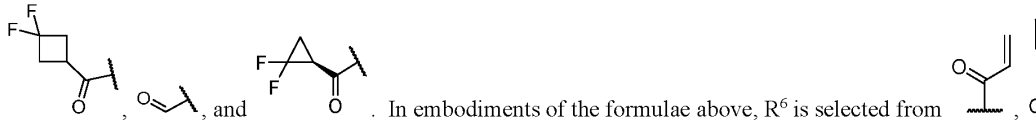
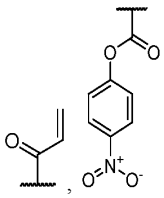
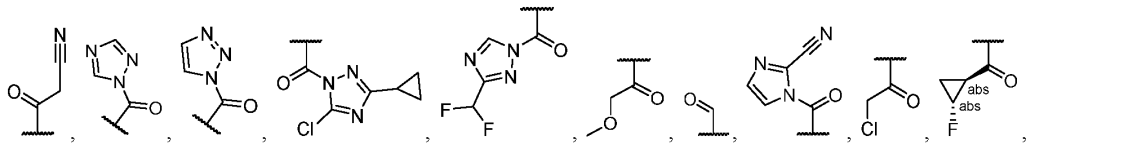
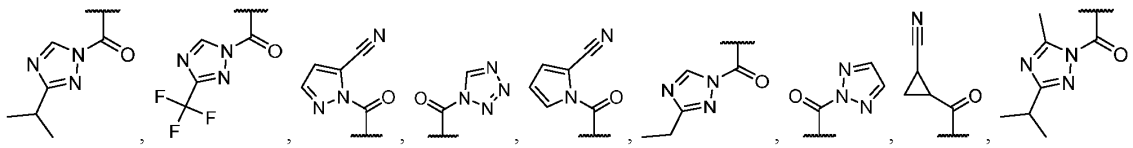
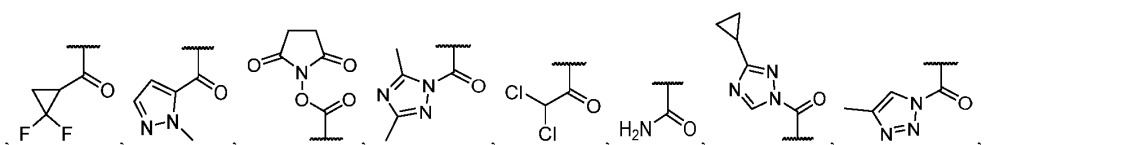
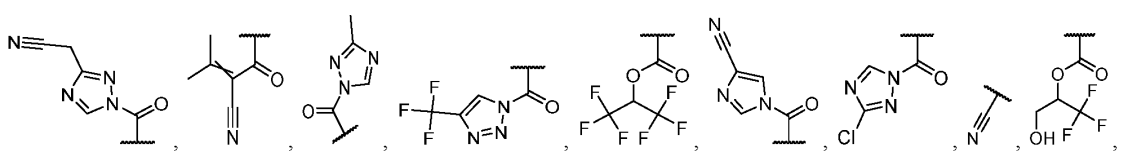
[324] In embodiments of the formulae above, R^5 is a 5-6 membered heteroaryl optionally substituted with one, two, three, or four R^{20k}, wherein the heteroaryl comprises one, two, three, or four, ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O), S(O), or $S(O)_2$ of L^2, L^2 is directly bonded to an N atom of R^5. In embodiments of the formulae above, R^5 is a 5 membered heteroaryl optionally substituted with one, two, three, or four R^{20k}, wherein the heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O), S(O), or $S(O)_2$ of L^2, L^2 is directly bonded to an N atom of R^5. In embodiments of the formulae above, R^5 is a pyrrolyl, pyrazolyl, imidazolyl, or triazolyl optionally substituted with one, two, three, or four R^{20k}, wherein when R^5 is directly bonded to a C(O), S(O), or $S(O)_2$ of L^2, L^2 is directly bonded to an N atom of R^5. In embodiments of embodiments of the formulae above, R^5 is a triazolyl optionally substituted with one, two, three, or four R^{20k}, wherein when R^5 is directly bonded to a C(O), S(O), or $S(O)_2$ of L^2, L^2 is directly bonded to an N atom of R^5. In embodiments of embodiments of the formulae above, R^5 is a pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, oxadiazolyl, thiadiazolyl, or triazolyl optionally substituted with one, two, three, or four R^{20k}, wherein when R^5 is directly bonded to a C(O), S(O), or $S(O)_2$ of L^2, L^2 is directly bonded to an N atom of R^5.

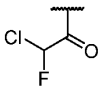
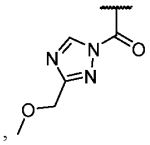
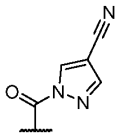
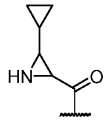
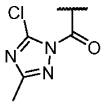
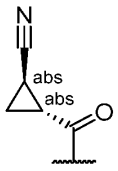
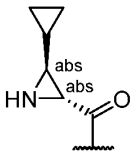
[325] In embodiments of the formulae above, L^2 is a -C(O)-, $-N(R^{4d})C(O)-$, or $-C(O)N(R^{4d})-$; and R^5 is a 5-6 membered heteroaryl optionally substituted with one, two, three, or four R^{20k}, wherein the heteroaryl comprises one, two, three, or four, ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N atom of R^5. In embodiments of the formulae above, L^2 is a -C(O)-, $-N(R^{4d})C(O)-$, or $-C(O)N(R^{4d})-$; and R^5 is a 5 membered heteroaryl optionally substituted with one, two, three, or four R^{20k}, wherein the heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N atom of R^5. In embodiments of the formulae above, L^2 is a -C(O)-, $-N(R^{4d})C(O)-$, or $-C(O)N(R^{4d})-$; and R^5 is a pyrrolyl, pyrazolyl, imidazolyl, or triazolyl optionally substituted with one, two, three, or four R^{20k}, wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N atom of R^5. In embodiments of the formulae above, L^2 is a -C(O)-, $-N(R^{4d})C(O)-$, or $-C(O)N(R^{4d})-$; and R^5 is a triazolyl optionally substituted with one, two, three, or four R^{20k}, wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N atom of R^5. In embodiments of the formulae above, L^2 is a -C(O)-, $-N(R^{4d})C(O)-$, or $-C(O)N(R^{4d})-$; and R^5 is a pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, oxadiazolyl, thiadiazolyl, or triazolyl optionally substituted with one, two, three, or four R^{20k}, wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N atom of R^5.

[326] In embodiments of the formulae above, R^5 is $C_{2\text{-}6}$alkenyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is $C_{2\text{-}6}$alkenyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is $C_{2\text{-}6}$alkenyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is $C_{2\text{-}6}$alkenyl optionally substituted with $-OR^{21}$. In embodiments of the formulae above, R^5 is $C_{2\text{-}6}$alkenyl optionally substituted with $-N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is $C_{2\text{-}6}$alkenyl optionally substituted with $C_{2\text{-}9}$heterocycloalkyl. In embodiments of the formulae above, R^5 is $C_{2\text{-}6}$alkenyl optionally substituted with $C_{1\text{-}5}$heteroaryl optionally substituted with one, two, or three $C_{1\text{-}6}$alkyl. In embodiments of the formulae

above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with $-N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl and/or CN. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with $-OR^{21}$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with $-N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with one, two, or three C_{1-6}alkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with $-N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with $-C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl substituted with Cl and optionally substituted with one or two R^{20k}. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-OR^{21}$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with one, two, or three C_{1-6}alkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with $-N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl and/or CN. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-OR^{21}$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with one, two, or three C_{1-6}alkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with $-N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl substituted with Cl and optionally substituted with one or two R^{20k}. In embodiments of the formulae above, R^5 is C_{3-5}cycloalkyl, optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{3-5}cycloalkyl, optionally substituted with C_{1-6}alkyl optionally substituted with one, two, or three halogen. In embodiments

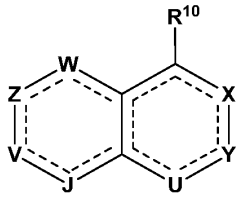
of the formulae above, R^5 is C_{3-5}cycloalkyl, optionally substituted with C_{1-6}alkyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{1-5}heterocycloalkyl, optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{1-5}heterocycloalkyl, optionally substituted with C_{1-6}alkyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{1-5}heterocycloalkyl, optionally substituted with C_{1-6}alkyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{1-6}alkyl, optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{1-6}alkyl, substituted with Cl and optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is $-S(O)_2R^{15}$. In embodiments of the formulae above, R^5 is -CN.

[327] In embodiments of the formulae above, R^6 is selected from  ,  , and . In embodiments of the formulae above, R^6 is selected from  ,  ,  , and . In embodiments of the formulae above, R^6 is selected from  ,  ,  ,  ,  , .

 ,  ,  ,  , and  . In embodiments of the formulae above, R^6 is selected from  and  .

[328] In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with $-N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with $-OR^{21}$. In embodiments of the formulae above, R^5 is C_{3-6}cycloalkyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{3-6}cycloalkyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{3-6}cycloalkyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{3-6}cycloalkyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{1-5}heteroaryl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{1-5}heteroaryl optionally substituted with C_{1-6}alkyl.

[329] In an aspect is provided a compound of Formula (A), or a pharmaceutically acceptable salt or solvate thereof:

 Formula (A);

wherein

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

Z is N, $C(R^8)$, $N(R^{8b})$, $C(R^8)(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

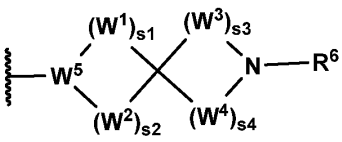
V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O)

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^7-R^7$;

L^7 is a bond, -O-, $-N(R^{14})-$, -C(O)-, -S-, $-S(O)_2-$, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is  ;

W^1, W^2, W^3, and W^4 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is an integer from 3 to 6;

s2 is an integer from 1 to 2;

s3 is an integer from 1 to 3;

s4 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $=C(R^{21b})_2$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl$)-S(O)_2R^{15}$, $-(C_{1-6}$alkyl$)-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl$)-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is $-L^2-R^5$; wherein R^6 is capable of forming a covalent bond with a RAS amino acid;

L^2 is a bond, -O-, $-N(R^{4d})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{4d}$-, $CR^{4c}R^{4c}$, $-OCR^{4c}R^{4c}$-, $-N(R^{4d})CR^{4c}R^{4c}$-, $-C(O)CR^{4c}R^{4c}$-, $-SCR^{4c}R^{4c}$-, $-S(O)_2CR^{4c}R^{4c}$-, $-S(O)CR^{4c}R^{4c}$-, $-P(O)R^{4d}CR^{4c}R^{4c}$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}$, $-CR^{4c}R^{4c}O$-, $-CR^{4c}R^{4c}N(R^{4d})$-, $-CR^{4c}R^{4c}C(O)$-, $-CR^{4c}R^{4c}S$-, $-CR^{4c}R^{4c}S(O)_2$-, $-CR^{4c}R^{4c}S(O)$-, $-CR^{4c}R^{4c}P(O)R^{4d}$-, $-N(R^{4d})C(O)$-, $-N(R^{4d})S(O)_2$-, $-N(R^{4d})S(O)$-, $-N(R^{4d})P(O)R^{4d}$-, $-C(O)N(R^{4d})$-, $-S(O)_2N(R^{4d})$-, $-S(O)N(R^{4d})$-, $-P(O)R^{4d}N(R^{4d})$-, -OC(O)-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{4d}$-, -C(O)O-, $-S(O)_2O$-, -S(O)O-, $-P(O)R^{4d}O$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}$-, $-OCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-SCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-CR^{4c}R^{4c}CR^{4c}R^{4c}O$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)$-, or $-CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}$-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, $-OCH_2C(O)OR^{14}$, $-OC(O)R^{14a}$, $-N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14a}$, and $-N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, and $-CH_2-C_{2-9}$heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{14}$, $-SR^{14}$, $-N(R^{14})(R^{14})$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14}$, $-N(R^{14})S(O)_2R^{14}$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, and $-OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-}

$_{6}$alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -C(O)OR^{14}, -C(O)N(R^{14})(R^{14}), -C(O)C(O)N(R^{14})(R^{14}), -OC(O)N(R^{14})(R^{14}), -C(O)R^{14a}, -$S(O)_2R^{14}$, -$S(O)_2$N(R^{14})(R^{14}), -OCH_2C(O)OR^{14}, and -OC(O)R^{14a}, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -N(R^{14})(R^{14}), -C(O)OR^{14}, -C(O)N(R^{14})(R^{14}), -C(O)C(O)N(R^{14})(R^{14}), -OC(O)N(R^{14})(R^{14}), -N(R^{14})C(O)N(R^{14})(R^{14}), -N(R^{14})C(O)OR^{14}, -N(R^{14})C(O)R^{14}, -N(R^{14})$S(O)_2R^{14}$, -C(O)R^{14a}, -$S(O)_2R^{14}$, -$S(O)_2$N(R^{14})(R^{14}), and -OC(O)R^{14a};

R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})$S(O)_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -$S(O)_2R^{15}$, -$S(O)_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2$N(R^{12})(R^{13}), wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k};

wherein R^5 is not

(i) a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; and

(ii) a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the N(R^{4d}) of L^2 when L^2 is -C(O)N(R^{4d})-;

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})$S(O)_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -$S(O)_2R^{15}$, -$S(O)_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -C(O)OR^{12}, -C(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is -L^1-R^{19};

R^{17b} is -L^{1b}-R^{19};

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, -N(R^{14})-, -C(O)-, -N(R^{14})C(O)-, -C(O)N(R^{14})-, -S-, -$S(O)_2$-, -S(O)-, -$S(O)_2$N(R^{14})-, -S(O)N(R^{14})-, -N(R^{14})S(O)-, -N(R^{14})$S(O)_2$-, -OCON(R^{14})-, -N(R^{14})C(O)O-, N(R^{1e}), C(O)N(R^{1c}), $S(O)_2$N(R^{1c}), S(O)N(R^{1c}), C(R^{1f})(R^{1g})O, C(R^{1f})(R^{1g})N(R^{1c}), and C(R^{1f})(R^{1g}); wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, -C(O)N(R^{14})-, C(O)N(R^{1c}), C(R^{1f})(R^{1g})O, C(R^{1f})(R^{1g})N(R^{1c}), and C(R^{1f})(R^{1g}); wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -C(O)OR^{12}, -C(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -CH$_2$C(O)N(R^{12})(R^{13}), -CH$_2$N(R^{14})C(O)R^{15}, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -O$R^{12'}$, -S$R^{12'}$, -N($R^{12'}$)(R^{13}), -N=(R^{15}), -C(O)O$R^{12'}$, -OC(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12'}$)($R^{13}$), -C(O)C(O)N($R^{12'}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12'}$)($R^{13}$)-,

S(=O)(=NH)N($R^{12'}$)(R^{13}), -CH_2C(O)N($R^{12'}$)(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, -CH_2S(O)$_2$N($R^{12'}$)(R^{13}), –(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -S(O)$_2R^{15}$, -S(O)$_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, -CH_2S(O)$_2$N(R^{12})(R^{13}), –(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -C(O)OR^{12}, -C(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, -CH_2S(O)$_2$N(R^{12})(R^{13}), –(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is C(R^3), C(R^3)(R^3), N(R^3), or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -S(O)$_2R^{15}$, -S(O)$_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, and -CH_2S(O)$_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}

$_{10}$cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -C(O)OR^{12}, -C(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -CH$_2$C(O)N(R^{12})(R^{13}), -CH$_2$N(R^{14})C(O)R^{15}, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} are each independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH$_2$-C_{6-10}aryl, -CH$_2$-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -N(R^{22})(R^{23}), =C(R^{21b})$_2$, -C(O)OR^{22}, -C(O)N(R^{22})(R^{23}), -C(O)C(O)N(R^{22})(R^{23}), -OC(O)N(R^{22})(R^{23}), -N(R^{24})C(O)N(R^{22})(R^{23}), -N(R^{24})C(O)OR^{25}, -N(R^{24})C(O)R^{21}, -N(R^{24})S(O)$_2$$R^{25}$, -C(O)$R^{21}$, -S(O)$_2$$R^{25}$, -S(O)$_2$N($R^{22}$)($R^{23}$), -OCH$_2$C(O)O$R^{22}$, and -OC(O)$R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH$_2$-C_{6-10}aryl, -CH$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -N(R^{22})(R^{23}), -C(O)OR^{22}, -C(O)N(R^{22})(R^{23}), -C(O)C(O)N(R^{22})(R^{23}), -OC(O)N(R^{22})(R^{23}), -N(R^{24})C(O)N(R^{22})(R^{23}), -N(R^{24})C(O)OR^{25}, -N(R^{24})C(O)R^{25}, -N(R^{24})S(O)$_2$$R^{25}$, -C(O)$R^{25}$, -S(O)$_2$$R^{25}$, -S(O)$_2$N($R^{22}$)($R^{23}$), and -OC(O)$R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which

is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

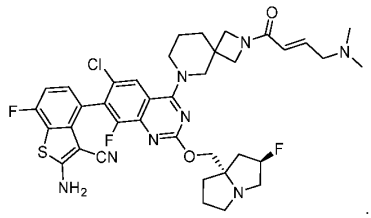
each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

------ indicates a single or double bond such that all valences are satisfied.

[330] In embodiments, R^5 is not a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; or a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is $-C(O)N(R^{4d})-$.

[331] In embodiments, R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2-$(6-12 membered heterocycloalkyl), C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-$(7-12 membered heteroaryl), 7-12 membered heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2-$(6-12 membered heterocycloalkyl), C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-$(7-12 membered heteroaryl), and 7-12 membered heteroaryl are optionally substituted with one, two, or three R^{20k};

[332] In embodiments of Formula (A), the compound is not 

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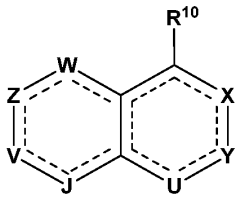
[333] In embodiments of Formula (A); W is a $C(R^{18})$ or C(O); Z is N, $C(R^8)$, or $N(R^{8b})$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^2)$; U is N; X is N; L^7 is a bond; s1 is 3 and s2 is 2, s1 is 4 and s2 is 1 or 2, s1 is 5 and s2 is 1 or 2, or s1 is 6 and s2 is 1 or 2; R^{17} is $-L^1-R^{19}$; and all other variables are as described herein for Formula (A) or embodiments thereof.

[334] In embodiments of Formula (A), R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2-$(6-12 membered heterocycloalkyl), C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-$(7-12 membered heteroaryl), 7-12 membered heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2-$(6-12 membered heterocycloalkyl), C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-$(7-12 membered heteroaryl), and 7-12 membered heteroaryl are optionally substituted with one, two, or three R^{20k}; wherein R^5 is not a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; and/or a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two

or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is $-C(O)N(R^{4d})-$.

[335] In embodiments of Formula (A), R^{19} is selected from a C_{2-11}heterocycloalkyl and C_{2-12}heteroaryl, wherein the C_{2-11}heterocycloalkyl and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}.

[336] In an aspect is provided a compound of Formula (B), or a pharmaceutically acceptable salt or solvate thereof:



Formula (B); wherein

1. Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and
   R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}; or
2. Y is N, $C(R^{2''})$, $C(R^{2''})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$; and
   R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-(C_{1-6}\text{alkyl})-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}\text{alkyl})-N(R^{14})C(O)R^{12}$, $-(C_{1-6}\text{alkyl})-S(O)_2R^{15}$, $-(C_{1-6}\text{alkyl})-N(R^{12})(R^{13})$, and $-(C_{1-6}\text{alkyl})-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

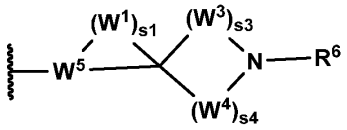
Z is N, $C(R^8)$, $N(R^{8b})$, $C(R^8)(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^7-R^7$;

L^7 is a bond, -O-, $-N(R^{14})-$, -C(O)-, -S-, $-S(O)_2-$, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is 

;

W^1, W^2, W^3, and W^4 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is an integer from 1 to 6;

s3 is an integer from 1 to 3;

s4 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is -L^2-R^5; wherein R^6 is capable of forming a covalent bond with a Ras amino acid;

L^2 is a bond, -O-, -$N(R^{4d})$-, -C(O)-, -S-, -$S(O)_2$-, -S(O)-, -$P(O)R^{4d}$-, $CR^{4c}R^{4c}$, -$OCR^{4c}R^{4c}$-, -$N(R^{4d})CR^{4c}R^{4c}$-, -$C(O)CR^{4c}R^{4c}$-, -$SCR^{4c}R^{4c}$-, -$S(O)_2CR^{4c}R^{4c}$-, -$S(O)CR^{4c}R^{4c}$-, -$P(O)R^{4d}CR^{4c}R^{4c}$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}$, -$CR^{4c}R^{4c}O$-, -$CR^{4c}R^{4c}N(R^{4d})$-, -$CR^{4c}R^{4c}C(O)$-, -$CR^{4c}R^{4c}S$-, -$CR^{4c}R^{4c}S(O)_2$-, -$CR^{4c}R^{4c}S(O)$-, -$CR^{4c}R^{4c}P(O)R^{4d}$-, -$N(R^{4d})C(O)$-, -$N(R^{4d})S(O)_2$-, -$N(R^{4d})S(O)$-, -$N(R^{4d})P(O)R^{4d}$-, -$C(O)N(R^{4d})$-, -$S(O)_2N(R^{4d})$-, -$S(O)N(R^{4d})$-, -$P(O)R^{4d}N(R^{4d})$-, -OC(O)-, -$OS(O)_2$-, -OS(O)-, -$OP(O)R^{4d}$-, -C(O)O-, -$S(O)_2O$-, -S(O)O-, -$P(O)R^{4d}O$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}$-, -$OCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$SCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, -$CR^{4c}R^{4c}CR^{4c}R^{4c}O$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2$-, -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)$-, or -$CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}$-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, -$OC(O)R^{14a}$, -$N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14a}$, and -$N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, and -$OC(O)R^{14a}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl,

C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, $C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$C(O)OR^{12}$, -$C(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is -L^1-R^{19};

R^{17b} is -L^{1b}-R^{19};

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, -$N(R^{14})$-, -C(O)-, -$N(R^{14})C(O)$-, -$C(O)N(R^{14})$-, -S-, -$S(O)_2$-, -S(O)-, -$S(O)_2N(R^{14})$-, -$S(O)N(R^{14})$-, -$N(R^{14})S(O)$-, -$N(R^{14})S(O)_2$-, -$OCON(R^{14})$-, -$N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, -$C(O)N(R^{14})$-, $C(O)N(R^{1e})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to

form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-C(O)OR^{12}$, $-C(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$, $-N{=}(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

$R^{2''}$ is $-OR^{12''}$, $-SR^{12'}$, $-N(R^{12'''})(R^{13})$, $-N{=}(R^{15})$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, or $S(=O)(=NH)N(R^{12'})(R^{13})$;

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, –

(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -C(O)OR^{12}, -C(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, -CH_2S(O)$_2$N(R^{12})(R^{13}), –(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is C(R^3), C(R^3)(R^3), N(R^3), or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -S(O)$_2R^{15}$, -S(O)$_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, and -CH_2S(O)$_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}

$_{10}$cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -C(O)OR^{12}, -C(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -CH$_2$C(O)N(R^{12})(R^{13}), -CH$_2$N(R^{14})C(O)R^{15}, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} are each independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH$_2$-C_{6-10}aryl, -CH$_2$-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -N(R^{22})(R^{23}), =C(R^{21b})$_2$, -C(O)OR^{22}, -C(O)N(R^{22})(R^{23}), -C(O)C(O)N(R^{22})(R^{23}), -OC(O)N(R^{22})(R^{23}), -N(R^{24})C(O)N(R^{22})(R^{23}), -N(R^{24})C(O)OR^{25}, -N(R^{24})C(O)R^{21}, -N(R^{24})S(O)$_2$$R^{25}$, -C(O)$R^{21}$, -S(O)$_2$$R^{25}$, -S(O)$_2$N($R^{22}$)($R^{23}$), -OCH$_2$C(O)O$R^{22}$, and -OC(O)$R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH$_2$-C_{6-10}aryl, -CH$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -N(R^{22})(R^{23}), -C(O)OR^{22}, -C(O)N(R^{22})(R^{23}), -C(O)C(O)N(R^{22})(R^{23}), -OC(O)N(R^{22})(R^{23}), -N(R^{24})C(O)N(R^{22})(R^{23}), -N(R^{24})C(O)OR^{25}, -N(R^{24})C(O)R^{25}, -N(R^{24})S(O)$_2$$R^{25}$, -C(O)$R^{25}$, -S(O)$_2$$R^{25}$, -S(O)$_2$N($R^{22}$)($R^{23}$), and -OC(O)$R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which

is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

===== indicates a single or double bond such that all valences are satisfied.

[337] In embodiments of Formula (B), Y is N, $C(R^2)$, $C(R^2)(R^{2e})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}.

[338] In embodiments of Formula (B), Y is N, $C(R^{2''})$, $C(R^{2''})(R^{2e})$, $N(R^{2b})$, S(O), or $S(O)_2$; and R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}.

[339] In embodiments of Formula (B), R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2$-C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2$-(6-12 membered heterocycloalkyl), C_{6-12}aryl, $-CH_2$-C_{6-12}aryl, $-CH_2$-(7-12 membered heteroaryl), 7-12 membered heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2$-C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2$-(6-12 membered heterocycloalkyl), C_{6-12}aryl, $-CH_2$-C_{6-12}aryl, $-CH_2$-(7-12 membered heteroaryl), and 7-12 membered heteroaryl are optionally substituted with one, two, or three R^{20k}.

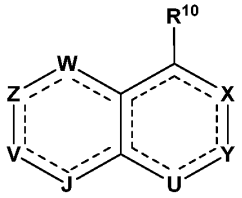
[340] In embodiments, R^5 is not a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; and/or a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is $-C(O)N(R^{4d})$-.

[341] In embodiments, R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2$-C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2$-(6-12 membered heterocycloalkyl), C_{6-12}aryl, $-CH_2$-C_{6-12}aryl, $-CH_2$-(7-12 membered heteroaryl), 7-12 membered heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2$-C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2$-(6-12 membered

heterocycloalkyl), C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-(7-12 membered heteroaryl), and 7-12 membered heteroaryl are optionally substituted with one, two, or three R^{20k}.

[342] In embodiments, $R^{2''}$ is -$OR^{12''}$, -$SR^{12'}$, -$N(R^{12'''})(R^{13})$, -$OC(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, or $S(=O)(=NH)N(R^{12'})(R^{13})$; each $R^{12'''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d}.

[343] In an aspect is provided a compound of Formula (C), or a pharmaceutically acceptable salt or solvate thereof:



Formula (C); wherein

1. Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and
   R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}; or
2. Y is N, $C(R^{2''})$, $C(R^{2''})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$; and
   R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

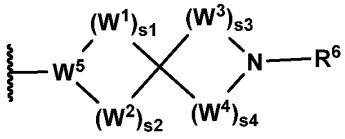
Z is N, $C(R^8)$, $N(R^{8b})$, $C(R^8)(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is -L^7-R^7;

L^7 is a bond, -O-, -$N(R^{14})$-, -C(O)-, -S-, -$S(O)_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is  ;

W^1, W^2, W^3, and W^4 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is an integer from 1 to 6;

s2 is an integer from 1 to 3;

s3 is an integer from 1 to 3;

s4 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is $-L^2-R^5$ and wherein R^6 is capable of forming a covalent bond with a RAS amino acid;

L^2 is a -C(O)-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, $-OCH_2C(O)OR^{14}$, $-OC(O)R^{14a}$, $-N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14a}$, and $-N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, and $-CH_2-C_{2-9}$heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{14}$, $-SR^{14}$, $-N(R^{14})(R^{14})$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14}$, $-N(R^{14})S(O)_2R^{14}$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, and $-OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, $-OCH_2C(O)OR^{14}$, and $-OC(O)R^{14a}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, and $-CH_2-C_{2-9}$heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl,

C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{14}$, $-SR^{14}$, $-N(R^{14})(R^{14})$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14}$, $-N(R^{14})S(O)_2R^{14}$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, and $-OC(O)R^{14a}$;

R^5 is C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, C_{6-12}aryl, or C_{1-11}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, C_{6-12}aryl, or C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k};

wherein R^5 is not

(i) a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; and

(ii) a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is $-C(O)N(R^{4d})$-;

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20e};

R^{8b} is selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-C(O)OR^{12}$, $-C(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20e};

R^{17} is $-L^1$-R^{19};

R^{17b} is $-L^{1b}$-R^{19};

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, $-N(R^{14})$-, -C(O)-, $-N(R^{14})C(O)$-, $-C(O)N(R^{14})$-, -S-, $-S(O)_2$-, -S(O)-, $-S(O)_2N(R^{14})$-, $-S(O)N(R^{14})$-, $-N(R^{14})S(O)$-, $-N(R^{14})S(O)_2$-, $-OCON(R^{14})$-, $-N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, $-C(O)N(R^{14})$-, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered

heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-C(O)OR^{12}$, $-C(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$, $-N=(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

$R^{2''}$ is $-OR^{12''}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$,), $-N=(R^{15})$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, or $S(=O)(=NH)N(R^{12'})(R^{13})$;

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-}$

$_{9}$heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -C(O)OR^{12}, -C(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, -CH_2S(O)$_2$N(R^{12})(R^{13}), –(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is C(R^3), C(R^3)(R^3), N(R^3), or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -S(O)$_2R^{15}$, -S(O)$_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, and -CH_2S(O)$_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-C(O)OR^{12}$, $-C(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} are each independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, C_{1-9}heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $=C(R^{21b})_2$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{21}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{21}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

------ indicates a single or double bond such that all valences are satisfied.

[344] In embodiments of Formula (C), Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}.

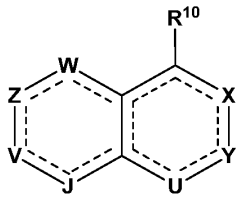
[345] In embodiments of Formula (C), Y is N, $C(R^{2''})$, $C(R^{2''})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$; and R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}.

[346] In embodiments, R^5 is not a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; and/or a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is $-C(O)N(R^{4d})$-;

[347] In embodiments, R^5 is C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, C_{6-12}aryl, or 7-12 membered heteroaryl, wherein the C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, C_{6-12}aryl, or 7-12 membered heteroaryl are optionally substituted with one, two, or three R^{20k}.

[348] In embodiments of Formula (C), R^5 is C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, C_{6-12}aryl, or 7-12 membered heteroaryl, wherein the C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, C_{6-12}aryl, or 7-12 membered heteroaryl are optionally substituted with one, two, or three R^{20k}; wherein R^5 is not a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; or a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is $-C(O)N(R^{4d})$-.

[349] In an aspect is provided a compound of Formula (D), or a pharmaceutically acceptable salt or solvate thereof:



Formula (D);

wherein

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

Z is N, $C(R^8)$, $N(R^{8b})$, $C(R^8)(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

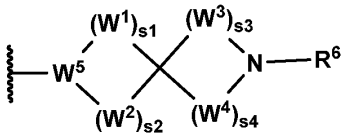
V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O)

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^7-R^7$;

L^7 is a bond, -O-, $-N(R^{14})-$, -C(O)-, -S-, $-S(O)_2-$, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is 

;

W^1, W^2, W^3, and W^4 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is an integer from 3 to 6;

s2 is an integer from 1 to 2;

s3 is an integer from 1 to 3;

s4 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $=C(R^{21b})_2$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl$)-S(O)_2R^{15}$, $-(C_{1-6}$alkyl$)-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl$)-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is $-L^2-R^5$; wherein R^6 is not capable of forming a covalent bond with the 12th amino acid of a mutant KRAS protein selected from KRAS G12D, KRAS G12C, and KRAS G12S and R^6 is not capable of forming a covalent bond with the 13th amino acid of a mutant KRAS protein selected from KRAS G13D, KRAS G13C, and KRAS G13S;

L^2 is a bond, -O-, $-N(R^{4d})-$, -C(O)-, -S-, $-S(O)_2-$, -S(O)-, $-P(O)R^{4d}-$, $CR^{4c}R^{4c}$, $-OCR^{4c}R^{4c}-$, $-N(R^{4d})CR^{4c}R^{4c}-$, $-C(O)CR^{4c}R^{4c}-$, $-SCR^{4c}R^{4c}-$, $-S(O)_2CR^{4c}R^{4c}-$, $-S(O)CR^{4c}R^{4c}-$, $-P(O)R^{4d}CR^{4c}R^{4c}-$, $-CR^{4c}R^{4c}CR^{4c}R^{4c}$, $-CR^{4c}R^{4c}O-$, $-CR^{4c}R^{4c}N(R^{4d})-$, $-CR^{4c}R^{4c}C(O)-$, $-CR^{4c}R^{4c}S-$, $-CR^{4c}R^{4c}S(O)_2-$, $-CR^{4c}R^{4c}S(O)-$, $-CR^{4c}R^{4c}P(O)R^{4d}-$, $-N(R^{4d})C(O)-$, $-N(R^{4d})S(O)_2-$, $-N(R^{4d})S(O)-$, $-N(R^{4d})P(O)R^{4d}-$, $-C(O)N(R^{4d})-$, $-S(O)_2N(R^{4d})-$, $-S(O)N(R^{4d})-$, $-P(O)R^{4d}N(R^{4d})-$, $-OC(O)-$, $-OS(O)_2-$, $-OS(O)-$, $-OP(O)R^{4d}-$, $-C(O)O-$, $-S(O)_2O-$, $-S(O)O-$, $-P(O)R^{4d}O-$, $-CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}-$, $-OCR^{4c}R^{4c}CR^{4c}R^{4c}-$, $-N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}-$, $-C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}-$, $-SCR^{4c}R^{4c}CR^{4c}R^{4c}-$, $-S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}-$, $-S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}-$, $-P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}-$, $-CR^{4c}R^{4c}CR^{4c}R^{4c}O-$, $-CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})-$, $-CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)-$, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S-$, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2-$, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)-$, or $-CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}-$;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, -$OC(O)R^{14a}$, -$N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14a}$, and -$N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, and -$OC(O)R^{14a}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is $-L^{1}-R^{19}$;

R^{17b} is $-L^{1b}-R^{19}$;

L^{1} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, $-N(R^{14})-$, -C(O)-, $-N(R^{14})C(O)-$, $-C(O)N(R^{14})-$, -S-, $-S(O)_2-$, -S(O)-, $-S(O)_2N(R^{14})-$, $-S(O)N(R^{14})-$, $-N(R^{14})S(O)-$, $-N(R^{14})S(O)_2-$, $-OCON(R^{14})-$, $-N(R^{14})C(O)O-$, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, $-C(O)N(R^{14})-$, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})-$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$,

-OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -$CH_2$C(O)N($R^{12}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, and -$CH_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -O$R^{12'}$, -S$R^{12'}$, -N($R^{12'}$)(R^{13}), -N=(R^{15}), -C(O)O$R^{12'}$, -OC(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12'}$)($R^{13}$), -C(O)C(O)N($R^{12'}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12'}$)($R^{13}$)-, S(=O)(=NH)N($R^{12'}$)($R^{13}$), -$CH_2$C(O)N($R^{12'}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, -$CH_2$S(O)$_2$N($R^{12'}$)($R^{13}$), –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -$CH_2$C(O)N($R^{12}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, -$CH_2$S(O)$_2$N($R^{12}$)($R^{13}$), –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -O$R^{12'}$, -S$R^{12'}$, -C(O)O$R^{12'}$, -OC(O)N($R^{12'}$)(R^{13}), -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N($R^{12'}$)(R^{13}), -C(O)C(O)N($R^{12'}$)(R^{13}), -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12'}$)($R^{13}$)-, S(=O)(=NH)N($R^{12'}$)($R^{13}$), -$CH_2$C(O)N($R^{12'}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, -$CH_2$S(O)$_2$N($R^{12'}$)($R^{13}$), –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is C(R^3), C(R^3)(R^3), N(R^3), or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -$CH_2$C(O)N($R^{12}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, and -$CH_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}

$_{10}$aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} are each independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, =$C(R^{21b})_2$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{21}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{21}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-}

$_9$heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

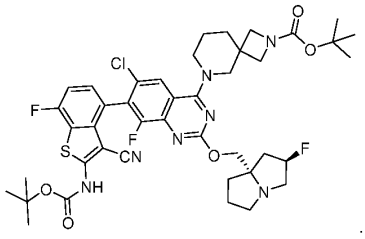
------ indicates a single or double bond such that all valences are satisfied.

[350] In embodiments, R^5 is not

(i) a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; and

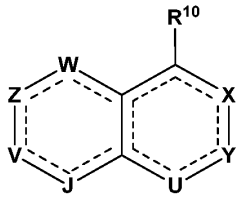
(ii) a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is -$C(O)N(R^{4d})$-;

[351] In embodiments, R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, -CH_2-(6-12 membered heterocycloalkyl), C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-(7-12 membered heteroaryl), 7-12 membered heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, -CH_2-(6-12 membered heterocycloalkyl), C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-(7-12 membered heteroaryl), and 7-12 membered heteroaryl are optionally substituted with one, two, or three R^{20k};

[352] In embodiments, R^{19} is selected from a C_{2-11}heterocycloalkyl and C_{2-12}heteroaryl, wherein the C_{2-11}heterocycloalkyl and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments, the compound is not  .

[353] In embodiments of Formula (D); W is a $C(R^{18})$ or C(O); Z is N, $C(R^{8})$, or $N(R^{8b})$; V is $C(R^{17})$; J is $C(R^{16})$; Y is $C(R^{2})$; U is N; X is N; L^{7} is a bond; s1 is 3 and s2 is 2, s1 is 4 and s2 is 1 or 2, s1 is 5 and s2 is 1 or 2, or s1 is 6 and s2 is 1 or 2; R^{17} is $-L^{1}-R^{19}$; and all other variables are as described herein for Formula (D) or embodiments thereof.

[354] In an aspect is provided a compound of Formula (E), or a pharmaceutically acceptable salt or solvate thereof:



Formula (E); wherein

1. Y is N, $C(R^{2})$, $C(R^{2})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and
   R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}; or
2. Y is N, $C(R^{2''})$, $C(R^{2''})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$; and
   R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl)$-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl)$-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl)$-S(O)_2R^{15}$, $-(C_{1-6}$alkyl)$-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl)$-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

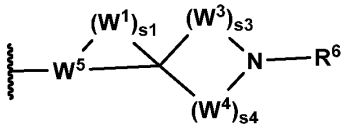
Z is N, $C(R^{8})$, $N(R^{8b})$, $C(R^{8})(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^{7}-R^{7}$;

L^{7} is a bond, -O-, $-N(R^{14})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is  ;

W^1, W^2, W^3, and W^4 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is an integer from 1 to 6;

s3 is an integer from 1 to 3;

s4 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl$)-S(O)_2R^{15}$, $-(C_{1-6}$alkyl$)-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl$)-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is $-L^2-R^5$; wherein R^6 is not capable of forming a covalent bond with the 12th amino acid of a mutant KRAS protein selected from KRAS G12D, KRAS G12C, and KRAS G12S and R^6 is not capable of forming a covalent bond with the 13th amino acid of a mutant KRAS protein selected from KRAS G13D, KRAS G13C, and KRAS G13S;

L^2 is a bond, -O-, $-N(R^{4d})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{4d}$-, $CR^{4c}R^{4c}$, $-OCR^{4c}R^{4c}$-, $-N(R^{4d})CR^{4c}R^{4c}$-, $-C(O)CR^{4c}R^{4c}$-, $-SCR^{4c}R^{4c}$-, $-S(O)_2CR^{4c}R^{4c}$-, $-S(O)CR^{4c}R^{4c}$-, $-P(O)R^{4d}CR^{4c}R^{4c}$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}$, $-CR^{4c}R^{4c}O$-, $-CR^{4c}R^{4c}N(R^{4d})$-, $-CR^{4c}R^{4c}C(O)$-, $-CR^{4c}R^{4c}S$-, $-CR^{4c}R^{4c}S(O)_2$-, $-CR^{4c}R^{4c}S(O)$-, $-CR^{4c}R^{4c}P(O)R^{4d}$-, $-N(R^{4d})C(O)$-, $-N(R^{4d})S(O)_2$-, $-N(R^{4d})S(O)$-, $-N(R^{4d})P(O)R^{4d}$-, $-C(O)N(R^{4d})$-, $-S(O)_2N(R^{4d})$-, $-S(O)N(R^{4d})$-, $-P(O)R^{4d}N(R^{4d})$-, -OC(O)-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{4d}$-, -C(O)O-, $-S(O)_2O$-, -S(O)O-, $-P(O)R^{4d}O$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}$-, $-OCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-SCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-CR^{4c}R^{4c}CR^{4c}R^{4c}O$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)$-, or $-CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}$-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, $-OCH_2C(O)OR^{14}$, $-OC(O)R^{14a}$, $-N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14a}$, and $-N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, and $-CH_2-C_{2-9}$heterocycloalkyl, are optionally

substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, -$OCH_2C(O)OR^{14}$, and -$OC(O)R^{14a}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -$N(R^{14})(R^{14})$, -$C(O)OR^{14}$, -$C(O)N(R^{14})(R^{14})$, -$C(O)C(O)N(R^{14})(R^{14})$, -$OC(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)N(R^{14})(R^{14})$, -$N(R^{14})C(O)OR^{14}$, -$N(R^{14})C(O)R^{14}$, -$N(R^{14})S(O)_2R^{14}$, -$C(O)R^{14a}$, -$S(O)_2R^{14}$, -$S(O)_2N(R^{14})(R^{14})$, and -$OC(O)R^{14a}$;

R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, $C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is -L^1-R^{19};

R^{17b} is -L^{1b}-R^{19};

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, -$N(R^{14})$-, -C(O)-, -$N(R^{14})C(O)$-, -$C(O)N(R^{14})$-, -S-, -$S(O)_2$-, -S(O)-, -$S(O)_2N(R^{14})$-, -$S(O)N(R^{14})$-, -$N(R^{14})S(O)$-, -$N(R^{14})S(O)_2$-, -$OCON(R^{14})$-, -$N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two,

or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, -C(O)N(R^{14})-, C(O)N(R^{1c}), C(R^{1f})(R^{1g})O, C(R^{1f})(R^{1g})N(R^{1c}), and C(R^{1f})(R^{1g}); wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -S(O)$_2R^{15}$, -S(O)$_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, and -CH_2S(O)$_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -S(O)$_2R^{15}$, -S(O)$_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, and -CH_2S(O)$_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -S(O)$_2R^{15}$, -S(O)$_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, and -CH_2S(O)$_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -S(O)$_2R^{15}$, -S(O)$_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, and -CH_2S(O)$_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -N($R^{12'}$)(R^{13}), -N=(R^{15}), -C(O)$OR^{12'}$, -OC(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2R^{15}$, -C(O)R^{12}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N($R^{12'}$)(R^{13}), -C(O)C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)R^{12}, -S(O)$_2R^{15}$, -S(O)$_2$N($R^{12'}$)(R^{13})-, S(=O)(=NH)N($R^{12'}$)(R^{13}), -CH_2C(O)N($R^{12'}$)(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -CH_2S(O)$_2R^{15}$, -CH_2S(O)$_2$N($R^{12'}$)(R^{13}),

–(C_1-C_6alkyl)-R^{12b}, –(C_{2-6}alkenyl)-R^{12b}, –(C_{2-6}alkynyl)-R^{12b}, -(C_{3-10}cycloalkyl)-R^{12b}, -(C_{2-9}heterocycloalkyl)-R^{12b}, -(C_{6-10}aryl)-R^{12b}, or –(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

$R^{2''}$ is -$OR^{12''}$, -$SR^{12'}$, -$N(R^{12'''})(R^{13})$, -N=(R^{15}), -$OC(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, or $S(=O)(=NH)N(R^{12'})(R^{13})$;

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12})(R^{13})$, –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -$C(O)OR^{12'}$, -$OC(O)N(R^{12'})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12'})(R^{13})$, -$C(O)C(O)N(R^{12'})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, -$CH_2C(O)N(R^{12'})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12'})(R^{13})$, –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -C(O)OR^{12}, -OC(O)$N(R^{12})(R^{13})$, -$N(R^{14})$C(O)$N(R^{12})(R^{13})$, -$N(R^{14})$C(O)OR^{15}, -$N(R^{14})S(O)_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)$N(R^{12})(R^{13})$, -C(O)C(O)$N(R^{12})(R^{13})$, -$N(R^{14})$C(O)R^{15}, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -CH_2C(O)$N(R^{12})(R^{13})$, -$CH_2N(R^{14})$C(O)R^{15}, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -C(O)OR^{12}, -OC(O)$N(R^{12})(R^{13})$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)$N(R^{12})(R^{13})$, -C(O)C(O)$N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -CH_2C(O)$N(R^{12})(R^{13})$, -$CH_2N(R^{14})$C(O)R^{15}, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} are each independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, =$C(R^{21b})_2$, -C(O)OR^{22}, -C(O)$N(R^{22})(R^{23})$, -C(O)C(O)$N(R^{22})(R^{23})$, -OC(O)$N(R^{22})(R^{23})$, -

$N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{21}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{21}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-CH_2-C_{6-10}$aryl, $-CH_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

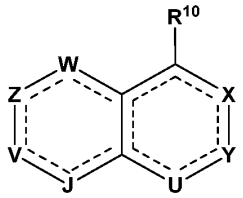
each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

------ indicates a single or double bond such that all valences are satisfied.

[355] In embodiments of Formula (E), Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of Formula (E), Y is N, $C(R^{2''})$, $C(R^{2''})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$; and R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments, R^5 is not a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; and/or a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is $-C(O)N(R^{4d})$-. In embodiments, R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2-$(6-12 membered heterocycloalkyl), C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-$(7-12 membered heteroaryl), 7-12 membered heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, -

$OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, 6-12 membered heterocycloalkyl, $-CH_2-$(6-12 membered heterocycloalkyl), C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-$(7-12 membered heteroaryl), and 7-12 membered heteroaryl are optionally substituted with one, two, or three R^{20k}; In embodiments, $R^{2''}$ is $-OR^{12''}$, $-SR^{12'}$, $-N(R^{12'''})(R^{13})$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, or $S(=O)(=NH)N(R^{12'})(R^{13})$; and each $R^{12'''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl, wherein C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2-C_{2-9}$heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2-C_{6-10}$aryl, $-C(R^{12c})_2-C_{1-9}$heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d}.

[356] In an aspect is provided a compound of Formula (F), or a pharmaceutically acceptable salt or solvate thereof:



Formula (F); wherein

1. Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and
   R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}; or
2. Y is N, $C(R^{2''})$, $C(R^{2''})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$; and
   R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl$)-S(O)_2R^{15}$, $-(C_{1-6}$alkyl$)-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl$)-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

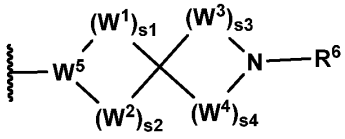
Z is N, $C(R^8)$, $N(R^{8b})$, $C(R^8)(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^7-R^7$;

L^7 is a bond, -O-, $-N(R^{14})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is  ;

W^1, W^2, W^3, and W^4 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is an integer from 1 to 6;

s2 is an integer from 1 to 3;

s3 is an integer from 1 to 3;

s4 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is $-L^2-R^5$; wherein R^6 is not capable of forming a covalent bond with the 12th amino acid of a mutant KRAS protein selected from KRAS G12D, KRAS G12C, and KRAS G12S and R^6 is not capable of forming a covalent bond with the 13th amino acid of a mutant KRAS protein selected from KRAS G13D, KRAS G13C, and KRAS G13S;

L^2 is a -C(O)-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, $-OCH_2C(O)OR^{14}$, $-OC(O)R^{14a}$, $-N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14a}$, and $-N(R^{14})S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, and $-CH_2-C_{2-9}$heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{14}$, $-SR^{14}$, $-N(R^{14})(R^{14})$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14}$, $-N(R^{14})S(O)_2R^{14}$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, and $-OC(O)R^{14a}$;

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2-C_{2-9}$heterocycloalkyl, $-OR^{14}$, $-SR^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, -

$C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, $-OCH_2C(O)OR^{14}$, and $-OC(O)R^{14a}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2-C_{3-10}$cycloalkyl, C_{2-9}heterocycloalkyl, and $-CH_2-C_{2-9}$heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{14}$, $-SR^{14}$, $-N(R^{14})(R^{14})$, $-C(O)OR^{14}$, $-C(O)N(R^{14})(R^{14})$, $-C(O)C(O)N(R^{14})(R^{14})$, $-OC(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)N(R^{14})(R^{14})$, $-N(R^{14})C(O)OR^{14}$, $-N(R^{14})C(O)R^{14}$, $-N(R^{14})S(O)_2R^{14}$, $-C(O)R^{14a}$, $-S(O)_2R^{14}$, $-S(O)_2N(R^{14})(R^{14})$, and $-OC(O)R^{14a}$;

R^5 is C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, C_{6-12}aryl, or C_{1-11}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, C_{6-12}aryl, or C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is $-L^1-R^{19}$;

R^{17b} is $-L^{1b}-R^{19}$;

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, $-N(R^{14})$-, -C(O)-, $-N(R^{14})C(O)$-, $-C(O)N(R^{14})$-, -S-, $-S(O)_2$-, -S(O)-, $-S(O)_2N(R^{14})$-, $-S(O)N(R^{14})$-, $-N(R^{14})S(O)$-, $-N(R^{14})S(O)_2$-, -OCON(R^{14})-, $-N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, $-C(O)N(R^{14})$-, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl,

and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$, $-N=(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

$R^{2''}$ is $-OR^{12''}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$,), $-N=(R^{15})$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, or $S(=O)(=NH)N(R^{12'})(R^{13})$;

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1-9}\text{heteroaryl})\text{-}R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-}

$_{6}$alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -$C(O)OR^{12'}$, -$OC(O)N(R^{12'})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12'})(R^{13})$, -$C(O)C(O)N(R^{12'})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, -$CH_2C(O)N(R^{12'})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12'})(R^{13})$, –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} are each independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, C_{1-9}heteroaryl, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $=C(R^{21b})_2$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{21}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{21}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

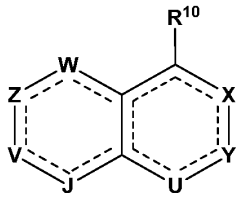
each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

------ indicates a single or double bond such that all valences are satisfied.

[357] In embodiments of Formula (F), Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of Formula (F), Y is N, $C(R^{2''})$, $C(R^{2''})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$; and R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments, R^5 is not a 3-5 membered heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, or three R^{20k}; and/or a 5-6 membered heteroaryl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}; wherein R^5 is (a) bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-, or (b) bonded through an R^5 ring carbon to the $N(R^{4d})$ of L^2 when L^2 is $-C(O)N(R^{4d})$-. In embodiments, R^5 is C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, C_{6-12}aryl, or 7-12 membered heteroaryl, wherein the C_{3-12}cycloalkyl, 6-12 membered heterocycloalkyl, C_{6-12}aryl, or 7-12 membered heteroaryl are optionally substituted with one, two, or three R^{20k};

[358] In an aspect is provided a compound of Formula (G), or a pharmaceutically acceptable salt or solvate thereof:



Formula (G);

wherein

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

Z is N, $C(R^8)$, $N(R^{8b})$, $C(R^8)(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

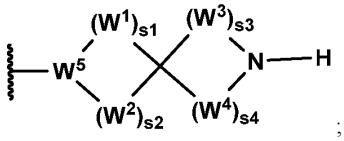
V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O)

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^7-R^7$;

L^7 is a bond, -O-, $-N(R^{14})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is  ;

W^1 and W^2 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^3 and W^4 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, S, O, and S(O);

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is an integer from 3 to 6;

s2 is an integer from 1 to 2; provided when s1 is 3, s2 is not 1;

s3 is an integer from 1 to 3;

s4 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $=C(R^{21b})_2$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl$)-S(O)_2R^{15}$, $-(C_{1-6}$alkyl$)-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl$)-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is $-L^1-R^{19}$;

R^{17b} is $-L^{1b}-R^{19}$;

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, $-N(R^{14})$-, -C(O)-, $-N(R^{14})C(O)$-, -

$C(O)N(R^{14})$-, -S-, $-S(O)_2$-, -S(O)-, $-S(O)_2N(R^{14})$-, $-S(O)N(R^{14})$-, $-N(R^{14})S(O)$-, $-N(R^{14})S(O)_2$-, $-OCON(R^{14})$-, $-N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, $-C(O)N(R^{14})$-, $C(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-}

$_{10}$aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$, $-N=(R^{15})$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1$-C_6alkyl)-R^{12b}, $-(C_{2-6}$alkenyl)-R^{12b}, $-(C_{2-6}$alkynyl)-R^{12b}, $-(C_{3-10}$cycloalkyl)-R^{12b}, $-(C_{2-9}$heterocycloalkyl)-R^{12b}, $-(C_{6-10}$aryl)-R^{12b}, or $-(C_{1-9}$heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-(C_1$-C_6alkyl)-R^{12b}, $-(C_{2-6}$alkenyl)-R^{12b}, $-(C_{2-6}$alkynyl)-R^{12b}, $-(C_{3-10}$cycloalkyl)-R^{12b}, $-(C_{2-9}$heterocycloalkyl)-R^{12b}, $-(C_{6-10}$aryl)-R^{12b}, or $-(C_{1-9}$heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1$-C_6alkyl)-R^{12b}, $-(C_{2-6}$alkenyl)-R^{12b}, $-(C_{2-6}$alkynyl)-R^{12b}, $-(C_{3-10}$cycloalkyl)-R^{12b}, $-(C_{2-9}$heterocycloalkyl)-R^{12b}, $-(C_{6-10}$aryl)-R^{12b}, or $-(C_{1-9}$heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, $-CH_2$-C_{1-9}heteroaryl,

and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, and R^{20m} are each independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, $=C(R^{21b})_2$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{21}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{21}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -

$S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

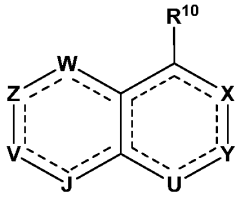
each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

------ indicates a single or double bond such that all valences are satisfied.

[359] In embodiments, W^3 and W^4 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, S, O, and S(O); s1 is an integer from 3 to 6; s2 is an integer from 1 to 2; provided when s1 is 3, s2 is not 1.

[360] In an aspect is provided a compound of Formula (H), or a pharmaceutically acceptable salt or solvate thereof:



Formula (H); wherein

1. Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and

   R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}; or

2. Y is N, $C(R^{2'''})$, $C(R^{2'''})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and

   R^{19} is selected from a C_{5-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{7-12}aryl, and C_{2-12}heteroaryl, wherein the C_{5-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{7-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

W is a N, $C(R^{18})$, $N(R^{18b})$, $C(R^{18})(R^{18a})$, C(O), S(O), or $S(O)_2$;

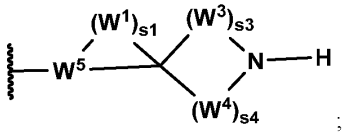
Z is N, $C(R^8)$, $N(R^{8b})$, $C(R^8)(R^{8a})$, C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^7-R^7$;

L^7 is a bond, -O-, $-N(R^{14})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is  ;

W^1, W^2, W^3, and W^4 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is an integer from 1 to 6;

s3 is an integer from 1 to 3;

s4 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is $-L^1-R^{19}$;

R^{17b} is $-L^{1b}-R^{19}$;

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, $-N(R^{14})$-, -C(O)-, $-N(R^{14})C(O)$-, $-C(O)N(R^{14})$-, -S-, $-S(O)_2$-, -S(O)-, $-S(O)_2N(R^{14})$-, $-S(O)N(R^{14})$-, $-N(R^{14})S(O)$-, $-N(R^{14})S(O)_2$-, $-OCON(R^{14})$-, $-N(R^{14})C(O)O$-, $N(R^{1e})$, $C(O)N(R^{1c})$, $S(O)_2N(R^{1c})$, $S(O)N(R^{1c})$, $C(R^{1f})(R^{1g})O$, $C(R^{1f})(R^{1g})N(R^{1c})$, and $C(R^{1f})(R^{1g})$; wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, -C(O)N(R^{14})-, C(O)N(R^{1c}), C(R^{1f})(R^{1g})O, C(R^{1f})(R^{1g})N(R^{1c}), and C(R^{1f})(R^{1g}); wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -CH$_2$C(O)N($R^{12}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, and -CH$_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -O$R^{12'}$, -S$R^{12'}$, -N($R^{12'}$)(R^{13}), -C(O)O$R^{12'}$, -OC(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12'}$)($R^{13}$), -C(O)C(O)N($R^{12'}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12'}$)($R^{13}$)-, S(=O)(=NH)N($R^{12'}$)($R^{13}$), -CH$_2$C(O)N($R^{12'}$)($R^{13}$), -CH$_2$N($R^{14}$)C(O)$R^{15}$, -CH$_2$S(O)$_2$$R^{15}$, -CH$_2$S(O)$_2$N($R^{12'}$)($R^{13}$), –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –

(C_{1-9}heteroaryl)-R^{12b}, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

$R^{2'''}$ is halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -$N(R^{12'})(R^{13})$, -$C(O)OR^{12'}$, -$OC(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12'})(R^{13})$, -$C(O)C(O)N(R^{12'})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, S(=O)(=NH)$N(R^{12'})(R^{13})$, -$CH_2C(O)N(R^{12'})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12'})(R^{13})$, –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, or -($C_{6-10}$aryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and C_{6-10}aryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12})(R^{13})$, –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -$OR^{12'}$, -$SR^{12'}$, -$C(O)OR^{12'}$, -$OC(O)N(R^{12'})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12'})(R^{13})$, -$C(O)C(O)N(R^{12'})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12'})(R^{13})$-, S(=O)(=NH)$N(R^{12'})(R^{13})$, -$CH_2C(O)N(R^{12'})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, -$CH_2S(O)_2N(R^{12'})(R^{13})$, –($C_1$-$C_6$alkyl)-$R^{12b}$, –($C_{2-6}$alkenyl)-$R^{12b}$, –($C_{2-6}$alkynyl)-$R^{12b}$, -($C_{3-10}$cycloalkyl)-$R^{12b}$, -($C_{2-9}$heterocycloalkyl)-$R^{12b}$, -($C_{6-10}$aryl)-$R^{12b}$, or –($C_{1-9}$heteroaryl)-$R^{12b}$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl,

and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, and R^{20m} are each independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl; and

------ indicates a single or double bond such that all valences are satisfied.

[361] In embodiments of Formula (H), Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and R^{19} is selected from a bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the bicyclic C_{5-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of Formula (H), Y is N, $C(R^{2'''})$, $C(R^{2'''})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O); and R^{19} is selected from a C_{5-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{7-12}aryl, and C_{2-12}heteroaryl, wherein the C_{5-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{7-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}.

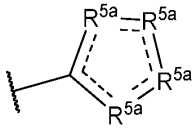
[362] In an aspect is provided a compound wherein V and J are each independently selected from C(O), $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$; X is C(O), $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N; and all other variables are as described for a compound of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), A, B, C, D, E, F, G, and H, or embodiments of any of the preceding formulae, a pharmaceutically acceptable salt, or solvate thereof; ------ indicates a single or double bond such that all valences are satisfied; and

[363] The individual embodiments herein below, or combinations thereof, are applicable to compounds described herein (e.g., Formula A, B, C, D, E, F, G, and H), or a pharmaceutically acceptable salt or solvate thereof.

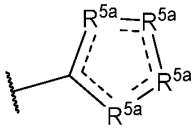
[364] In embodiments of the formulae above, Y is N, $C(R^{2''})$, $C(R^{2''})(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$; and R^{19} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}.

[365] In embodiments of the formulae above, Y is $C(R^{2''})$; $R^{2''}$ is $-OR^{12''}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, or $S(=O)(=NH)N(R^{12'})(R^{13})$; and each $R^{12''}$ is independently selected from C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2$-C_{6-10}aryl, $-C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-C(R^{12c})_2$-C_{6-10}aryl, $-C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, Y is $C(R^{2''})(R^{2c})$; $R^{2''}$ is $-OR^{12''}$, $-SR^{12'}$, $-N(R^{12'})(R^{13})$, $-OC(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, or $S(=O)(=NH)N(R^{12'})(R^{13})$; and each $R^{12''}$ is independently selected from C_{2-6}alkyl, C_{2-6}alkenyl,

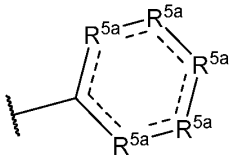
C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -C(R^{12c})$_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -C(R^{12c})$_2$-C_{6-10}aryl, -C(R^{12c})$_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d}.

[366] In embodiments of the formulae above, L^2 is -C(O)-; and R^5 is a C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, or C_{1-11}heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, L^2 is -C(O)-; and R^5 is a C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, C_{6-12}aryl, or C_{1-11}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, C_{6-12}aryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, L^2 is a bond, -C(O)NH-, -NHC(O)-, or -C(O)-; L^2 is bonded to a carbon atom of R^5; and R^5 is selected from -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, C_{6-12}aryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, C_{6-12}aryl, and C_{1-11}heteroaryl, are optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, L^2 is -C(O)-; L^2 is bonded to a carbon atom of R^5; and R^5 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, C_{6-12}aryl, and C_{1-11}heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, C_{6-12}aryl, and C_{1-11}heteroaryl, are optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, L^2 is -C(O)-; L^2 is bonded to a carbon atom of R^5; and R^5 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and 5-6 membered heteroaryl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and 5-6 membered heteroaryl are optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, L^2 is -C(O)-; R^5 is a heteroaryl having the formula: 

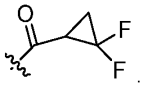
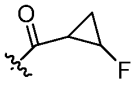
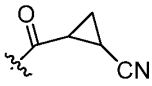
; R^{5a} is independently O, S, CH, C(R^{20k}), N, NH, or N(R^{20k}); R^5 comprises 0-3 independent R^{20k}; and 0-4 R^{5a} are independently N, NH, or N(R^{20k}). In embodiments of the formulae above, L^2 is -C(O)-; and R^5 is a heteroaryl having the formula:



; R^{5a} is independently CH, C(R^{20k}), N, NH, or N(R^{20k}); R^5 comprises 0-3 independent R^{20k}; and 0-4 R^{5a} are independently N, NH, or N(R^{20k}). In embodiments of the formulae above, L^2 is -C(O)-; R^5 is



; R^{5a} is independently CH, C(R^{20k}), CH(R^{20k}), CH_2, C(R^{20k})$_2$, N, NH, or N(R^{20k}); R^5 comprises 0-3 independent R^{20k}; and 0-4 R^{5a} are independently N, NH, or N(R^{20k}). In embodiments of the formulae above, L^2 is -C(O)-; and R^5 is C_{2-6}alkenyl, wherein the C_{2-6}alkenyl is optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, L^2 is -C(O)-; and R^5 is C_{2-6}alkynyl, wherein the C_{2-6}alkynyl is optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, L^2 is -C(O)-; and R^5 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, L^2 is -C(O)-; and R^5 is a C_{3-12}cycloalkyl optionally substituted with one, two or three R^{20k}. In embodiments of

the formulae above, L^2 is -C(O)-; and R^5 is a cyclopropyl optionally substituted with one, two or three R^{20k} selected from halogen and CN. In embodiments of the formulae above, R^6 is  . In embodiments of the formulae above, R^6 is  . In embodiments of the formulae above, R^6 is  . In embodiments of the formulae above, R^6 is .

[367] In embodiments of the formulae above, R^6 is not capable of forming a covalent bond with the 12th amino acid of a mutant KRAS protein selected from KRAS G12D, KRAS G12C, and KRAS G12S. In embodiments of the formulae above, R^6 is not capable of forming a covalent bond with the 12th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is not capable of forming a covalent bond with the 13th amino acid of a mutant KRAS protein selected from KRAS G13D, KRAS G13C, and KRAS G13S. In embodiments of the formulae above, R^6 is not capable of forming a covalent bond with the 13th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is not capable of forming a covalent bond with a KRAS amino acid. In embodiments of the formulae above, R^6 is not capable of forming a covalent bond with a Ras amino acid sidechain.

[368] In embodiments of the formulae above, W^1 and W^3 are independently selected from NH, CH_2, C(O), S, O, S(O), and $S(O)_2$.

[369] In embodiments of the formulae above, W^1 and W^3 are independently CH_2.

[370] In embodiments of the formulae above, W^2 is independently selected from a bond, NH, CH_2, C(O), S, O, S(O), and $S(O)_2$.

[371] In embodiments of the formulae above, W^1 is $N(R^1)$. In embodiments of the formulae above, W^1 is $N(R^4)$. In embodiments of the formulae above, W^1 is $C(R^1)(R^1)$. In embodiments of the formulae above, W^1 is $C(R^1)(R^4)$. In embodiments of the formulae above, W^1 is $C(R^4)(R^4)$. In embodiments of the formulae above, W^1 is C(O). In embodiments of the formulae above, W^1 is S. In embodiments of the formulae above, W^1 is O. In embodiments of the formulae above, W^1 is S(O). In embodiments of the formulae above, W^1 is $S(O)_2$. In embodiments of the formulae above, W^1 is NH. In embodiments of the formulae above, W^1 is CH_2.

[372] In embodiments of the formulae above, W^2 is $N(R^1)$. In embodiments of the formulae above, W^2 is $N(R^4)$. In embodiments of the formulae above, W^2 is $C(R^1)(R^1)$. In embodiments of the formulae above, W^2 is $C(R^1)(R^4)$. In embodiments of the formulae above, W^2 is $C(R^4)(R^4)$. In embodiments of the formulae above, W^2 is C(O). In embodiments of the formulae above, W^2 is S. In embodiments of the formulae above, W^2 is O. In embodiments of the formulae above, W^2 is S(O). In embodiments of the formulae above, W^2 is $S(O)_2$. In embodiments of the formulae above, W^2 is NH. In embodiments of the formulae above, W^2 is CH_2.

[373] In embodiments of the formulae above, W^3 is $N(R^1)$. In embodiments of the formulae above, W^3 is $N(R^4)$. In embodiments of the formulae above, W^3 is $C(R^1)(R^1)$. In embodiments of the formulae above, W^3 is $C(R^1)(R^4)$. In embodiments of the formulae above, W^3 is $C(R^4)(R^4)$. In embodiments of the formulae above, W^3 is C(O). In embodiments of the formulae above, W^3 is S. In embodiments of the formulae above, W^3 is O. In embodiments of the formulae above, W^3 is S(O). In embodiments of the formulae above, W^3 is $S(O)_2$. In embodiments of the formulae above, W^3 is NH. In embodiments of the formulae above, W^3 is CH_2.

[374] In embodiments of the formulae above, W^4 is $N(R^1)$. In embodiments of the formulae above, W^4 is $N(R^4)$. In embodiments of the formulae above, W^4 is $C(R^1)(R^1)$. In embodiments of the formulae above, W^4 is $C(R^1)(R^4)$. In

embodiments of the formulae above, W^4 is $C(R^4)(R^4)$. In embodiments of the formulae above, W^4 is C(O). In embodiments of the formulae above, W^4 is S. In embodiments of the formulae above, W^4 is O. In embodiments of the formulae above, W^4 is S(O). In embodiments of the formulae above, W^4 is $S(O)_2$. In embodiments of the formulae above, W^4 is NH. In embodiments of the formulae above, W^4 is CH_2. In embodiments of the formulae above, W^5 is N. In embodiments of the formulae above, W^5 is $C(R^1)$. In embodiments of the formulae above, W^5 is $C(R^4)$. In embodiments of the formulae above, W^5 is CH.

[375] In embodiments of the formulae above, s1 is 1. In embodiments of the formulae above, s1 is 2. In embodiments of the formulae above, s1 is 3. In embodiments of the formulae above, s1 is 4. In embodiments of the formulae above, s1 is 5. In embodiments of the formulae above, s1 is 6. In embodiments of the formulae above, s2 is 1. In embodiments of the formulae above, s2 is 2. In embodiments of the formulae above of Formula (III), s2 is 3. In embodiments of the formulae above, s3 is 1. In embodiments of the formulae above, s3 is 2. In embodiments of the formulae above, s3 is 3. In embodiments of the formulae above, s4 is 1. In embodiments of the formulae above, s4 is 2. In embodiments of the formulae above, s4 is 3.

[376] In embodiments of the formulae above, R^5 is not a 5 or 6 membered partially unsaturated heterocycloalkyl or a 5 or 6 membered heteroaryl optionally substituted with one, two or three R^{20k}, wherein the partially unsaturated 5 or 6 membered heterocycloalkyl or 5 or 6 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and is bonded to L^2 through a ring nitrogen.

[377] In embodiments of the formulae above, R^5 is not a 5-10 membered spirocyclic bicyclic heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, three, or four R^{20k};

[378] In embodiments of the formulae above, R^5 is not a 5-6 membered partially unsaturated heterocycloalkyl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}, wherein R^5 is bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-.

[379] In embodiments of the formulae above, R^5 is not a 5-10 membered spirocyclic bicyclic heterocycloalkyl comprising at least one nitrogen ring atom optionally substituted with one, two, three, or four R^{20k}; and a 5-6 membered partially unsaturated heterocycloalkyl comprising one, two, or three ring nitrogen atoms that is optionally substituted with one, two or three R^{20k}, wherein R^5 is bonded through an R^5 ring nitrogen to L^2 when L^2 is -C(O)-.

[380] In embodiments of the formulae above of the compound, R^{12} is independently $C_{1\text{-}6}$alkyl. In embodiments of the formulae above, R^{12} is independently $C_{2\text{-}6}$alkenyl. In embodiments of the formulae above, R^{12} is independently $C_{2\text{-}6}$alkynyl. In embodiments of the formulae above, R^{12} is independently $C_{3\text{-}10}$cycloalkyl. In embodiments of the formulae above, R^{12} is independently $-CH_2$-$C_{3\text{-}10}$cycloalkyl. In embodiments of the formulae above, R^{12} is independently $C_{2\text{-}9}$heterocycloalkyl. In embodiments of the formulae above, R^{12} is independently $-CH_2$-$C_{2\text{-}9}$heterocycloalkyl. In embodiments of the formulae above, R^{12} is independently $C_{6\text{-}10}$aryl. In embodiments of the formulae above, R^{12} is independently $-CH_2$-$C_{6\text{-}10}$aryl. In embodiments of the formulae above, R^{12} is independently $-CH_2$-$C_{1\text{-}9}$heteroaryl. In embodiments of the formulae above, R^{12} is independently $C_{1\text{-}9}$heteroaryl

[381] In embodiments of the formulae above of the compound, R^{12} is independently $C_{1\text{-}6}$alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently $C_{2\text{-}6}$alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently $C_{2\text{-}6}$alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently $C_{3\text{-}10}$cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently $-CH_2$-$C_{3\text{-}10}$cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently $C_{2\text{-}9}$heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of

the formulae above, R^{12} is independently -CH_2-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently C_{1-9}heteroaryl. In additional embodiments, R^{12} is independently hydrogen.

[382] In embodiments of the formulae above, R^{12} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently (spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}.

[383] In embodiments of the formulae above of the compound, R^{12} is independently methylene optionally substituted with one or two R^{20d}. In embodiments of the formulae above of the compound, R^{12} is independently methylene. In embodiments of the formulae above of the compound, R^{12} is independently ethylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above of the compound, R^{12} is independently ethylene. In embodiments of the formulae above of the compound, R^{12} is independently propylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above of the compound, R^{12} is independently propylene. In embodiments of the formulae above, R^{12} is independently -CH_2-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12} is independently -CH_2-(spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}.

[384] In embodiments of the formulae above, $R^{12'}$ is independently hydrogen. In embodiments of the formulae above, $R^{12'}$ is independently C_{1-6}alkyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-6}alkenyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-6}alkynyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12'}$ is independently C_{6-10}aryl. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl. In embodiments of the formulae above, $R^{12'}$ is independently and C_{1-9}heteroaryl.

[385] In embodiments of the formulae above, $R^{12'}$ is independently C_{1-6}alkyl optionally substituted with one, two, or

three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'}$ is independently C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}.

[386] In embodiments of the formulae above, $R^{12''}$ is independently C_{1-6}alkyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkenyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkynyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12''}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12''}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12''}$ is independently C_{6-10}aryl. In embodiments of the formulae above, $R^{12''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl. In embodiments of the formulae above, $R^{12''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl. In embodiments of the formulae above, $R^{12''}$ is independently and C_{1-9}heteroaryl.

[387] In embodiments of the formulae above, $R^{12''}$ is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''}$ is independently C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}.

[388] In embodiments of the formulae above, $R^{12'''}$ is independently hydrogen. In embodiments of the formulae above, $R^{12'''}$ is independently C_{1-6}alkyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{3-6}alkyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkenyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkynyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$- C_{4-10}cycloalkyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-}

$_9$heterocycloalkyl. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12'''}$ is independently C_{6-10}aryl. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl. In embodiments of the formulae above, $R^{12'''}$ is independently and C_{1-9}heteroaryl.

[389] In embodiments of the formulae above, $R^{12'''}$ is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{3-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{4-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12'''}$ is independently C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}.

[390] In embodiments of the formulae above, $R^{12''''}$ is independently hydrogen. In embodiments of the formulae above, $R^{12''''}$ is independently C_{1-6}alkyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{3-6}alkyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-6}alkenyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-6}alkynyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{12''''}$ is independently C_{6-10}aryl. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl. In embodiments of the formulae above, $R^{12''''}$ is independently and C_{1-9}heteroaryl.

[391] In embodiments of the formulae above, $R^{12''''}$ is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{3-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently -$C(R^{12c})_2$-C_{1-9}heteroaryl

optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{12''''}$ is independently C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}.

[392] In embodiments of the formulae above, R^{12b} is independently C_{1-6}alkyl. In embodiments of the formulae above, R^{12b} is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently methylene optionally substituted with one or two R^{20d}. In embodiments of the formulae above, R^{12b} is independently methylene. In embodiments of the formulae above, R^{12b} is independently ethylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently ethylene. In embodiments of the formulae above, R^{12b} is independently propylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently propylene. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-(spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}.

[393] In embodiments of the formulae above, R^{12b} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently (spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}.

[394] In embodiments of the formulae above, R^{12b} is independently C_{2-6}alkenyl. In embodiments of the formulae above, R^{12b} is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^{12b} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{12b} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{12b} is independently C_{6-10}aryl. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{6-10}aryl. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{1-9}heteroaryl. In embodiments of the formulae above, R^{12b} is independently C_{1-9}heteroaryl

[395] In embodiments of the formulae above, R^{12b} is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the

formulae above, R^{12b} is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently -CH_2-C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{12b} is independently C_{1-9}heteroaryl. In additional embodiments, R^{12b} is independently hydrogen.

[396] In embodiments of the formulae above, $R^{2'''}$ is independently -$OR^{12'''}$. In embodiments of the formulae above, $R^{2'''}$ is independently -$SR^{12'}$. In embodiments of the formulae above, $R^{2'''}$ is independently -$N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is independently -$OC(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is independently -$N(R^{14})C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is independently -$N(R^{14})C(O)OR^{15}$. In embodiments of the formulae above, $R^{2'''}$ is independently -$N(R^{14})S(O)_2R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is independently -$S(O)R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is independently -$OC(O)R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is independently -$N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is independently -$S(O)_2R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is independently -$S(O)_2N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is independently $S(=O)(=NH)N(R^{12'})(R^{13})$.

[397] In embodiments of the formulae above, $R^{2'''}$ is independently C_{1-6}alkyl. In embodiments of the formulae above, $R^{2'''}$ is independently C_{2-6}alkenyl. In embodiments of the formulae above, $R^{2'''}$ is independently C_{2-6}alkynyl. In embodiments of the formulae above, $R^{2'''}$ is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, $R^{2'''}$ is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, $R^{2'''}$ is independently C_{6-10}aryl. In embodiments of the formulae above, $R^{2'''}$ is independently and C_{1-9}heteroaryl.

[398] In embodiments of the formulae above, $R^{2'''}$ is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently methylene optionally substituted with one or two R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently methylene. In embodiments of the formulae above, $R^{2'''}$ is independently ethylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently ethylene. In embodiments of the formulae above, $R^{2'''}$ is independently propylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently propylene. In embodiments of the formulae above, $R^{2'''}$ is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}.

[399] In additional embodiments, $R^{2'''}$ is independently halogen. In additional embodiments, $R^{2'''}$ is independently -CN. In embodiments of the formulae above, $R^{2'''}$ is -$OR^{12'}$. In embodiments of the formulae above, $R^{2'''}$ is -$SR^{12'}$. In embodiments of the formulae above, $R^{2'''}$ is -$N(R^{12''})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is -$N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is -$C(O)OR^{12'}$. In embodiments of the formulae above, $R^{2'''}$ is -$OC(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is -$N(R^{14})C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is -$N(R^{14})C(O)OR^{15}$. In embodiments of the formulae above, $R^{2'''}$ is -$N(R^{14})S(O)_2R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is -$C(O)R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is -$S(O)R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is -$OC(O)R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is -$C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is -$C(O)C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is -$N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is -$S(O)_2R^{15}$. In embodiments of

the formulae above, $R^{2'''}$ is $-S(O)_2N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is $S(=O)(=NH)N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is $-CH_2C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, $R^{2'''}$ is $-CH_2N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is $-CH_2S(O)_2R^{15}$. In embodiments of the formulae above, $R^{2'''}$ is $-CH_2S(O)_2N(R^{12'})(R^{13})$.

[400] In embodiments of the formulae above, $R^{2'''}$ is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently (monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently (monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently (spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently (spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently (fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently (spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$. In embodiments of the formulae above, $R^{2'''}$ is independently $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$ optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{2-6}\text{alkenyl})\text{-}R^{12b}$ optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{2-6}\text{alkynyl})\text{-}R^{12b}$ optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{3-10}\text{cycloalkyl})\text{-}R^{12b}$ optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{2-9}\text{heterocycloalkyl})\text{-}R^{12b}$ optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, $R^{2'''}$ is independently, $-(C_{6-10}\text{aryl})\text{-}R^{12b}$ optionally substituted with one, two, or three R^{20d}.

[401] In embodiments of the formulae above, R^{2c} is independently C_{1-6}alkyl. In embodiments of the formulae above, R^{2c} is independently C_{2-6}alkenyl. In embodiments of the formulae above, R^{2c} is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^{2c} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{2c} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{2c} is independently C_{6-10}aryl. In embodiments of the formulae above, R^{2c} is independently C_{1-9}heteroaryl.

[402] In embodiments of the formulae above, R^{2c} is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently methylene optionally substituted with one or two R^{20d}. In embodiments of the formulae above, R^{2c} is independently methylene. In embodiments of the formulae above, R^{2c} is independently ethylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently ethylene. In embodiments of the formulae above, R^{2c} is independently propylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently propylene. In embodiments of the formulae above, R^{2c} is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is

independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently and C_{1-9}heteroaryl. In additional embodiments, R^{2c} is independently hydrogen.

[403] In additional embodiments, R^{2c} is independently halogen. In additional embodiments, R^{2c} is independently -CN. In embodiments of the formulae above, R^{2c} is $-OR^{12}$. In embodiments of the formulae above, R^{2c} is $-SR^{12}$. In embodiments of the formulae above, R^{2c} is $-N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{2c} is $-C(O)OR^{12}$. In embodiments of the formulae above, R^{2c} is $-OC(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{2c} is $-N(R^{14})C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{2c} is $-N(R^{14})C(O)OR^{15}$. In embodiments of the formulae above, R^{2c} is $-N(R^{14})S(O)_2R^{15}$. In embodiments of the formulae above, R^{2c} is $-C(O)R^{15}$. In embodiments of the formulae above, R^{2c} is $-S(O)R^{15}$. In embodiments of the formulae above, R^{2c} is $-OC(O)R^{15}$. In embodiments of the formulae above, R^{2c} is $-C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{2c} is $-C(O)C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{2c} is $-N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^{2c} is $-S(O)_2R^{15}$. In embodiments of the formulae above, R^{2c} is $-S(O)_2N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{2c} is $S(=O)(=NH)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{2c} is $-CH_2C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{2c} is $-CH_2N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^{2c} is $-CH_2S(O)_2R^{15}$. In embodiments of the formulae above, R^{2c} is $-CH_2S(O)_2N(R^{12})(R^{13})$.

[404] In embodiments of the formulae above, R^{2c} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently (monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently (monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently (spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently (spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently (fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently (spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently $-(C_1$-C_6alkyl)-R^{12b}. In embodiments of the formulae above, R^{2c} is independently, $-(C_{2-6}$alkenyl)-R^{12b}. In embodiments of the formulae above, R^{2c} is independently, $-(C_{2-6}$alkynyl)-R^{12b}. In embodiments of the formulae above, R^{2c} is independently, -(C_{3-10}cycloalkyl)-R^{12b}. In embodiments of the formulae above, R^{2c} is independently, -(C_{2-9}heterocycloalkyl)-R^{12b}. In embodiments of the formulae above, R^{2c} is independently, -(C_{6-10}aryl)-R^{12b}. In embodiments of the formulae above, R^{2c} is independently, or $-(C_{1-9}$heteroaryl)-R^{12b}. In embodiments of the formulae above, R^{2c} is independently $-(C_1$-C_6alkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently, $-(C_{2-6}$alkenyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently, $-(C_{2-6}$alkynyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently, -(C_{3-10}cycloalkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently, -(C_{2-9}heterocycloalkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently, -(C_{6-10}aryl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2c} is independently, $-(C_{1-9}$heteroaryl)-R^{12b} optionally substituted with one, two, or three R^{20d}.

[405] In additional embodiments, R^{2b} is independently -CN. In embodiments of the formulae above, R^{2b} is $-OR^{12'}$. In embodiments of the formulae above, R^{2b} is $-SR^{12'}$. In embodiments of the formulae above, R^{2b} is $-C(O)OR^{12'}$. In embodiments of the formulae above, R^{2b} is $-OC(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-C(O)R^{15}$. In embodiments of the formulae above, R^{2b} is $-S(O)R^{15}$. In embodiments of the formulae above, R^{2b} is -

$OC(O)R^{15}$. In embodiments of the formulae above, R^{2b} is $-C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-C(O)C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-S(O)_2R^{15}$. In embodiments of the formulae above, R^2 is $-S(O)_2N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $S(=O)(=NH)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-CH_2C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^{2b} is $-CH_2N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^{2b} is $-CH_2S(O)_2R^{15}$. In embodiments of the formulae above, R^{2b} is $-CH_2S(O)_2N(R^{12'})(R^{13})$.

[406] In embodiments of the formulae above, R^{2b} is independently $C_{1\text{-}6}$alkyl. In embodiments of the formulae above, R^{2b} is independently $C_{2\text{-}6}$alkenyl. In embodiments of the formulae above, R^{2b} is independently $C_{2\text{-}6}$alkynyl. In embodiments of the formulae above, R^{2b} is independently $C_{3\text{-}10}$cycloalkyl. In embodiments of the formulae above, R^{2b} is independently $C_{2\text{-}9}$heterocycloalkyl. In embodiments of the formulae above, R^{2b} is independently $C_{6\text{-}10}$aryl. In embodiments of the formulae above, R^{2b} is independently and $C_{1\text{-}9}$heteroaryl.

[407] In embodiments of the formulae above, R^{2b} is independently $C_{1\text{-}6}$alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently methylene optionally substituted with one or two R^{20d}. In embodiments of the formulae above, R^{2b} is independently methylene. In embodiments of the formulae above, R^{2b} is independently ethylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently ethylene. In embodiments of the formulae above, R^{2b} is independently propylene optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently propylene. In embodiments of the formulae above, R^{2b} is independently $C_{2\text{-}6}$alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently $C_{2\text{-}6}$alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently $C_{3\text{-}10}$cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently $C_{2\text{-}9}$heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently $C_{6\text{-}10}$aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently and $C_{1\text{-}9}$heteroaryl. In additional embodiments, R^{2b} is independently hydrogen.

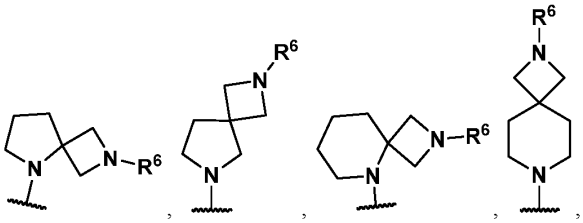
[408] In embodiments of the formulae above, R^{2b} is independently $C_{2\text{-}9}$heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (monocyclic $C_{2\text{-}8}$heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (monocyclic $C_{3\text{-}5}$heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (spirocyclic $C_{2\text{-}11}$heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (spirocyclic $C_{3\text{-}11}$heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (fused $C_{2\text{-}11}$heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently (spirocyclic $C_{6\text{-}8}$heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$. In embodiments of the formulae above, R^{2b} is independently, $-(C_{2\text{-}6}\text{alkenyl})\text{-}R^{12b}$. In embodiments of the formulae above, R^{2b} is independently, $-(C_{2\text{-}6}\text{alkynyl})\text{-}R^{12b}$. In embodiments of the formulae above, R^{2b} is independently, $-(C_{3\text{-}10}\text{cycloalkyl})\text{-}R^{12b}$. In embodiments of the formulae above, R^{2b} is independently, $-(C_{2\text{-}9}\text{heterocycloalkyl})\text{-}R^{12b}$. In embodiments of the formulae above, R^{2b} is independently, $-(C_{6\text{-}10}\text{aryl})\text{-}R^{12b}$. In embodiments of the formulae above, R^{2b} is independently, or $-(C_{1\text{-}9}\text{heteroaryl})\text{-}R^{12b}$. In embodiments of the formulae above, R^{2b} is independently $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$ optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, $-(C_{2\text{-}6}\text{alkenyl})\text{-}R^{12b}$ optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, $-(C_{2\text{-}6}\text{alkynyl})\text{-}R^{12b}$ optionally substituted with

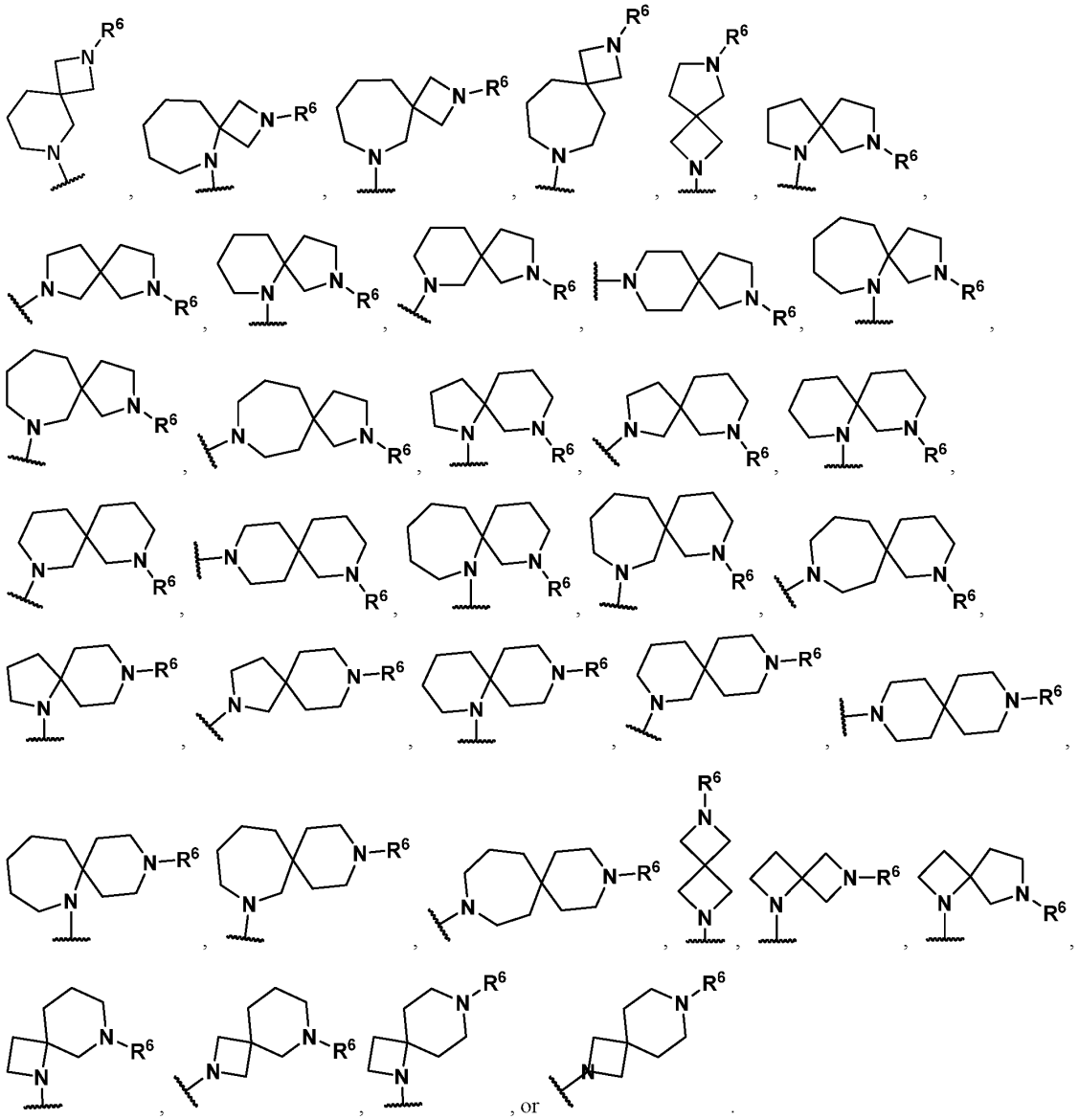
one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, -(C_{3-10}cycloalkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, -(C_{2-9}heterocycloalkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, -(C_{6-10}aryl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^{2b} is independently, –(C_{1-9}heteroaryl)-R^{12b} optionally substituted with one, two, or three R^{20d}.

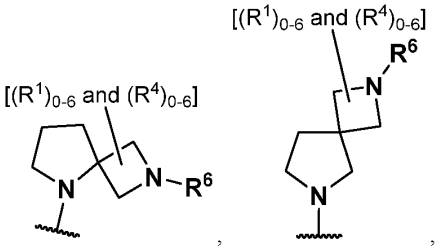
[409] In embodiments of the formulae above, each R^{12c} is independently hydrogen. In embodiments of the formulae above, each R^{12c} is independently halogen. In embodiments of the formulae above, each R^{12c} is independently oxo. In embodiments of the formulae above, each R^{12c} is independently -CN. In embodiments of the formulae above, each R^{12c} is independently C_{1-6}alkyl. In embodiments of the formulae above, each R^{12c} is independently C_{2-6}alkenyl. In embodiments of the formulae above, each R^{12c} is independently C_{2-6}alkynyl. In embodiments of the formulae above, each R^{12c} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{3-10}cycloalkyl. In embodiments of the formulae above, each R^{12c} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, each R^{12c} is independently C_{6-10}aryl. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{6-10}aryl. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{1-9}heteroaryl. In embodiments of the formulae above, each R^{12c} is independently C_{1-9}heteroaryl. In embodiments of the formulae above, each R^{12c} is independently -OR^{21}. In embodiments of the formulae above, each R^{12c} is independently -SR^{21}. In embodiments of the formulae above, each R^{12c} is independently -$N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$C(O)OR^{22}$. In embodiments of the formulae above, each R^{12c} is independently -$C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$C(O)C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$OC(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$N(R^{24})C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$N(R^{24})C(O)OR^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$N(R^{24})S(O)_2R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$C(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$S(O)_2R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -$S(O)_2N(R^{22})(R^{23})$. In embodiments of the formulae above, each R^{12c} is independently -$OCH_2C(O)OR^{22}$. In embodiments of the formulae above, each R^{12c} is independently -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{1-6}alkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{2-6}alkenyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{2-6}alkynyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{3-10}cycloalkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-}

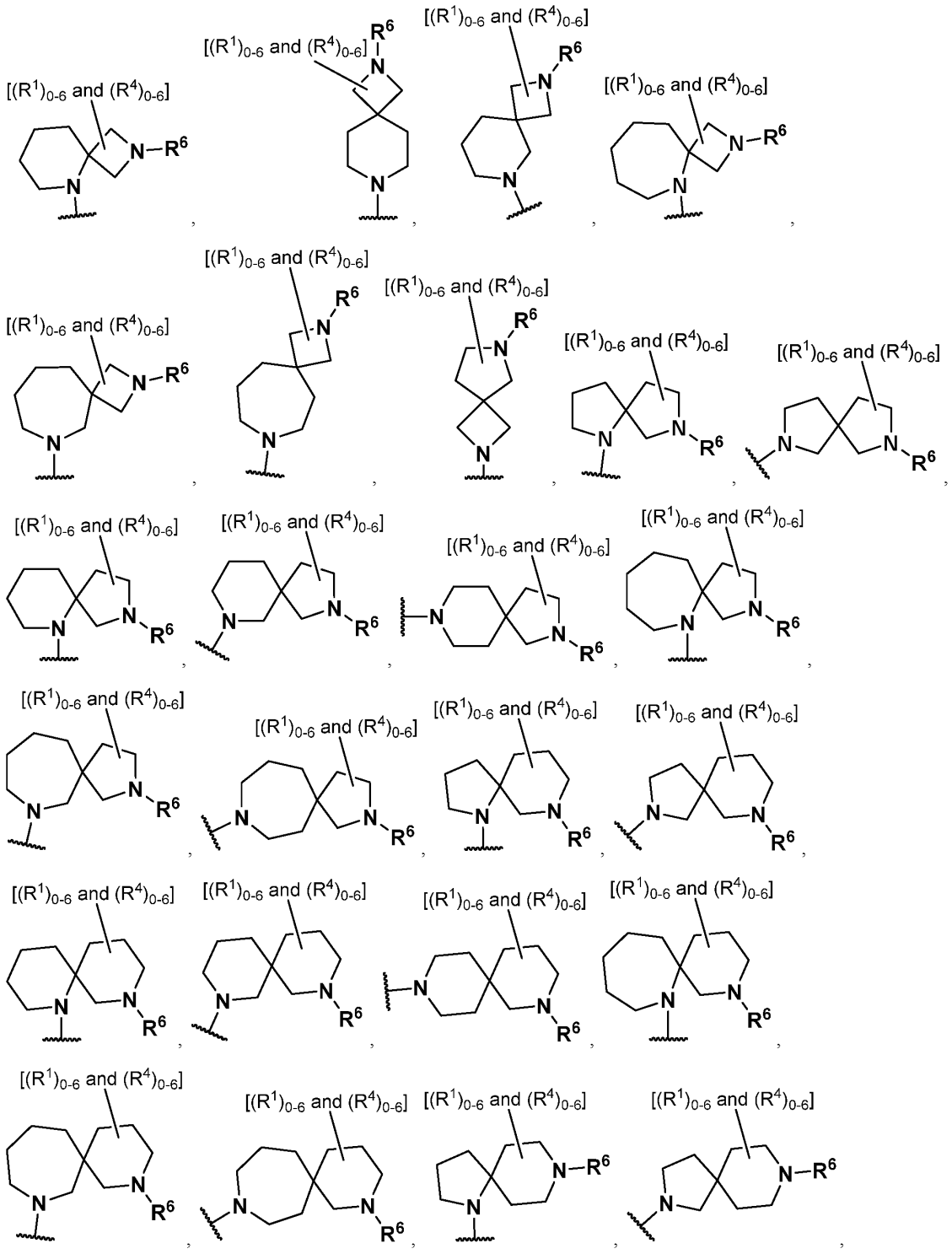
$_{6}$haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{3-10}cycloalkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{2-9}heterocycloalkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{2-9}heterocycloalkyl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{6-10}aryl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{6-10}aryl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently -CH_2-C_{1-9}heteroaryl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently C_{1-9}heteroaryl substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each R^{12c} is independently methyl. In embodiments of the formulae above, each R^{12c} is independently ethyl. In embodiments of the formulae above, each R^{12c} is independently propyl.

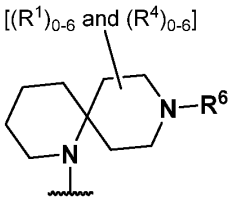
[410] The individual embodiments herein below, or combinations thereof, are applicable to compounds described herein (e.g., Formula A, B, C, D, E, F, G, and H), or a pharmaceutically acceptable salt or solvate thereof.

[411] In embodiments of the formulae above, R^7 is  ,



[412] In embodiments of the formulae above, R^7 is 


[(R1)0-6 and (R4)0-6]
R6
N



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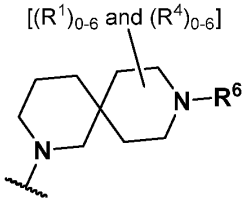

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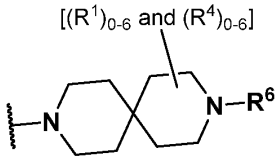

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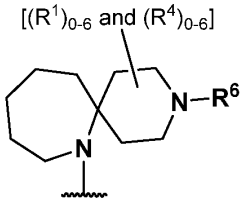

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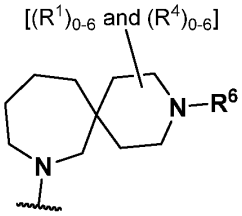

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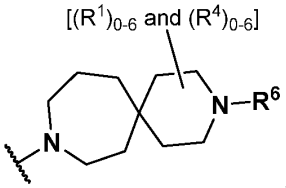

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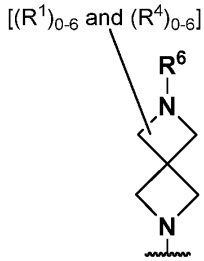

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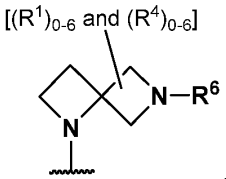

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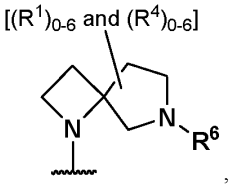

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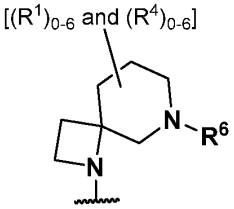

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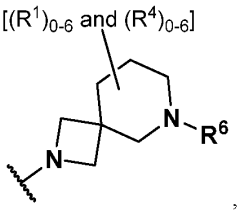

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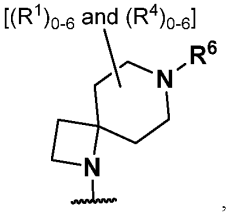

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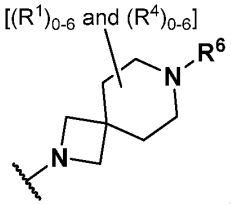

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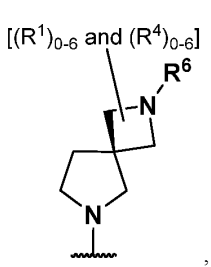
[413] In embodiments of the formulae above, R^7 is


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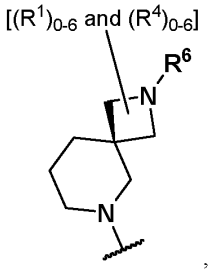

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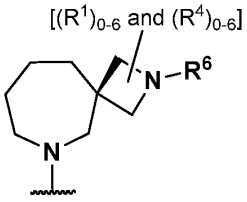

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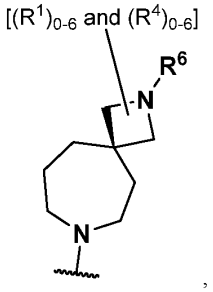

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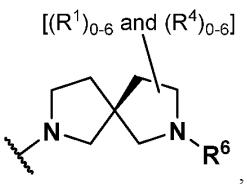

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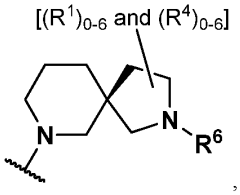

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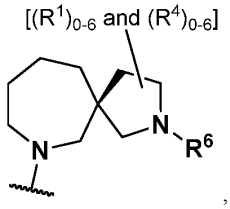

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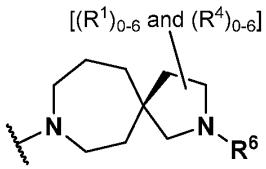

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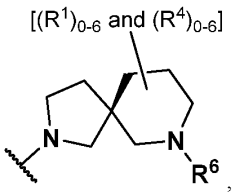

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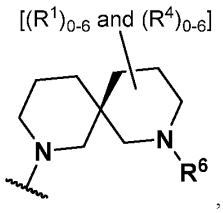

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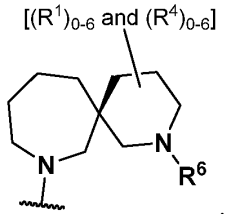

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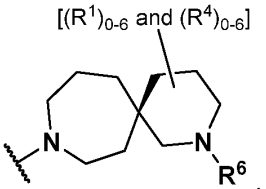

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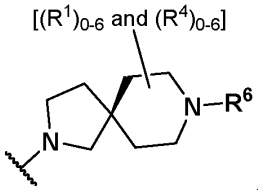

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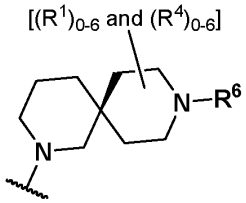

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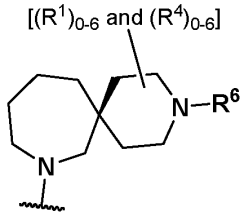

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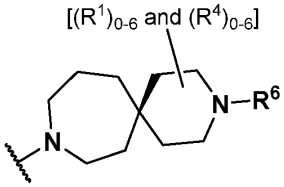

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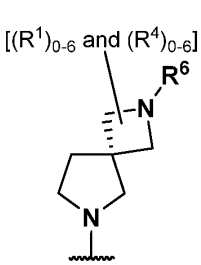

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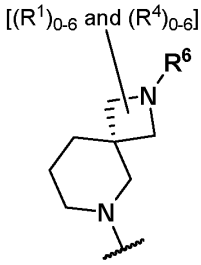

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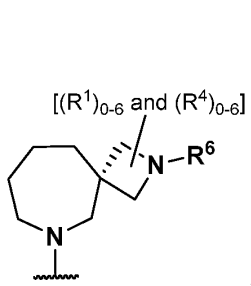
[414] In embodiments of the formulae above, R^7 is



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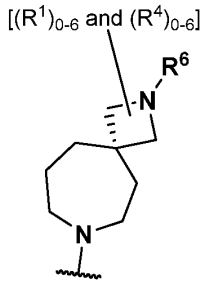

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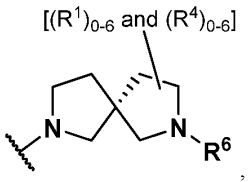

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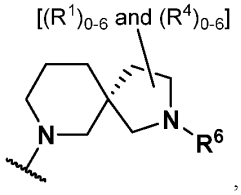

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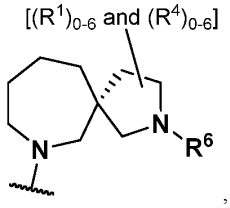

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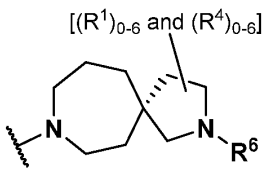

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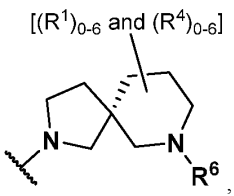

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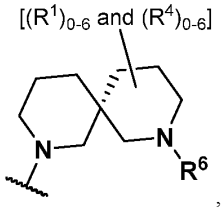

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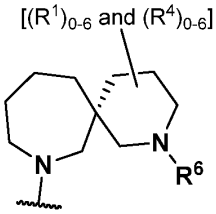

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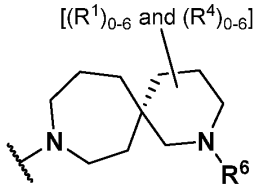

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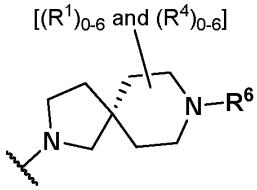

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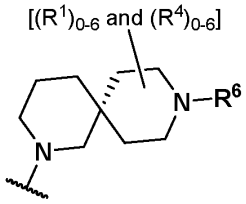

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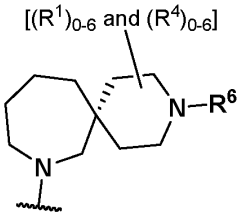

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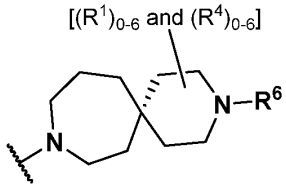

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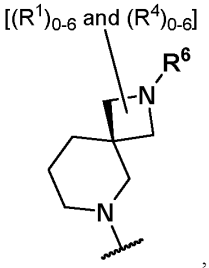

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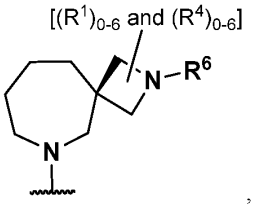

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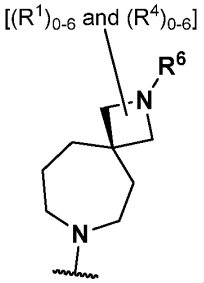
[415] In embodiments of the formulae above, R^7 is



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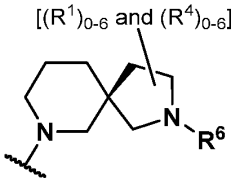

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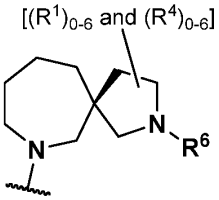

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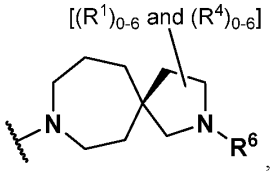

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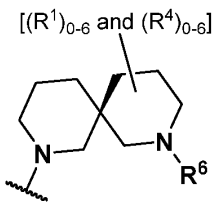

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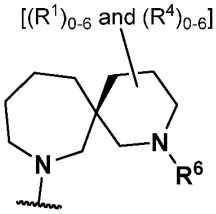

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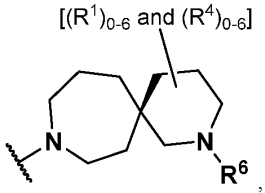

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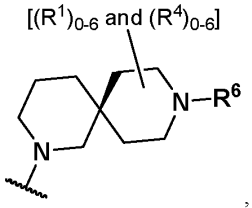

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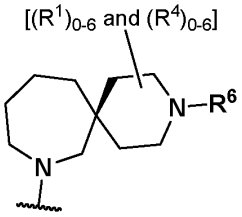

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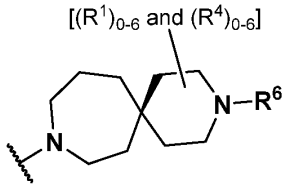
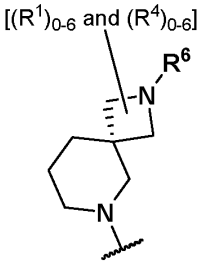
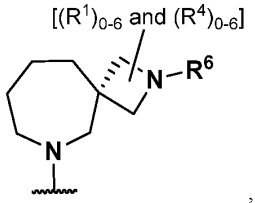
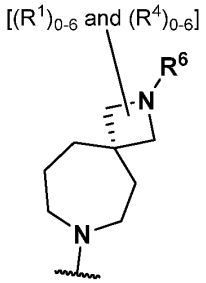
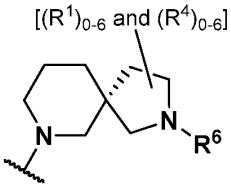
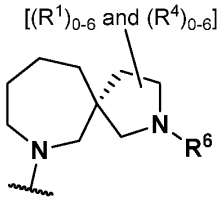
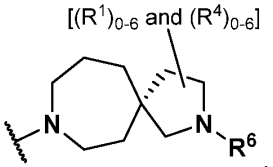
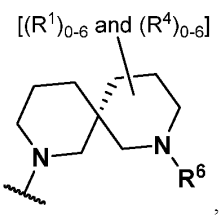
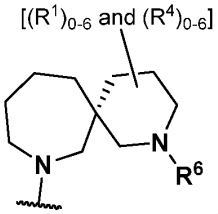
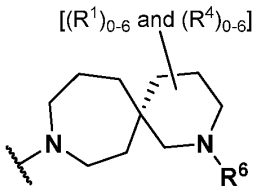
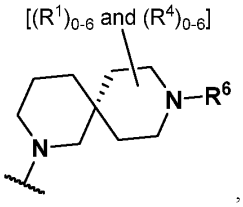
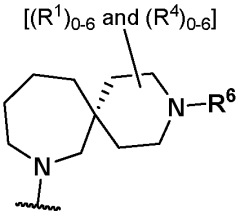
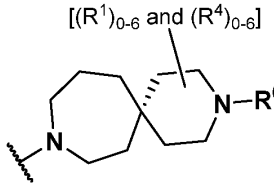
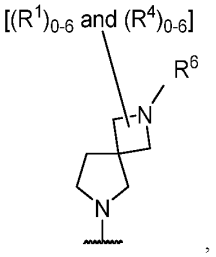
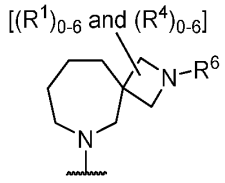
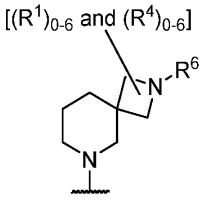


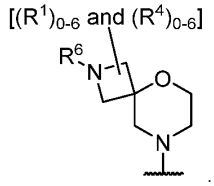
, or .

[416] In embodiments of the formulae above, R^7 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and .

[417] It will be understood that when one or more floating substituent(s) is/are shown extending from one ring in a polycyclic ring system (e.g., fused ring system, bridged ring system, or spirocyclic ring system), the one or more floating substituent(s), may be bonded to the ring from which the one or more floating substituents are shown extending or may be bonded to any other ring in the polycyclic ring system and when multiple substituents are represented by the floating substituents, each substituent may be bonded to the same or different rings in the polycyclic ring system, unless indicated otherwise.

[418] In embodiments of the formulae above, R^7 is selected from,  ,  ,



, and 

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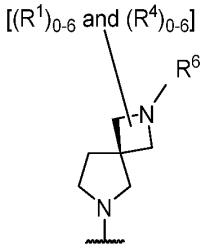
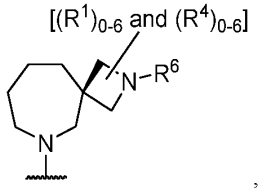
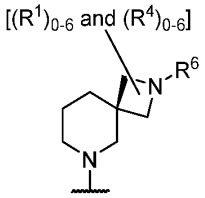
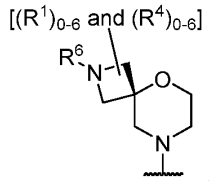


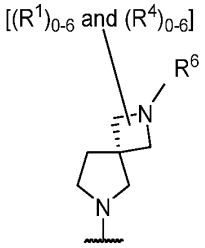


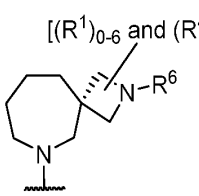
[419] In embodiments of the formulae above, R^7 is selected from, , ,

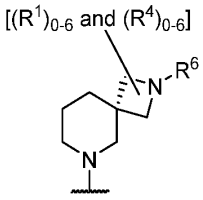


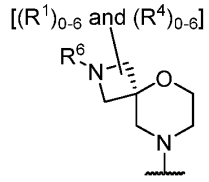
, and 

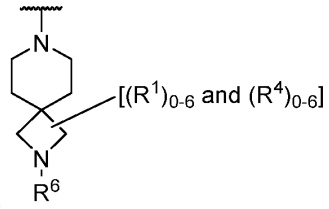
. In embodiments of the formulae above, R^7 is selected from,

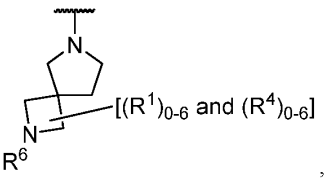


, 

, 

, and 

. In embodiments of the formulae above, R^7 is selected from 

, 

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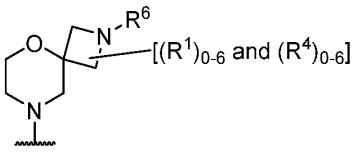
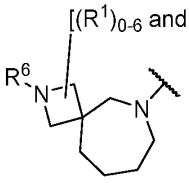
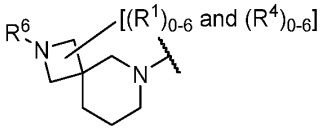


, 

, 

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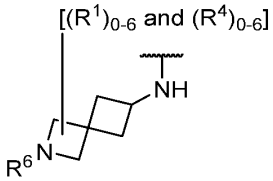
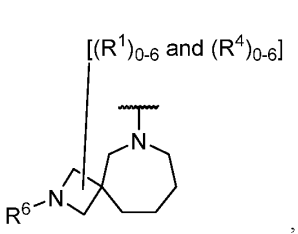


. In embodiments of the formulae above, R^7 is selected from



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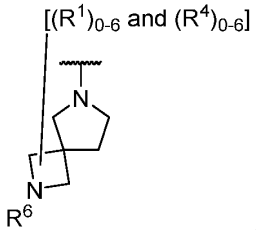

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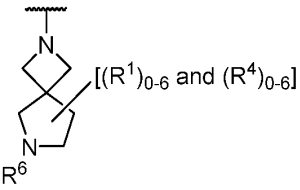

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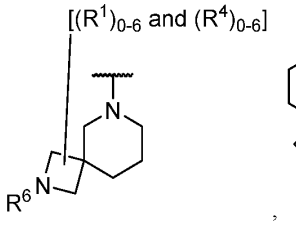

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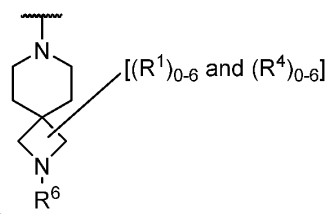

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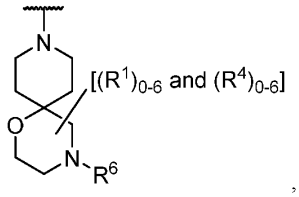

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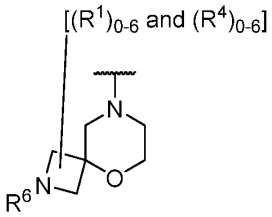

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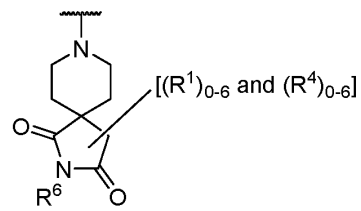

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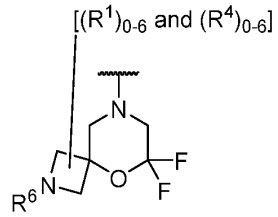

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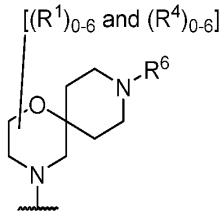

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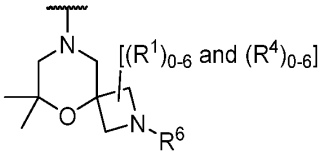

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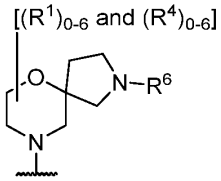

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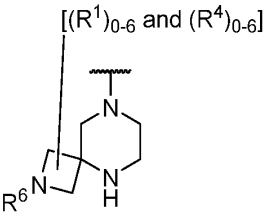

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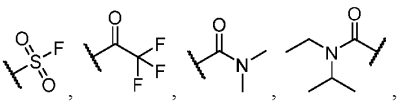
[420] In embodiments of the formulae above, R^6 is selected from

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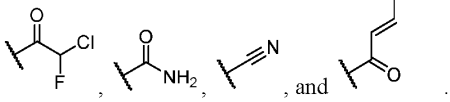
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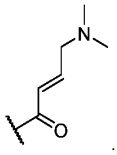
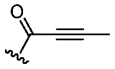

. In embodiments of the formulae above, R^6 is selected from

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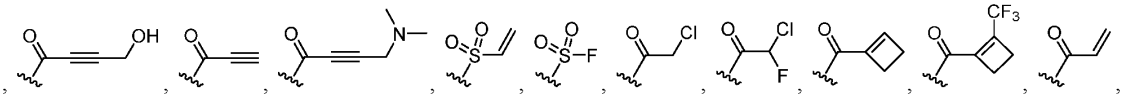
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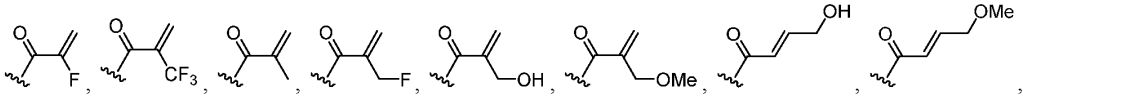
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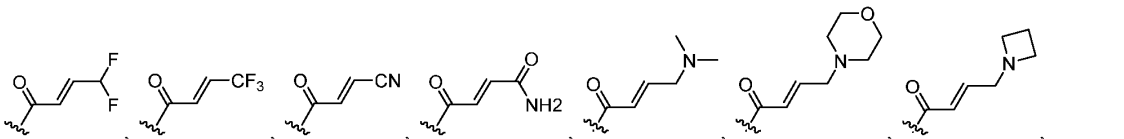
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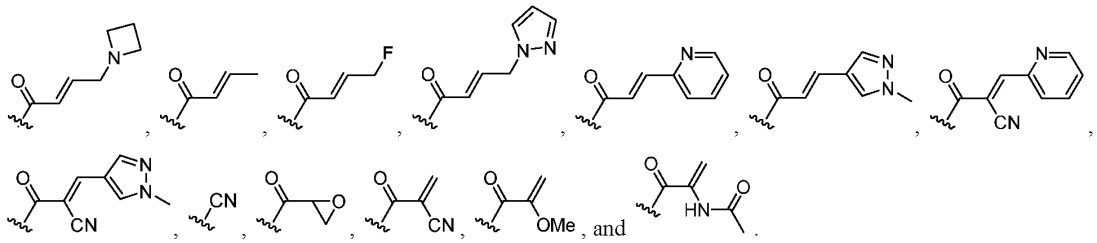
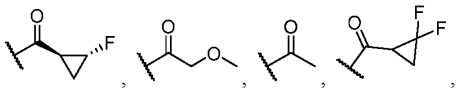
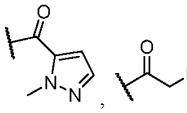
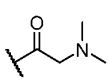
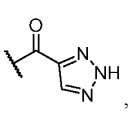
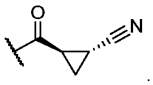
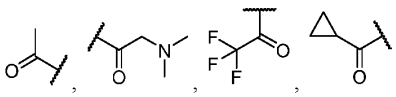
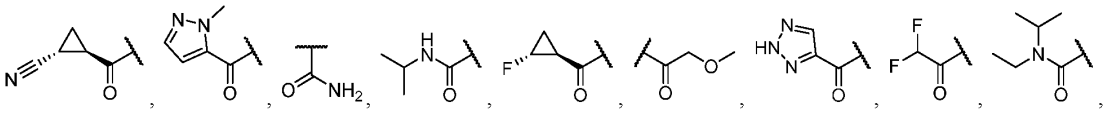
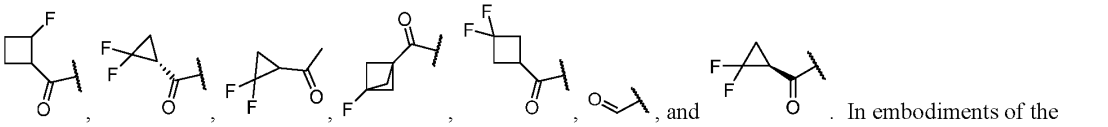
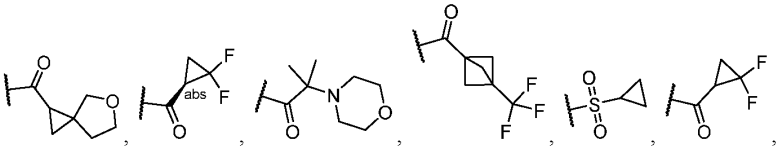


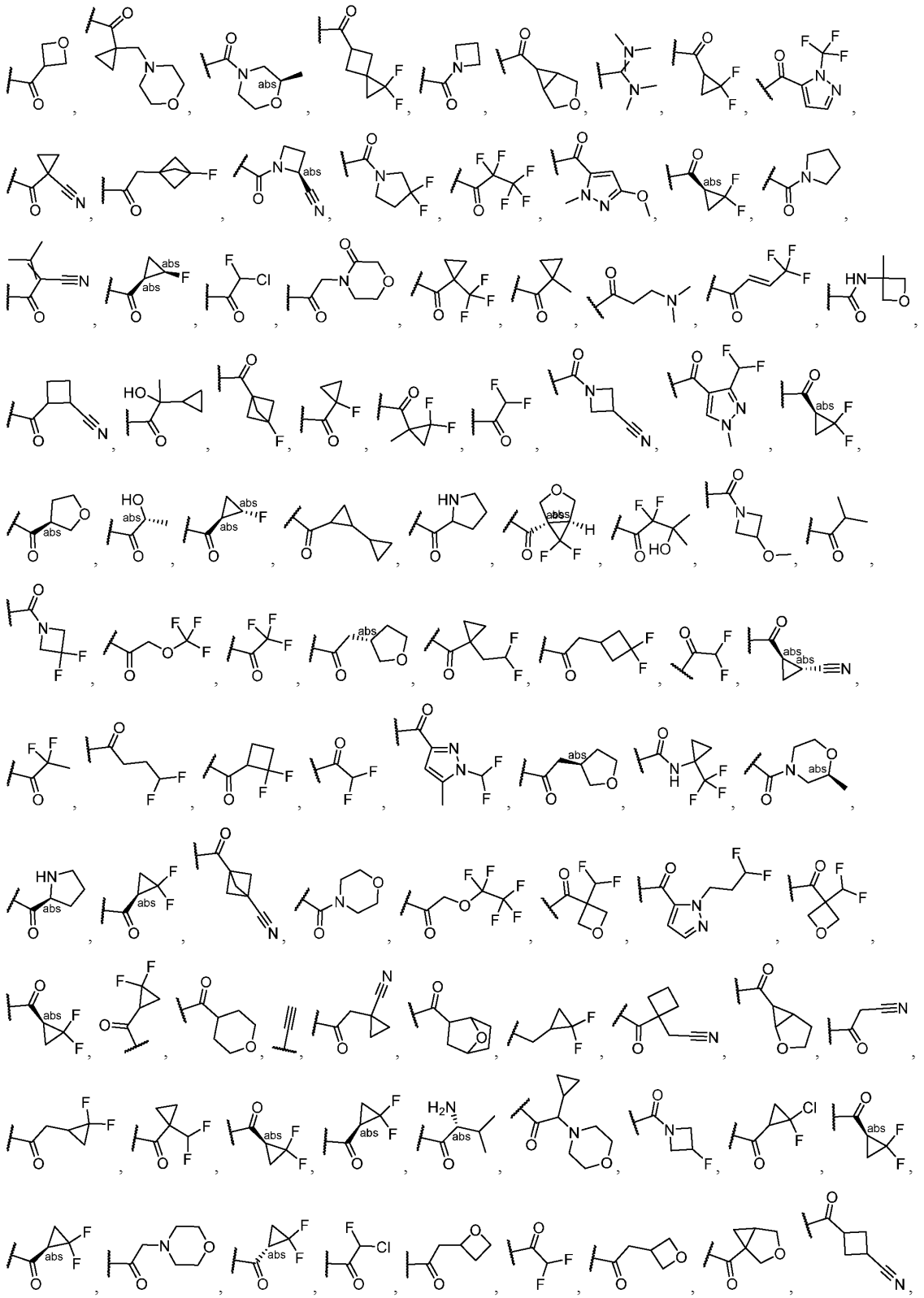
[421] The individual embodiments herein below, or combinations thereof, are applicable to compounds described herein (e.g., Formula A, B, C, D, E, F, G, and H), or a pharmaceutically acceptable salt or solvate thereof.

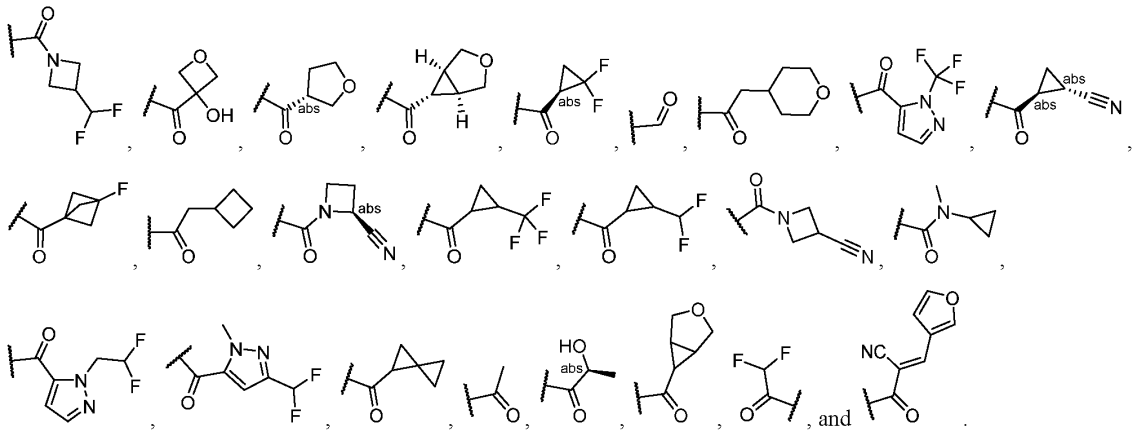
[422] In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with $-OR^{21}$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with $-N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with one, two, or three C_{1-6}alkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with $-N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl and/or CN. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with $-OR^{21}$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with $-N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with one, two, or three C_{1-6}alkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with C_{1-5}heteroaryl optionally substituted with $-N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl optionally substituted with $-C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkenyl substituted with Cl and optionally substituted with one or two R^{20k}. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-OR^{21}$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with one, two, or three C_{1-6}alkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with $-N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, R^5

is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl and/or CN. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-OR^{21}$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with one, two, or three C_{1-6}alkyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with C_{1-5}heteroaryl optionally substituted with $-N(R^{24})C(O)R^{25}$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl optionally substituted with $-C(O)N(R^{22})(R^{23})$. In embodiments of the formulae above, R^5 is C_{2-6}alkynyl substituted with Cl and optionally substituted with one or two R^{20k}. In embodiments of the formulae above, R^5 is C_{3-5}cycloalkyl, optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{3-5}cycloalkyl, optionally substituted with C_{1-6}alkyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{3-5}cycloalkyl, optionally substituted with C_{1-6}alkyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{1-5}heterocycloalkyl, optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{1-5}heterocycloalkyl, optionally substituted with C_{1-6}alkyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{1-5}heterocycloalkyl, optionally substituted with C_{1-6}alkyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{1-6}alkyl, optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{1-6}alkyl, substituted with Cl and optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is $-S(O)_2R^{15}$. In embodiments of the formulae above, R^5 is -CN.

[423] In embodiments of the formulae above, R^6 is selected from  ,  ,  ,  , , and  .

[424] In embodiments of the formulae above, R^6 is selected from  ,  ,  , , and . In embodiments of the formulae above, R^6 is selected from  .

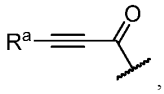


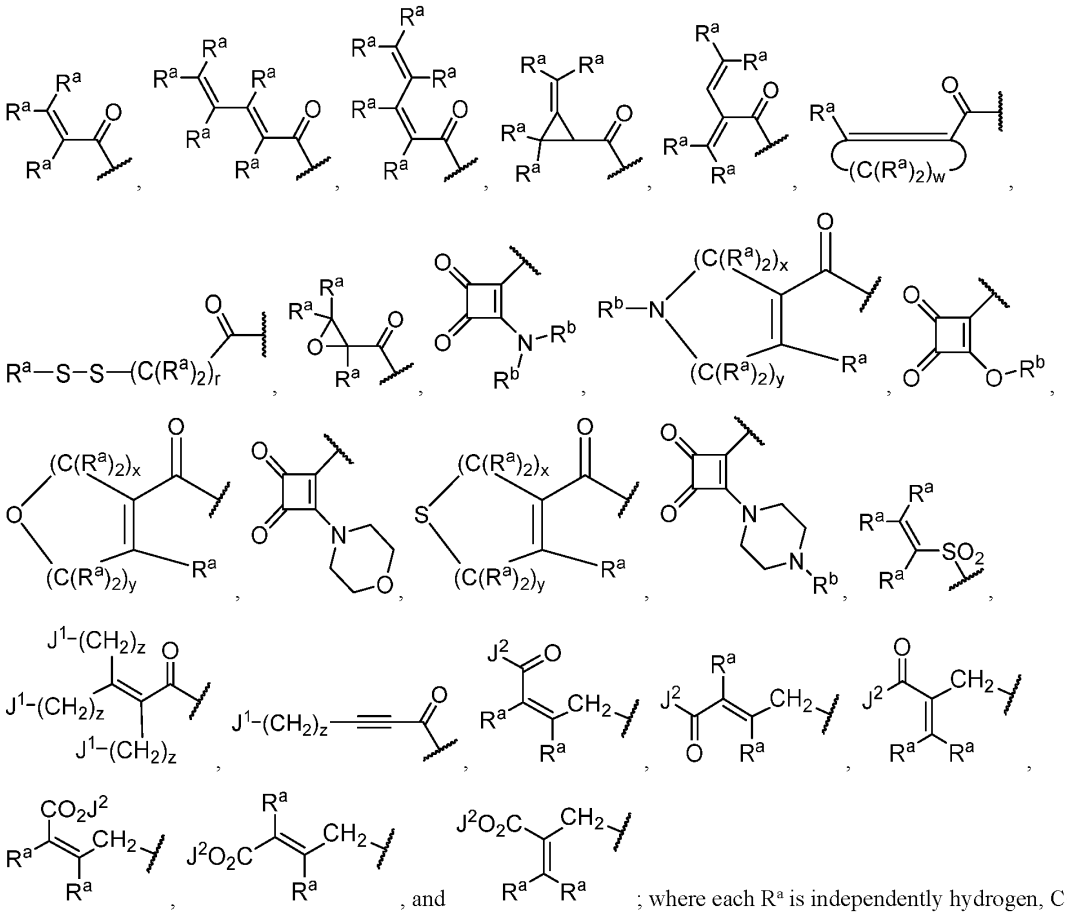


[425] In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with -N(R^{22})(R^{23}). In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{1-6}alkyl optionally substituted with -OR^{21}. In embodiments of the formulae above, R^5 is C_{3-6}cycloalkyl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{3-6}cycloalkyl optionally substituted with -CN. In embodiments of the formulae above, R^5 is C_{3-6}cycloalkyl optionally substituted with one, two, or three halogen. In embodiments of the formulae above, R^5 is C_{3-6}cycloalkyl optionally substituted with one, two, or three F. In embodiments of the formulae above, R^5 is C_{1-5}heteroaryl optionally substituted with one, two, or three R^{20k}. In embodiments of the formulae above, R^5 is C_{1-5}heteroaryl optionally substituted with methyl. In embodiments of the formulae above, R^5 is C_{1-5}heteroaryl optionally substituted with C_{1-6}alkyl. In embodiments of the formulae above, R^5 is -N(R^{12})(R^{13}); R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted with one, two, or three R^{20d}; and R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl.

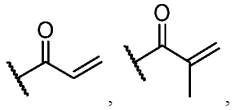
[426] The individual embodiments herein below, or combinations thereof, are applicable to compounds described herein (e.g., Formula A, B, or C), or a pharmaceutically acceptable salt or solvate thereof.

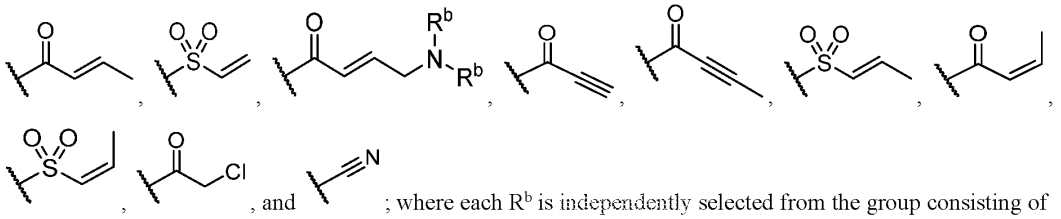
[427] In embodiments of the formulae above, R^6 is capable of forming a covalent bond with a Ras amino acid sidechain. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with a KRAS amino acid. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 12th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 12th amino acid of a mutant KRAS protein selected from KRAS G12D, KRAS G12C, and KRAS G12S. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 13th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 13th amino acid of a mutant KRAS protein selected from KRAS G13D, KRAS G13C, and KRAS G13S.

[428] In embodiments of the formulae above, R^6 is selected from the group consisting of  ,



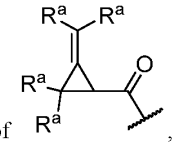
; where each R^a is independently hydrogen, C_{1-6}alkyl, carboxy, C_{1-6}carboalkoxy, phenyl, C_{2-7}carboalkyl, R^c-$(C(R^b)_2)_z$-, R^c-$(C(R^b)_2)_w$-M-$(C(R^b)_2)_r$-, $(R^d)(R^e)$CH-M-$(C(R^b)_2)_r$-, or Het-J^3-$(C(R^b)_2)_r$-; each R^b is independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-7}carboalkyl, C_{2-7}carboxyalkyl, phenyl, or phenyl optionally substituted with one or more halogen, C_{1-6}alkoxy, trifluoromethyl, amino, C_{1-3}alkylamino, C_{2-6}dialkylamino, nitro, azido, halomethyl, C_{2-7}alkoxymethyl, C_{2-7}alkanoyloxymethyl, C_{1-6}alkylthio, hydroxy, carboxyl, C_{2-7}carboalkoxy, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, C_{1-6}alkanoylamino, or C_{1-6}alkyl; each R^c is independently $-NR^bR^b$ or $-OR^b$; R^d and R^e are each, independently, $-(C(R^b)_2)_r$-NR^bR^b, or $-(C(R^b)_2)_r$-OR^b; each J^1 is independently hydrogen, chlorine, fluorine, or bromine; J^2 is C_{1-6}alkyl or hydrogen; each M is independently $-N(R^b)$-, -O-, $-N[(C(R^b)_2)_w$-$NR^bR^b]$-, or $-N[(C(R^b)_2)_w$-$OR^b]$-; each J^3 is independently $-N(R^b)$-, -O-, or a bond; each Het is independently a heterocycle, optionally mono- or di-substituted on carbon or nitrogen with R^b and optionally mono-substituted on carbon with $-CH_2OR^b$; wherein the heterocycle is selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, piperazine, tetrahydrofuran, and tetrahydropyran; each r is independently 1-4; each w is independently 2-4; x is 0-1; y is 0-4, and each z is independently 1-6; wherein the sum of x+y is 2-4.

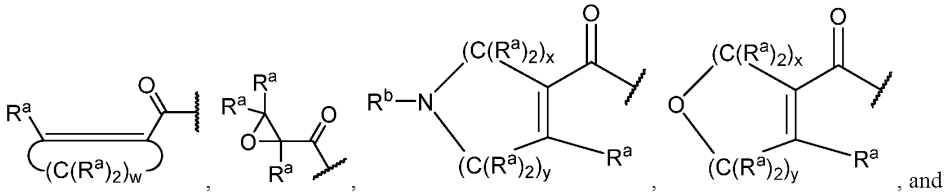
[429] In embodiments of the formulae above, R^6 is selected from the group consisting of 



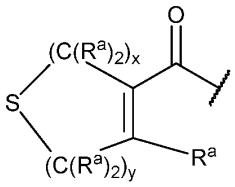
; where each R^b is independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_6 alkoxy, and C_1-C_6 alkyl.

[430] In embodiments of the formulae above, L^2 is a bond, -C(O)NH-, -NHC(O)-, or -C(O)-; and R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynylIn embodiments of the formulae above, R^6 is capable of forming a covalent bond with a Ras amino acid. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with a KRAS amino acid. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 12th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 12th amino acid of a mutant KRAS protein selected from KRAS G12D, KRAS G12C, and KRAS G12S. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 13th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 13th amino acid of a mutant KRAS protein selected from KRAS G13D, KRAS G13C, and KRAS G13S.

[431] In embodiments of the formulae above, R^6 is selected from the group consisting of  ,



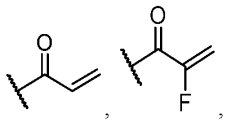
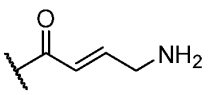
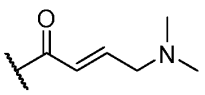
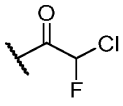
, and

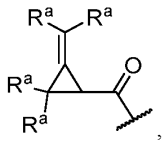
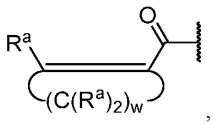
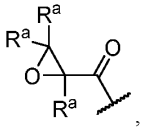
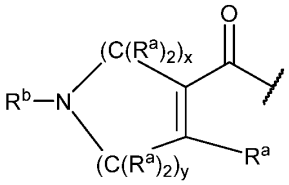
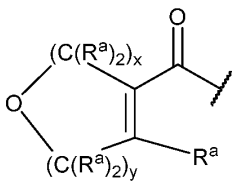
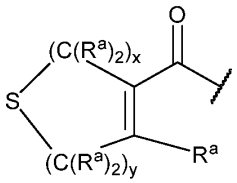


; where each R^a is independently hydrogen, C_{1-6}alkyl, carboxy, C_{1-6}carboalkoxy, phenyl, C_{2-7}carboalkyl, R^c-$(C(R^b)_2)_z$-, R^c-$(C(R^b)_2)_w$-M-$(C(R^b)_2)_r$-, $(R^d)(R^e)CH$-M-$(C(R^b)_2)_r$-, or Het-J^3-$(C(R^b)_2)_r$-; each R^b is independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-7}carboalkyl, C_{2-7}carboxyalkyl, phenyl, or phenyl optionally substituted with one or more halogen, C_{1-6}alkoxy, trifluoromethyl, amino, C_{1-3}alkylamino, C_{2-6}dialkylamino, nitro, azido, halomethyl, C_{2-7}alkoxymethyl, C_{2-7}alkanoyloxymethyl, C_{1-6}alkylthio, hydroxy, carboxyl, C_{2-7}carboalkoxy, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, C_{1-6}alkanoylamino, or C_{1-6}alkyl; each R^c is independently $-NR^bR^b$ or $-OR^b$; R^d and R^e are each, independently, $-(C(R^b)_2)_r-NR^bR^b$, or $-(C(R^b)_2)_r-OR^b$; each J^1 is independently hydrogen, chlorine, fluorine, or bromine; J^2 is C_{1-6}alkyl or hydrogen; each M is independently $-N(R^b)-$, -O-, $-N[(C(R^b)_2)_w-NR^bR^b]-$, or $-N[(C(R^b)_2)_w-OR^b]-$; each J^3 is independently $-N(R^b)-$, -O-, or a bond; each Het is independently a heterocycle, optionally mono- or di-substituted on carbon or nitrogen with R^b and optionally mono-substituted on carbon with $-CH_2OR^b$; wherein the heterocycle is selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine,

imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, piperazine, tetrahydrofuran, and tetrahydropyran; each r is independently 1-4; each w is independently 2-4; x is 0-1; y is 0-4, and each z is independently 1-6; wherein the sum of x+y is 2-4.

[432] In embodiments of the formulae above, R^6 is capable of forming a covalent bond with a Ras amino acid sidechain. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with a KRAS amino acid. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 12th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 12th amino acid of a mutant KRAS protein selected from KRAS G12D, KRAS G12C, and KRAS G12S. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 13th amino acid of a human KRAS protein. In embodiments of the formulae above, R^6 is capable of forming a covalent bond with the 13th amino acid of a mutant KRAS protein selected from KRAS G13D, KRAS G13C, and KRAS G13S.

[433] In embodiments of the formulae above, R^6 is selected from the group consisting of  ,  ,  ,  , and .

[434] In embodiments of the formulae above, R^6 is selected from the group consisting of  ,  ,  ,  ,  , and  ; where each R^a is independently hydrogen, C_{1-6}alkyl, carboxy, C_{1-6}carboalkoxy, phenyl, C_{2-7}carboalkyl, R^c-$(C(R^b)_2)_z$-, R^c-$(C(R^b)_2)_w$-M-$(C(R^b)_2)_r$-, $(R^d)(R^e)CH$-M-$(C(R^b)_2)_r$-, or Het-J^3-$(C(R^b)_2)_r$-; each R^b is independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{2-7}carboalkyl, C_{2-7}carboxyalkyl, phenyl, or phenyl optionally substituted with one or more halogen, C_{1-6}alkoxy, trifluoromethyl, amino, C_{1-3}alkylamino, C_{2-6}dialkylamino, nitro, azido, halomethyl, C_{2-7}alkoxymethyl, C_{2-7}alkanoyloxymethyl, C_{1-6}alkylthio, hydroxy, carboxyl, C_{2-7}carboalkoxy, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, C_{1-6}alkanoylamino, or C_{1-6}alkyl; each R^e is independently $-NR^bR^b$ or $-OR^b$; R^d and R^e are each, independently, $-(C(R^b)_2)_r-NR^bR^b$, or $-(C(R^b)_2)_r-OR^b$; each J^1 is independently hydrogen, chlorine, fluorine, or bromine; J^2 is C_{1-6}alkyl or hydrogen; each M is independently $-N(R^b)-$, -O-, $-N[(C(R^b)_2)_w-NR^bR^b]-$, or $-N[(C(R^b)_2)_w-OR^b]-$; each J^3 is independently $-N(R^b)-$, -O-, or a bond; each Het is independently a heterocycle, optionally mono- or di-substituted on carbon or nitrogen with R^b and optionally mono-substituted on carbon with $-CH_2OR^b$; wherein the heterocycle is selected from the group consisting of

morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, piperazine, tetrahydrofuran, and tetrahydropyran; each r is independently 1-4; each w is independently 2-4; x is 0-1; y is 0-4, and each z is independently 1-6; wherein the sum of x+y is 2-4.

[435] The individual embodiments herein below, or combinations thereof, are applicable to compounds of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), and (H), or embodiments of any of the preceding formulae, a pharmaceutically acceptable salt, or solvate thereof.

[436] In embodiments of the formulae above, Y is N. In embodiments of the formulae above, Y is C(O). In embodiments of the formulae above, Y is $C(R^2)$. In embodiments of the formulae above, Y is $C(R^2)(R^{2c})$. In embodiments of the formulae above, Y is S(O). In embodiments of the formulae above, Y is $S(O)_2$. In embodiments of the formulae above, X is N. In embodiments of the formulae above, X is $C(R^3)$. In embodiments of the formulae above, X is $C(R^3)(R^3)$. In embodiments of the formulae above, X is $N(R^3)$. In embodiments of the formulae above, U is N. In embodiments of the formulae above, U is $C(R^{2c})$. In embodiments of the formulae above, U is $C(R^{2c})(R^{2c})$. In embodiments of the formulae above, U is $N(R^{2b})$. In embodiments of the formulae above, U is S(O). In embodiments of the formulae above, U is $S(O)_2$. In embodiments of the formulae above, U is C(O). In embodiments of the formulae above, W is a N. In embodiments of the formulae above, W is a $C(R^{18})$. In embodiments of the formulae above, W is a $N(R^{18b})$. In embodiments of the formulae above, W is a $C(R^{18})(R^{18a})$. In embodiments of the formulae above, W is a C(O). In embodiments of the formulae above, W is a S(O). In embodiments of the formulae above, W is a $S(O)_2$. In embodiments of the formulae above, Z is N. In embodiments of the formulae above, Z is $C(R^8)$. In embodiments of the formulae above, Z is $N(R^{8b})$. In embodiments of the formulae above, Z is $C(R^8)(R^{8a})$. In embodiments of the formulae above, Z is C(O). In embodiments of the formulae above, Z is S(O). In embodiments of the formulae above, Z is $S(O)_2$. In embodiments of the formulae above, V is $N(R^{16b})$. In embodiments of the formulae above, V is N. In embodiments of the formulae above, V is $C(R^{16})(R^{16a})$. In embodiments of the formulae above, V is $C(R^{16})$. In embodiments of the formulae above, V is $N(R^{17b})$. In embodiments of the formulae above, V is $C(R^{17})(R^{16a})$. In embodiments of the formulae above, V is $C(R^{17})$. In embodiments of the formulae above, J is $N(R^{16b})$. In embodiments of the formulae above, J is N. In embodiments of the formulae above, J is $C(R^{16})(R^{16a})$. In embodiments of the formulae above, J is $C(R^{16})$. In embodiments of the formulae above, J is $N(R^{17b})$. In embodiments of the formulae above, J is $C(R^{17})(R^{16a})$. In embodiments of the formulae above, J is $C(R^{17})$.

[437] In embodiments of the formulae above, L^7 is a bond. In embodiments of the formulae above, L^7 is -O-. In embodiments of the formulae above, L^7 is $-N(R^{14})-$. In embodiments of the formulae above, L^7 is -C(O)-. In embodiments of the formulae above, L^7 is -S-. In embodiments of the formulae above, L^7 is $-S(O)_2-$. In embodiments of the formulae above, L^7 is -S(O)-. In embodiments of the formulae above, L^7 is -NH-. In embodiments of the formulae above, L^7 is CH_2. In embodiments of the formulae above, L^7 is $-OCH_2-$. In embodiments of the formulae above, L^7 is $-N(H)CH_2-$. In embodiments of the formulae above, L^7 is $-C(O)CH_2-$. In embodiments of the formulae above, L^7 is $-SCH_2-$. In embodiments of the formulae above, L^7 is $-S(O)_2CH_2-$. In embodiments of the formulae above, L^7 is $-S(O)CH_2-$. In embodiments of the formulae above, L^7 is $-P(O)(CH_3)CH_2-$. In embodiments of the formulae above, L^7 is $-CH_2CH_2-$. In embodiments of the formulae above, L^7 is $-CH_2O-$. In embodiments of the formulae above, L^7 is $-CH_2N(H)-$. In embodiments of the formulae above, L^7 is $-CH_2C(O)-$. In embodiments of the formulae above, L^7 is $-CH_2S-$. In embodiments of the formulae above, L^7 is $-CH_2S(O)_2-$. In embodiments of the formulae above, L^7 is $-CH_2S(O)-$. In embodiments of the formulae above, L^7 is $-CH_2P(O)CH_3-$. In embodiments of the formulae above, L^7 is $-N(H)C(O)-$. In embodiments of the formulae above, L^7 is $-N(H)P(O)CH_3-$. In embodiments of the formulae above, L^7

is -C(O)N(H)-. In embodiments of the formulae above, L^7 is -$CH_2CH_2CH_2$-. In embodiments of the formulae above, L^7 is -OCH_2CH_2-. In embodiments of the formulae above, L^7 is -N(H)CH_2CH_2-. In embodiments of the formulae above, L^7 is -C(O)CH_2CH_2-. In embodiments of the formulae above, L^7 is -SCH_2CH_2-. In embodiments of the formulae above, L^7 is -$S(O)_2CH_2CH_2$-. In embodiments of the formulae above, L^7 is -S(O)CH_2CH_2-. In embodiments of the formulae above, L^7 is -P(O)$(CH_3)CH_2CH_2$-. In embodiments of the formulae above, L^7 is -CH_2CH_2O-. In embodiments of the formulae above, L^7 is -$CH_2CH_2N(H)$-. In embodiments of the formulae above, L^7 is -$CH_2CH_2C(O)$-. In embodiments of the formulae above, L^7 is -CH_2CH_2S-. In embodiments of the formulae above, L^7 is -$CH_2CH_2S(O)_2$-. In embodiments of the formulae above, L^7 is -$CH_2CH_2S(O)$-. In embodiments of the formulae above, L^7 is -$CH_2CH_2P(O)(CH_3)$-. In embodiments of the formulae above, L^7 is -$CH_2CH_2CH_2CH_2$-. In embodiments of the formulae above, L^7 is C_{1-4}alkyl optionally substituted with one, two or three R^{20a}. In embodiments of the formulae above, L^7 is C_1alkyl optionally substituted with one, two or three R^{20a}. In embodiments of the formulae above, L^7 is C_2alkyl optionally substituted with one, two or three R^{20a}. In embodiments of the formulae above, L^7 is C_3alkyl optionally substituted with one, two or three R^{20a}. In embodiments of the formulae above, L^7 is C_4alkyl optionally substituted with one, two or three R^{20a}. In embodiments of the formulae above, L^7 is 2-4 membered heteroalkyl linker optionally substituted with one, two or three R^{20a}. In embodiments of the formulae above, L^7 is 2 membered heteroalkyl linker optionally substituted with one, two or three R^{20a}. In embodiments of the formulae above, L^7 is 3 membered heteroalkyl linker optionally substituted with one, two or three R^{20a}. In embodiments of the formulae above, L^7 is 4 membered heteroalkyl linker optionally substituted with one, two or three R^{20a}. In embodiments of the formulae above, L^7 is -$CH_2C(O)N(H)$-. In embodiments of the formulae above, L^7 is -$CH_2CH_2C(O)N(H)$-. In embodiments of the formulae above, L^7 is -$CH_2N(H)C(O)$-. In embodiments of the formulae above, L^7 is -$CH_2CH_2N(H)C(O)$-.

[438] In embodiments of the formulae above, L^2 is a bond. In embodiments of the formulae above, L^2 is -O-. In embodiments of the formulae above, L^2 is -$N(R^{4d})$-. In embodiments of the formulae above, L^2 is -C(O)-. In embodiments of the formulae above, L^2 is -S-. In embodiments of the formulae above, L^2 is -$S(O)_2$-. In embodiments of the formulae above, L^2 is -S(O)-. In embodiments of the formulae above, L^2 is -$P(O)R^{4d}$-. In embodiments of the formulae above, L^2 is $CR^{4c}R^{4c}$. In embodiments of the formulae above, L^2 is -$OCR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$N(R^{4d})CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$C(O)CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$SCR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$S(O)_2CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$S(O)CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$P(O)R^{4d}CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}$. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}O$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}N(R^{4d})$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}C(O)$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}S$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}S(O)_2$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}S(O)$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}P(O)R^{4d}$-. In embodiments of the formulae above, L^2 is -$N(R^{4d})C(O)$-. In embodiments of the formulae above, L^2 is -$N(R^{4d})S(O)_2$-. In embodiments of the formulae above, L^2 is -$N(R^{4d})S(O)$-. In embodiments of the formulae above, L^2 is -$N(R^{4d})P(O)R^{4d}$-. In embodiments of the formulae above, L^2 is -$C(O)N(R^{4d})$-. In embodiments of the formulae above, L^2 is -$S(O)_2N(R^{4d})$-. In embodiments of the formulae above, L^2 is -$S(O)N(R^{4d})$-. In embodiments of the formulae above, L^2 is -$P(O)R^{4d}N(R^{4d})$-. In embodiments of the formulae above, L^2 is -OC(O)-. In embodiments of the formulae above, L^2 is -$OS(O)_2$-. In embodiments of the formulae above, L^2 is -OS(O)-. In embodiments of the formulae above, L^2 is -$OP(O)R^{4d}$-. In embodiments of the formulae above, L^2 is -C(O)O-. In embodiments of the formulae above, L^2 is -$S(O)_2O$-. In embodiments of the formulae above, L^2 is -S(O)O-. In embodiments of the formulae above, L^2 is -$P(O)R^{4d}O$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}$-. In embodiments of

the formulae above, L^2 is -$OCR^{4c}R^{4c}CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$SCR^{4c}R^{4c}CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}O$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}S$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})C(O)$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}N(R^{4d})C(O)$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)N(R^{4d})$-. In embodiments of the formulae above, L^2 is -$CR^{4c}R^{4c}C(O)N(R^{4d})$-.

[439] In embodiments of the formulae above, L^2 is -NH-. In embodiments of the formulae above, L^2 is -$P(O)CH_3$-. In embodiments of the formulae above, L^2 is CH_2. In embodiments of the formulae above, L^2 is -OCH_2-. In embodiments of the formulae above, L^2 is -$N(H)CH_2$-. In embodiments of the formulae above, L^2 is -$C(O)CH_2$-. In embodiments of the formulae above, L^2 is -SCH_2-. In embodiments of the formulae above, L^2 is -$S(O)_2CH_2$-. In embodiments of the formulae above, L^2 is -$S(O)CH_2$-. In embodiments of the formulae above, L^2 is -$P(O)(CH_3)CH_2$-. In embodiments of the formulae above, L^2 is -CH_2CH_2-. In embodiments of the formulae above, L^2 is -CH_2O-. In embodiments of the formulae above, L^2 is -$CH_2N(H)$-. In embodiments of the formulae above, L^2 is -$CH_2C(O)$-. In embodiments of the formulae above, L^2 is -CH_2S-. In embodiments of the formulae above, L^2 is -$CH_2S(O)_2$-. In embodiments of the formulae above, L^2 is -$CH_2S(O)$-. In embodiments of the formulae above, L^2 is -$CH_2P(O)CH_3$-. In embodiments of the formulae above, L^2 is -$N(H)C(O)$-. In embodiments of the formulae above, L^2 is -$N(H)S(O)_2$-. In embodiments of the formulae above, L^2 is -$N(H)S(O)$-. In embodiments of the formulae above, L^2 is -$N(H)P(O)CH_3$-. In embodiments of the formulae above, L^2 is -$C(O)N(H)$-. In embodiments of the formulae above, L^2 is -$S(O)_2N(H)$-. In embodiments of the formulae above, L^2 is -$S(O)N(H)$-. In embodiments of the formulae above, L^2 is -$P(O)(CH_3)N(H)$-. In embodiments of the formulae above, L^2 is -$OC(O)$-. In embodiments of the formulae above, L^2 is -$OS(O)_2$-. In embodiments of the formulae above, L^2 is -$OS(O)$-. In embodiments of the formulae above, L^2 is -$OP(O)CH_3$-. In embodiments of the formulae above, L^2 is -$C(O)O$-. In embodiments of the formulae above, L^2 is -$S(O)_2O$-. In embodiments of the formulae above, L^2 is -$S(O)O$-. In embodiments of the formulae above, L^2 is -$P(O)(CH_3)O$-. In embodiments of the formulae above, L^2 is -$CH_2CH_2CH_2$-. In embodiments of the formulae above, L^2 is -OCH_2CH_2-. In embodiments of the formulae above, L^2 is -$N(H)CH_2CH_2$-. In embodiments of the formulae above, L^2 is -$C(O)CH_2CH_2$-. In embodiments of the formulae above, L^2 is -SCH_2CH_2-. In embodiments of the formulae above, L^2 is -$S(O)_2CH_2CH_2$-. In embodiments of the formulae above, L^2 is -$S(O)CH_2CH_2$-. In embodiments of the formulae above, L^2 is -$P(O)(CH_3)CH_2CH_2$-. In embodiments of the formulae above, L^2 is -CH_2CH_2O-. In embodiments of the formulae above, L^2 is -$CH_2CH_2N(H)$-. In embodiments of the formulae above, L^2 is -$CH_2CH_2C(O)$-. In embodiments of the formulae above, L^2 is -CH_2CH_2S-. In embodiments of the formulae above, L^2 is -$CH_2CH_2S(O)_2$-. In embodiments of the formulae above, L^2 is -$CH_2CH_2S(O)$-. In embodiments of the formulae above, L^2 is -$CH_2CH_2P(O)(CH_3)$-. In embodiments of the formulae above, L^2 is -$CH_2CH_2N(H)C(O)$-. In embodiments of the formulae above, L^2 is -$CH_2N(H)C(O)$-. In embodiments of the formulae above, L^2 is -$CH_2CH_2C(O)N(H)$-. In embodiments of the formulae above, L^2 is -$CH_2C(O)N(H)$-.

[440] In embodiments of the formulae above,, R^{4c} is independently hydrogen. In embodiments of the formulae above, R^{4c} is independently halogen. In embodiments of the formulae above, R^{4c} is independently -CN. In

embodiments of the formulae above, R^{4c} is independently C_{1-6}alkyl. In embodiments of the formulae above, R^{4c} is independently C_{2-6}alkenyl. In embodiments of the formulae above, R^{4c} is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^{4c} is independently C_{1-6}haloalkyl. In embodiments of the formulae above, R^{4c} is independently C_{1-6}alkoxy. In embodiments of the formulae above, R^{4c} is independently C_{1-6}haloalkoxy. In embodiments of the formulae above, R^{4c} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{4c} is independently -CH_2-C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{4c} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{4c} is independently -CH_2-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{4c} is independently -OR^{14}. In embodiments of the formulae above, R^{4c} is independently -SR^{14}. In embodiments of the formulae above, R^{4c} is independently -$C(O)OR^{14}$. In embodiments of the formulae above, R^{4c} is independently -$C(O)N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4c} is independently -$C(O)C(O)N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4c} is independently -$OC(O)N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4c} is independently -$C(O)R^{14a}$. In embodiments of the formulae above, R^{4c} is independently -$S(O)_2R^{14}$. In embodiments of the formulae above, R^{4c} is independently -$S(O)_2N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4c} is independently -$OCH_2C(O)OR^{14}$. In embodiments of the formulae above, R^{4c} is independently -$OC(O)R^{14a}$. In embodiments of the formulae above, R^{4c} is independently -$N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4c} is independently -$N(R^{14})C(O)N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4c} is independently -$N(R^{14})C(O)OR^{14}$. In embodiments of the formulae above, R^{4c} is independently -$N(R^{14})C(O)R^{14a}$. In embodiments of the formulae above, R^{4c} is independently -$N(R^{14})S(O)_2R^{14}$.

[441] In embodiments of the formulae above, R^{4d} is independently hydrogen. In embodiments of the formulae above, R^{4d} is independently -CN. In embodiments of the formulae above, R^{4d} is independently C_{1-6}alkyl. In embodiments of the formulae above, R^{4d} is independently C_{2-6}alkenyl. In embodiments of the formulae above, R^{4d} is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^{4d} is independently C_{1-6}haloalkyl. In embodiments of the formulae above, R^{4d} is independently C_{1-6}alkoxy. In embodiments of the formulae above, R^{4d} is independently C_{1-6}haloalkoxy. In embodiments of the formulae above, R^{4d} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{4d} is independently -CH_2-C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{4d} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{4d} is independently -CH_2-C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{4d} is independently -OR^{14}. In embodiments of the formulae above, R^{4d} is independently -SR^{14}. In embodiments of the formulae above, R^{4d} is independently -$C(O)OR^{14}$. In embodiments of the formulae above, R^{4d} is independently -$C(O)N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4d} is independently -$C(O)C(O)N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4d} is independently -$OC(O)N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4d} is independently -$C(O)R^{14a}$. In embodiments of the formulae above, R^{4d} is independently -$S(O)_2R^{14}$. In embodiments of the formulae above, R^{4d} is independently -$S(O)_2N(R^{14})(R^{14})$. In embodiments of the formulae above, R^{4d} is independently -$OCH_2C(O)OR^{14}$. In embodiments of the formulae above, R^{4d} is independently -$OC(O)R^{14a}$.

[442] In embodiments of the formulae above, L^2 is selected from a -C(O)-, -$N(R^{4d})C(O)$-, -$C(O)N(R^{4d})$-, and -$CH_2N(R^{4d})C(O)$-. In embodiments of the formulae above, L^2 is selected from a bond, -C(O)NH-, -NHC(O)-, and -C(O)-.

[443] In embodiments of the formulae above, L^2 is a bond, -C(O)NH-, -NHC(O)-, or -C(O)-; and R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, C_{1-11}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -

$OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k}.

[444] In embodiments of the formulae above, L^2 is a bond, -C(O)NH-, -NHC(O)-, or -C(O)-; and R^5 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, C_{1-11}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20k}.

[445] In embodiments of the formulae above, R^1 is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently $-CH_2-C_{3-10}$cycloalkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently $-CH_2-C_{2-9}$heterocycloalkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently $-CH_2-C_{6-10}$aryl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently $-CH_2-C_{1-9}$heteroaryl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently C_{1-9}heteroaryl. In additional embodiments, R^1 is independently hydrogen.

[446] In embodiments of the formulae above, R^1 is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently (monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently (monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently (spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently (spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently (fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently (spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}.

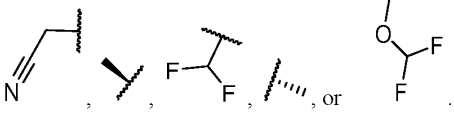
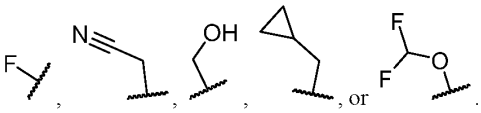
[447] In embodiments of the formulae above, R^1 is independently methyl optionally substituted with one or two R^{20a}. In embodiments of the formulae above, R^1 is independently methyl. In embodiments of the formulae above, R^1 is independently ethyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently ethyl. In embodiments of the formulae above, R^1 is independently propyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently propyl. In embodiments of the

formulae above, R^1 is independently -CH_2-C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently -CH_2-(monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently -CH_2-(monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently -CH_2-(spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently -CH_2-(spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently -CH_2-(fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^1 is independently -CH_2-(spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20a}.

[448] In embodiments of the formulae above, R^4 is independently C_{1-6}alkyl. In embodiments of the formulae above, R^4 is independently C_{2-6}alkenyl. In embodiments of the formulae above, R^4 is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^4 is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^4 is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^4 is independently C_{6-10}aryl. In embodiments of the formulae above, R^4 is independently and C_{1-9}heteroaryl.

[449] In select embodiments, R^4 is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^4 is independently methyl optionally substituted with one or two R^{20a}. In embodiments of the formulae above, R^4 is independently methyl. In embodiments of the formulae above, R^4 is independently ethyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^4 is independently ethyl. In embodiments of the formulae above, R^4 is independently propyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^4 is independently propyl. In embodiments of the formulae above, R^4 is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^4 is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^4 is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^4 is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^4 is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20a}. In embodiments of the formulae above, R^4 is independently and C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20a}.

[450] In additional embodiments, R^4 is independently hydrogen. In additional embodiments, R^4 is independently halogen. In additional embodiments, R^4 is independently -CN. In embodiments of the formulae above, R^4 is -OR^{12}. In embodiments of the formulae above, R^4 is -SR^{12}. In embodiments of the formulae above, R^4 is -$N(R^{12})(R^{13})$. In embodiments of the formulae above, R^4 is -$C(O)OR^{12}$. In embodiments of the formulae above, R^4 is -$OC(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^4 is -$N(R^{14})C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^4 is -$N(R^{14})C(O)OR^{15}$. In embodiments of the formulae above, R^4 is -$N(R^{14})S(O)_2R^{15}$. In embodiments of the formulae above, R^4 is -$C(O)R^{15}$. In embodiments of the formulae above, R^4 is -$S(O)R^{15}$. In embodiments of the formulae above, R^4 is -$OC(O)R^{15}$. In embodiments of the formulae above, R^4 is -$C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^4 is -$C(O)C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^4 is -$N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^4 is -$S(O)_2R^{15}$. In embodiments of the formulae above, R^4 is -$S(O)_2N(R^{12})(R^{13})$. In embodiments of the formulae above, R^4 is $S(=O)(=NH)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^4 is -$CH_2C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^4 is -$CH_2N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^4 is -$CH_2S(O)_2R^{15}$. In embodiments of the formulae above, R^4 is -$CH_2S(O)_2N(R^{12})(R^{13})$. In

embodiments of the formulae above, R^4 is  . In embodiments of the formulae above, R^4 is  .

[451] In embodiments of the formulae above, L^1 is a bond. In embodiments of the formulae above, L^1 is C_1-C_4alkyl. In embodiments of the formulae above, L^1 is C_2-C_4alkenyl. In embodiments of the formulae above, L^1 is C_2-C_4alkynyl. In embodiments of the formulae above, L^1 is -O-. In embodiments of the formulae above, L^1 is -N(R^{14})-. In embodiments of the formulae above, L^1 is -C(O)-. In embodiments of the formulae above, L^1 is -N(R^{14})C(O)-. In embodiments of the formulae above, L^1 is -C(O)N(R^{14})-. In embodiments of the formulae above, L^1 is -S-. In embodiments of the formulae above, L^1 is -S(O)$_2$-. In embodiments of the formulae above, L^1 is -S(O)-. In embodiments of the formulae above, L^1 is -S(O)$_2$N(R^{14})-. In embodiments of the formulae above, L^1 is -S(O)N(R^{14})-. In embodiments of the formulae above, L^1 is -N(R^{14})S(O)-. In embodiments of the formulae above, L^1 is -N(R^{14})S(O)$_2$-. In embodiments of the formulae above, L^1 is -OCON(R^{14})-. In embodiments of the formulae above, L^1 is -N(R^{14})C(O)O-. In embodiments of the formulae above, L^1 is N(R^{1e}). In embodiments of the formulae above, L^1 is C(O)N(R^{1c}). In embodiments of the formulae above, L^1 is S(O)$_2$N(R^{1c}). In embodiments of the formulae above, L^1 is S(O)N(R^{1c}). In embodiments of the formulae above, L^1 is C(R^{1f})(R^{1g})O. In embodiments of the formulae above, L^1 is C(R^{1f})(R^{1g})N(R^{1c}). . In embodiments of the formulae above, L^1 is C(R^{1f})(R^{1g}).

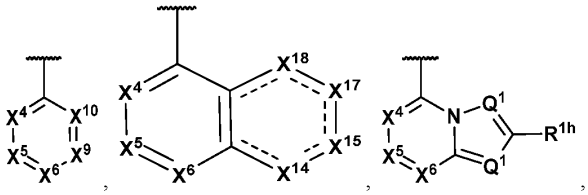
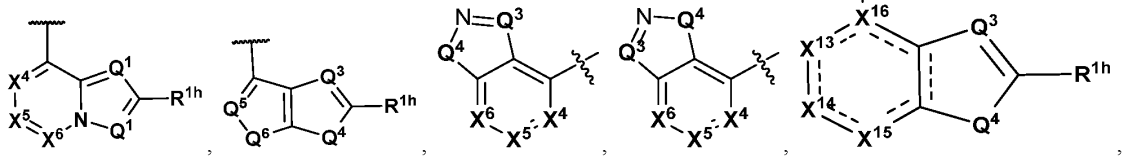
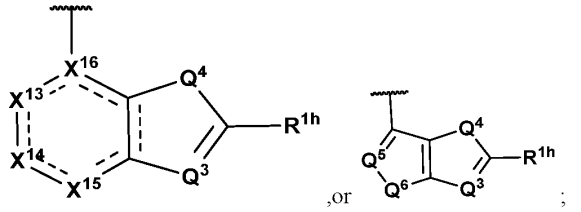
[452] In embodiments of the formulae above, L^{1b} is a bond. In embodiments of the formulae above, L^{1b} is C_1-C_4alkyl. In embodiments of the formulae above, L^{1b} is C_2-C_4alkenyl. In embodiments of the formulae above, L^{1b} is C_2-C_4alkynyl. In embodiments of the formulae above, L^{1b} is -C(O)-. In embodiments of the formulae above, L^{1b} is -C(O)N(R^{14})-. In embodiments of the formulae above, L^{1b} is C(O)N(R^{1c}). In embodiments of the formulae above, L^{1b} is C(R^{1f})(R^{1g})O. In embodiments of the formulae above, L^{1b} is C(R^{1f})(R^{1g})N(R^{1c}). In embodiments of the formulae above, L^{1b} is C(R^{1f})(R^{1g}).

[453] The individual embodiments herein below, or combinations thereof, are applicable to compounds of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), and (H), or embodiments of any of the preceding formulae, a pharmaceutically acceptable salt, or solvate thereof.

[454] In embodiments of the formulae above, R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is selected from a bicyclic C_{4-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl, wherein the C_{4-12}cycloalkyl, bicyclic C_{2-11}heterocycloalkyl, bicyclic C_{7-12}aryl, and bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is selected from a bridged bicyclic C_{4-12}cycloalkyl, bridged bicyclic C_{2-11}heterocycloalkyl, bridged bicyclic C_{7-12}aryl, and bridged bicyclic C_{2-12}heteroaryl, wherein the bridged bicyclic C_{4-12}cycloalkyl, bridged bicyclic C_{2-11}heterocycloalkyl, bridged bicyclic C_{7-12}aryl, and bridged bicyclic C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is selected from a fused bicyclic C_{4-12}cycloalkyl, fused bicyclic C_{2-11}heterocycloalkyl, fused bicyclic C_{7-12}aryl, and fused bicyclic C_{2-12}heteroaryl, wherein the fused bicyclic C_{4-12}cycloalkyl, fused bicyclic C_{2-11}heterocycloalkyl, fused bicyclic C_{7-12}aryl, and fused bicyclic C_{2-12}heteroaryl are

optionally substituted with one, two, three, four, five, six, or seven R^{1i}.

[455] In embodiments of the formulae above, R^{19} is a C_{3-12}cycloalkyl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a C_{2-11}heterocycloalkyl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a C_{6-12}aryl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a C_{2-12}heteroaryl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a C_{3-12}cycloalkyl. In embodiments of the formulae above, R^{19} is a C_{2-11}heterocycloalkyl. In embodiments of the formulae above, R^{19} is a C_{6-12}aryl. In embodiments of the formulae above, R^{19} is a C_{2-12}heteroaryl. In embodiments of the formulae above, R^{19} is a monocyclic C_{3-9}cycloalkyl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a monocyclic C_{1-8}heterocycloalkyl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a monocyclic phenyl optionally substituted with one, two, three, four, or five R^{1i}. In embodiments of the formulae above, R^{19} is a monocyclic C_{1-5}heteroaryl optionally substituted with one, two, three, four, or five R^{1i}. In embodiments of the formulae above, R^{19} is a spirocyclic C_{5-12}cycloalkyl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a spirocyclic C_{2-11}heterocycloalkyl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a fused C_{4-12}cycloalkyl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a fused C_{2-11}heterocycloalkyl optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a fused C_{6-12}aryl, optionally substituted with one, two, three, four, five, six, or seven R^{1i}. In embodiments of the formulae above, R^{19} is a fused 5 to 12 membered heteroaryl optionally substituted with one, two, three, four, five, six, or seven R^{1i}.

[456] In embodiments of the formulae above, R^{19} is:  ,  ,  ,or ;

Q^1, Q^3, and Q^5 are independently selected from N and $C(R^{1d})$;

Q^4 and Q^6 are independently selected from O, S, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

X^4, X^5, X^6, X^9, X^{10} are independently selected from $C(R^{1a})$ and N;

X^{13} is selected from a bond, $C(R^{1a})$, N, C(O), $C(R^{1a})(R^{1b})$, $C(O)C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})N(R^{1c})$,

and $N(R^{1c})$;

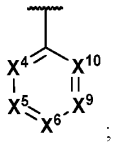
X^{14}, X^{15}, X^{17}, X^{18} are independently selected from a C(O), $C(R^{1a})$, N, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

X^{16} are independently selected from C, N, and $C(R^{1a})$;

each R^{1a}, R^{1b}, R^{1d}, and R^{1h} are each independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1a} and R^{1b} bonded to the same carbon are joined to form a 3-10 membered heterocycloalkyl ring or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or two R^{1a} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, C_{6-10}aryl ring, 5-12 membered heteroaryl ring, or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or R^{1h} and one of R^{1a}, R^{1b}, R^{1c}, and R^{1d} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, and C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; and

each R^{1c} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}.

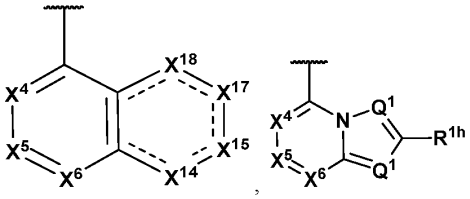
[457] In embodiments of the formulae above, R^{19} is:



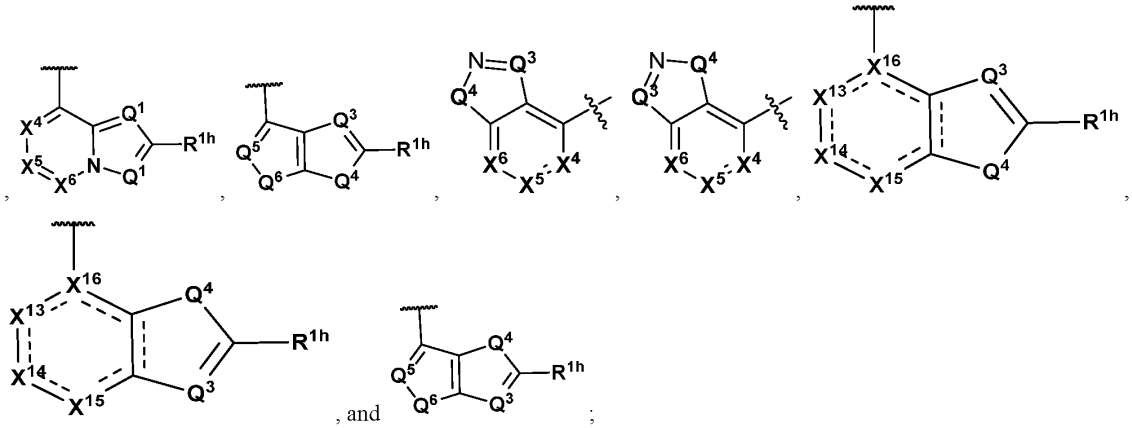
;

X^4, X^5, X^6, X^9, X^{10} are independently selected from $C(R^{1a})$ and N; and

each R^{1a} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}.

[458] In embodiments of the formulae above, R^{19} is selected from: 

,



, and ;

Q^1, Q^3, and Q^5 are independently selected from N and $C(R^{1d})$;

Q^4 and Q^6 are independently selected from O, S, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

X^4, X^5, X^6, X^9, X^{10} are independently selected from $C(R^{1a})$ and N;

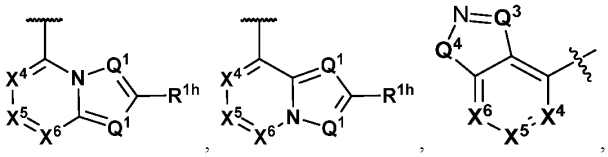
X^{13} is selected from a bond, $C(R^{1a})$, N, C(O), $C(R^{1a})(R^{1b})$, $C(O)C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})N(R^{1c})$, and $N(R^{1c})$;

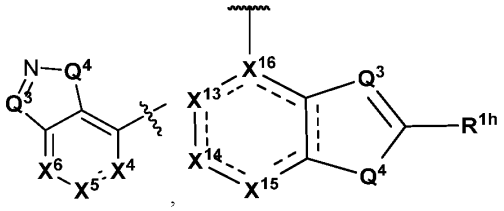
X^{14}, X^{15}, X^{17}, X^{18} are independently selected from a C(O), $C(R^{1a})$, N, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

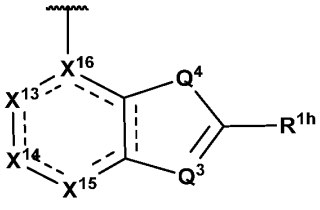
X^{16} is independently selected from C, N, and $C(R^{1a})$;

each R^{1a}, R^{1b}, R^{1d}, and R^{1h} are each independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1a} and R^{1b} bonded to the same carbon are joined to form a 3-10 membered heterocycloalkyl ring or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or two R^{1a} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, C_{6-10}aryl ring, 5-12 membered heteroaryl ring, or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or R^{1h} and one of R^{1a}, R^{1b}, R^{1c}, and R^{1d} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, and C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; and

each R^{1c} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}.

[459] In embodiments of the formulae above, R^{19} is: 



, 

, or .

[460] In embodiments of the formulae above, Q^1 is N. In embodiments of the formulae above, Q^1 is $C(R^{1d})$. In embodiments of the formulae above, Q^3 is N. In embodiments of the formulae above, Q^3 is $C(R^{1d})$. In embodiments of the formulae above, Q^5 is N. In embodiments of the formulae above, Q^5 is $C(R^{1d})$.

[461] In embodiments of the formulae above, Q^4 is O. In embodiments of the formulae above, Q^4 is S. In embodiments of the formulae above, Q^4 is $C(R^{1a})(R^{1b})$. In embodiments of the formulae above, Q^4 is $N(R^{1c})$. In embodiments of the formulae above, Q^6 is O. In embodiments of the formulae above, Q^6 is S. In embodiments of the formulae above, Q^6 is $C(R^{1a})(R^{1b})$. In embodiments of the formulae above, Q^6 is $N(R^{1c})$.

[462] In embodiments of the formulae above, X^4 is $C(R^{1a})$. In embodiments of the formulae above, X^4 is N. In embodiments of the formulae above, X^5 is $C(R^{1a})$. In embodiments of the formulae above, X^5 is N. In embodiments of the formulae above, X^6 is $C(R^{1a})$. In embodiments of the formulae above, X^6 is N. In embodiments of the formulae above, X^9 is $C(R^{1a})$. In embodiments of the formulae above, X^9 is N. In embodiments of the formulae above, X^{10} is $C(R^{1a})$. In embodiments of the formulae above, X^{10} is N.

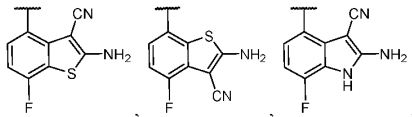
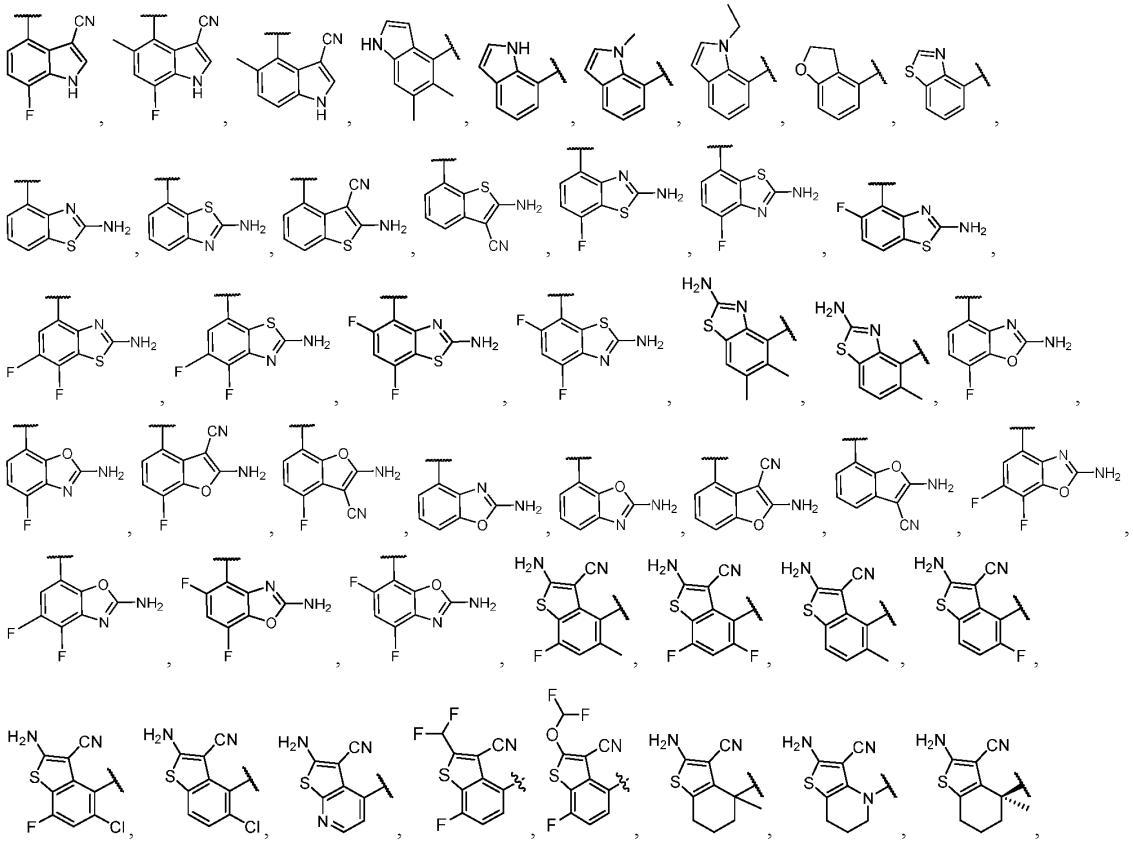
[463] In embodiments of the formulae above, X^{13} is a bond. In embodiments of the formulae above, X^{13} is $C(R^{1a})$. In embodiments of the formulae above, X^{13} is N. In embodiments of the formulae above, X^{13} is C(O). In embodiments of the formulae above, X^{13} is $C(R^{1a})(R^{1b})$. In embodiments of the formulae above, X^{13} is $C(O)C(R^{1a})(R^{1b})$. In embodiments of the formulae above, X^{13} is $C(R^{1a})(R^{1b})C(R^{1a})(R^{1b})$. In embodiments of the formulae above, X^{13} is $C(R^{1a})(R^{1b})N(R^{1c})$. In embodiments of the formulae above, X^{13} is $N(R^{1c})$.

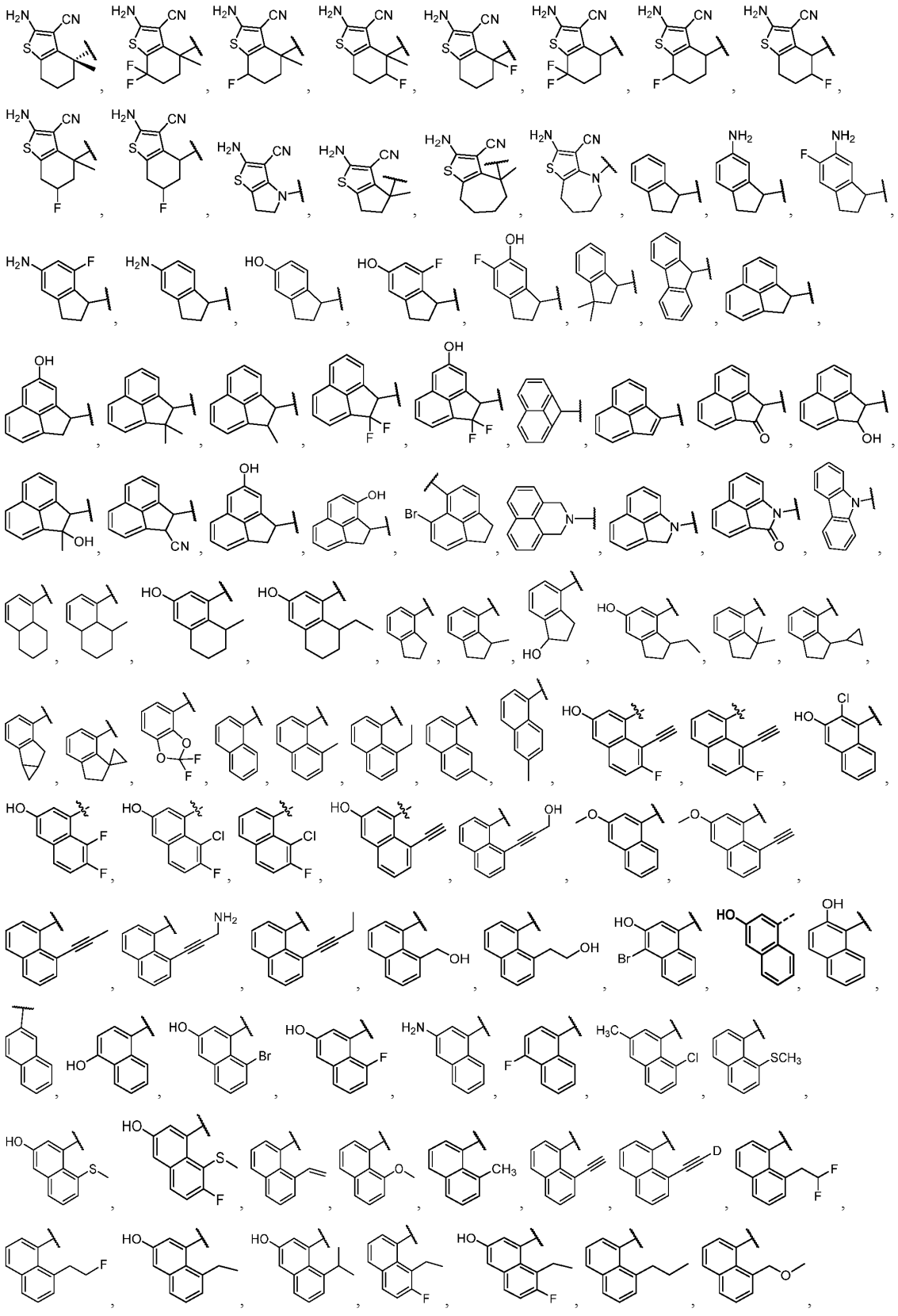
[464] In embodiments of the formulae above, X^{14} is $C(R^{1a})$. In embodiments of the formulae above, X^{14} is N. In embodiments of the formulae above, X^{14} is C(O). In embodiments of the formulae above, X^{14} is $C(R^{1a})(R^{1b})$. In embodiments of the formulae above, X^{14} is $N(R^{1c})$. In embodiments of the formulae above, X^{15} is $C(R^{1a})$. In embodiments of the formulae above, X^{15} is N. In embodiments of the formulae above, X^{15} is C(O). In embodiments of the formulae above, X^{15} is $C(R^{1a})(R^{1b})$. In embodiments of the formulae above, X^{15} is $N(R^{1c})$. In embodiments of the formulae above, X^{17} is $C(R^{1a})$. In embodiments of the formulae above, X^{17} is N. In embodiments of the formulae above, X^{17} is C(O). In embodiments of the formulae above, X^{17} is $C(R^{1a})(R^{1b})$. In embodiments of the formulae above, X^{17} is $N(R^{1c})$. In embodiments of the formulae above, X^{18} is $C(R^{1a})$. In embodiments of the formulae above, X^{18} is N. In embodiments of the formulae above, X^{18} is C(O). In embodiments of the formulae above, X^{18} is $C(R^{1a})(R^{1b})$. In embodiments of the formulae above, X^{18} is $N(R^{1c})$.

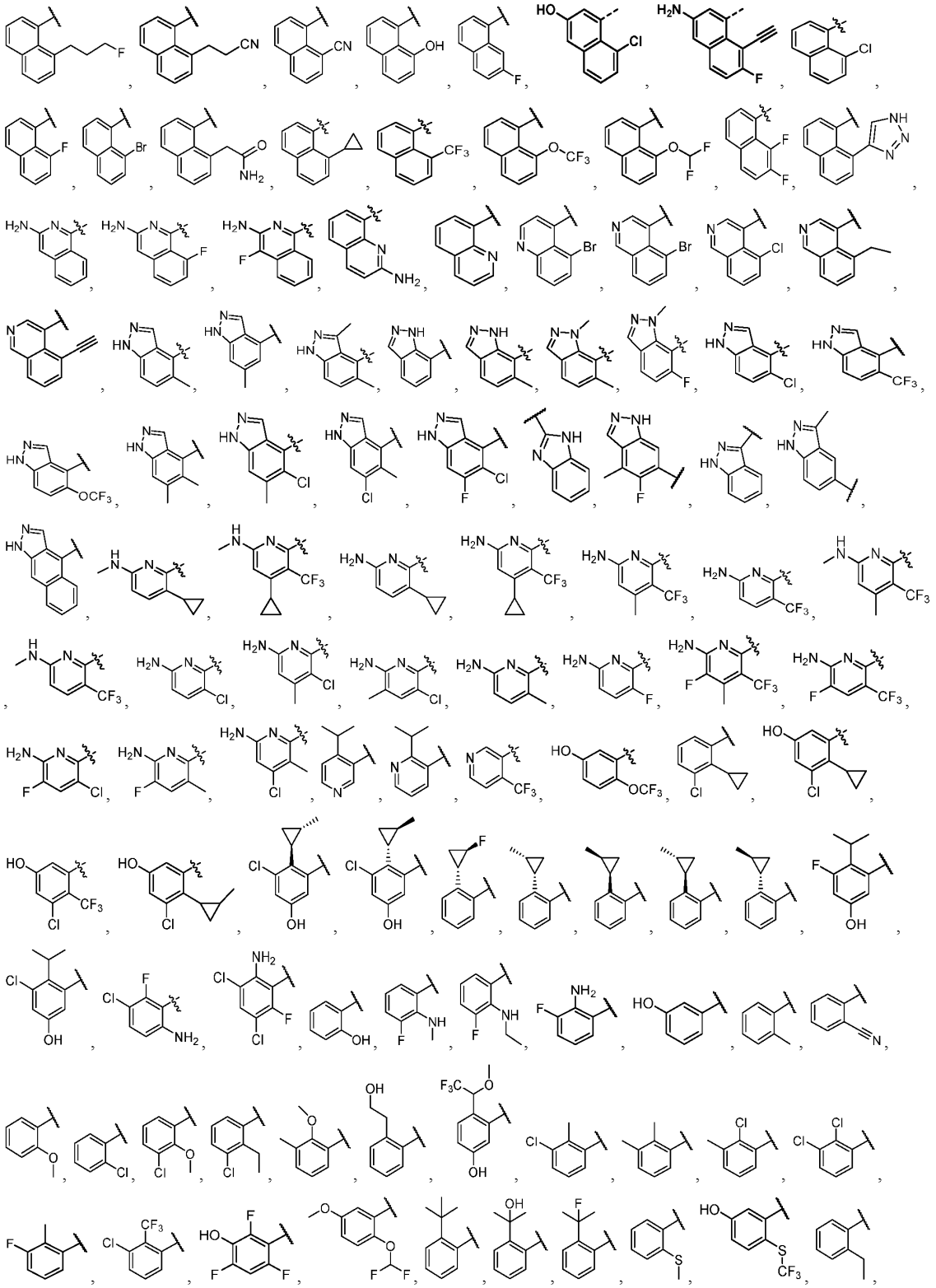
[465] In embodiments of the formulae above, X^{16} is C. In embodiments of the formulae above, X^{16} is N. In embodiments of the formulae above, X^{16} is $C(R^{1a})$.

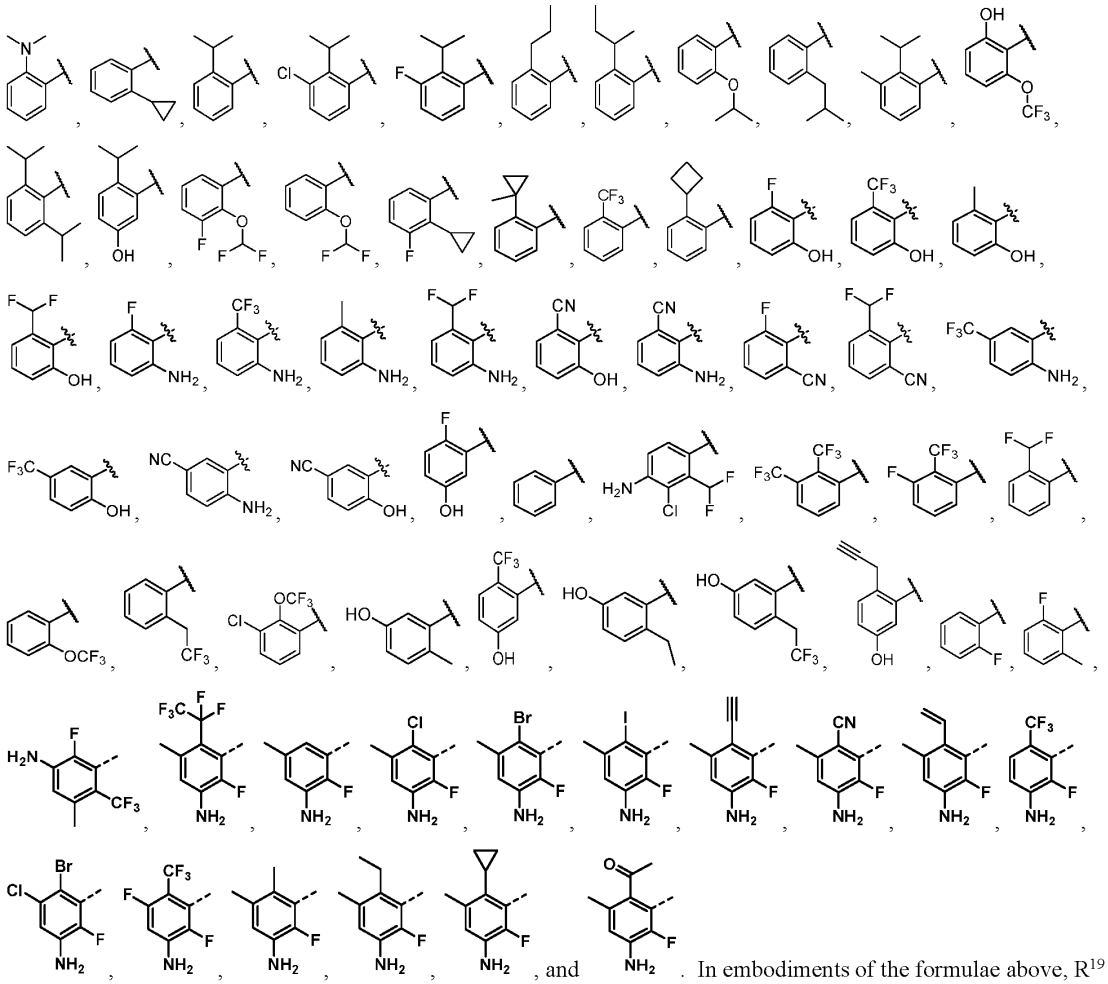
[466] In embodiments of the formulae above, R^{1i} is halogen. In embodiments of the formulae above, R^{1i} is -CN. In embodiments of the formulae above, R^{1i} is $C_{1\text{-}6}$alkyl. In embodiments of the formulae above, R^{1i} is $C_{2\text{-}6}$alkenyl. In embodiments of the formulae above, R^{1i} is $C_{2\text{-}6}$alkynyl. In embodiments of the formulae above, R^{1i} is $C_{3\text{-}10}$cycloalkyl. In embodiments of the formulae above, R^{1i} is $C_{2\text{-}9}$heterocycloalkyl. In embodiments of the formulae above, R^{1i} is $C_{6\text{-}10}$aryl. In embodiments of the formulae above, R^{1i} is $C_{1\text{-}9}$heteroaryl. In embodiments of the formulae above, R^{1i} is $C_{1\text{-}6}$alkyl optionally substituted with one, two, or three R^{20i}. In embodiments of the formulae above, R^{1i} is $C_{2\text{-}6}$alkenyl optionally substituted with one, two, or three R^{20i}. In embodiments of the formulae above, R^{1i} is $C_{2\text{-}6}$alkynyl optionally substituted

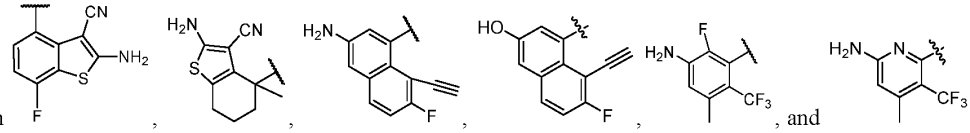
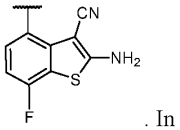
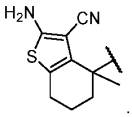
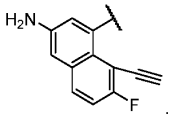
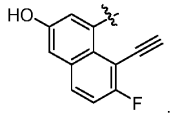
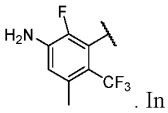
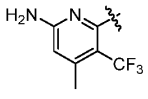
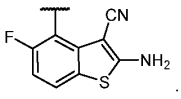
with one, two, or three R^{20i}. In embodiments of the formulae above, R^{1i} is C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20i}. In embodiments of the formulae above, R^{1i} is C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20i}. In embodiments of the formulae above, R^{1i} is C_{6-10}aryl optionally substituted with one, two, or three R^{20i}. In embodiments of the formulae above, R^{1i} is C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20i}. In embodiments of the formulae above, R^{1i} is $-OR^{12}$. In embodiments of the formulae above, R^{1i} is $-SR^{12}$. In embodiments of the formulae above, R^{1i} is $-N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{1i} is $-C(O)OR^{12}$. In embodiments of the formulae above, R^{1i} is $-OC(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{1i} is $-N(R^{14})C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{1i} is $-N(R^{14})C(O)OR^{15}$. In embodiments of the formulae above, R^{1i} is $-N(R^{14})S(O)_2R^{15}$. In embodiments of the formulae above, R^{1i} is $-C(O)R^{15}$. In embodiments of the formulae above, R^{1i} is $-S(O)R^{15}$. In embodiments of the formulae above, R^{1i} is $-OC(O)R^{15}$. In embodiments of the formulae above, R^{1i} is $-C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{1i} is $-C(O)C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{1i} is $-N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^{1i} is $-S(O)_2R^{15}$. In embodiments of the formulae above, R^{1i} is $-S(O)_2N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{1i} is $S(=O)(=NH)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{1i} is $-CH_2C(O)N(R^{12})(R^{13})$. In embodiments of the formulae above, R^{1i} is $-CH_2N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^{1i} is $-CH_2S(O)_2R^{15}$. In embodiments of the formulae above, R^{1i} is $-CH_2S(O)_2N(R^{12})(R^{13})$.

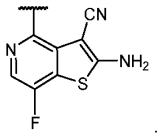
[467] In embodiments of the formulae above, R^{19} is selected from  , 



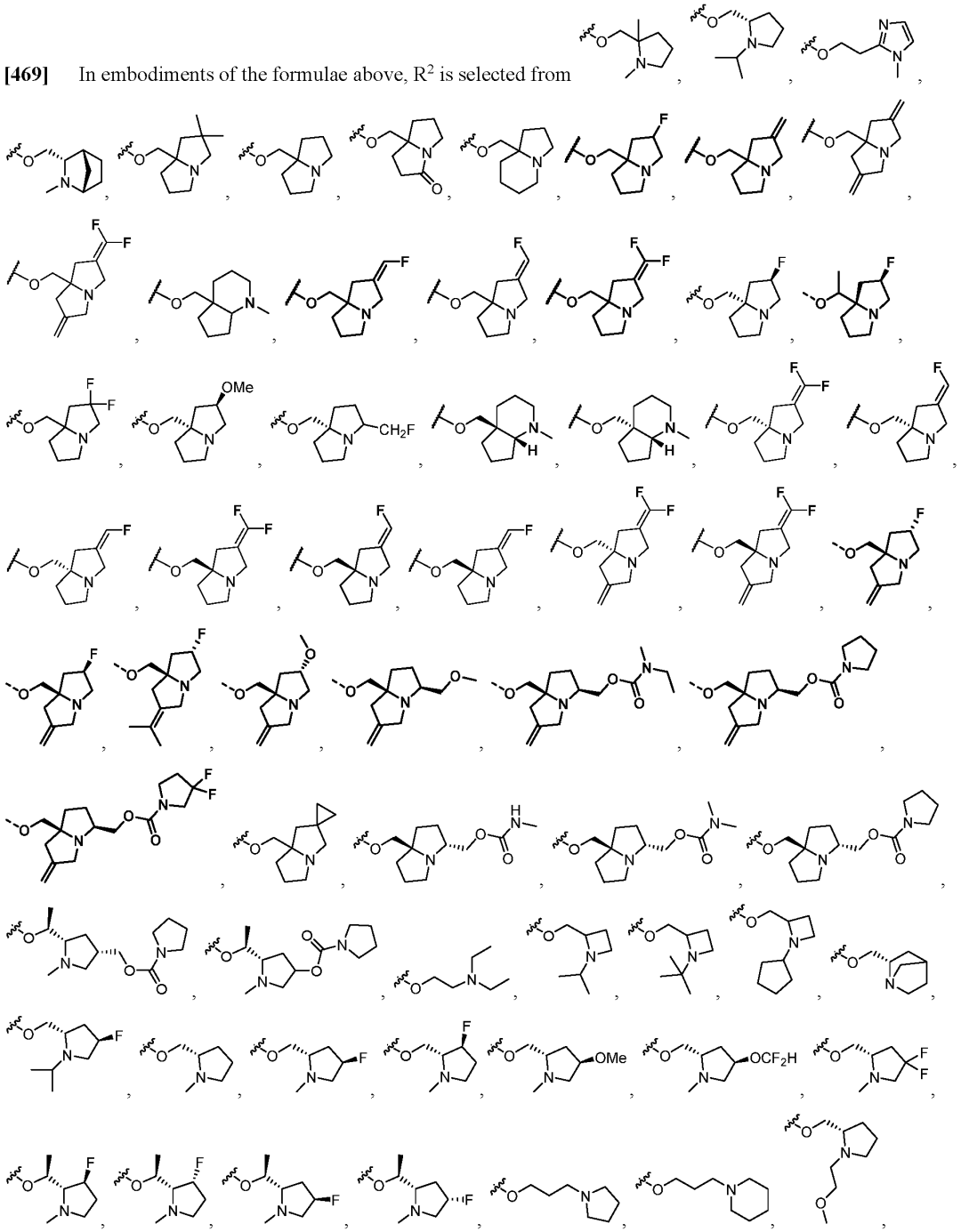


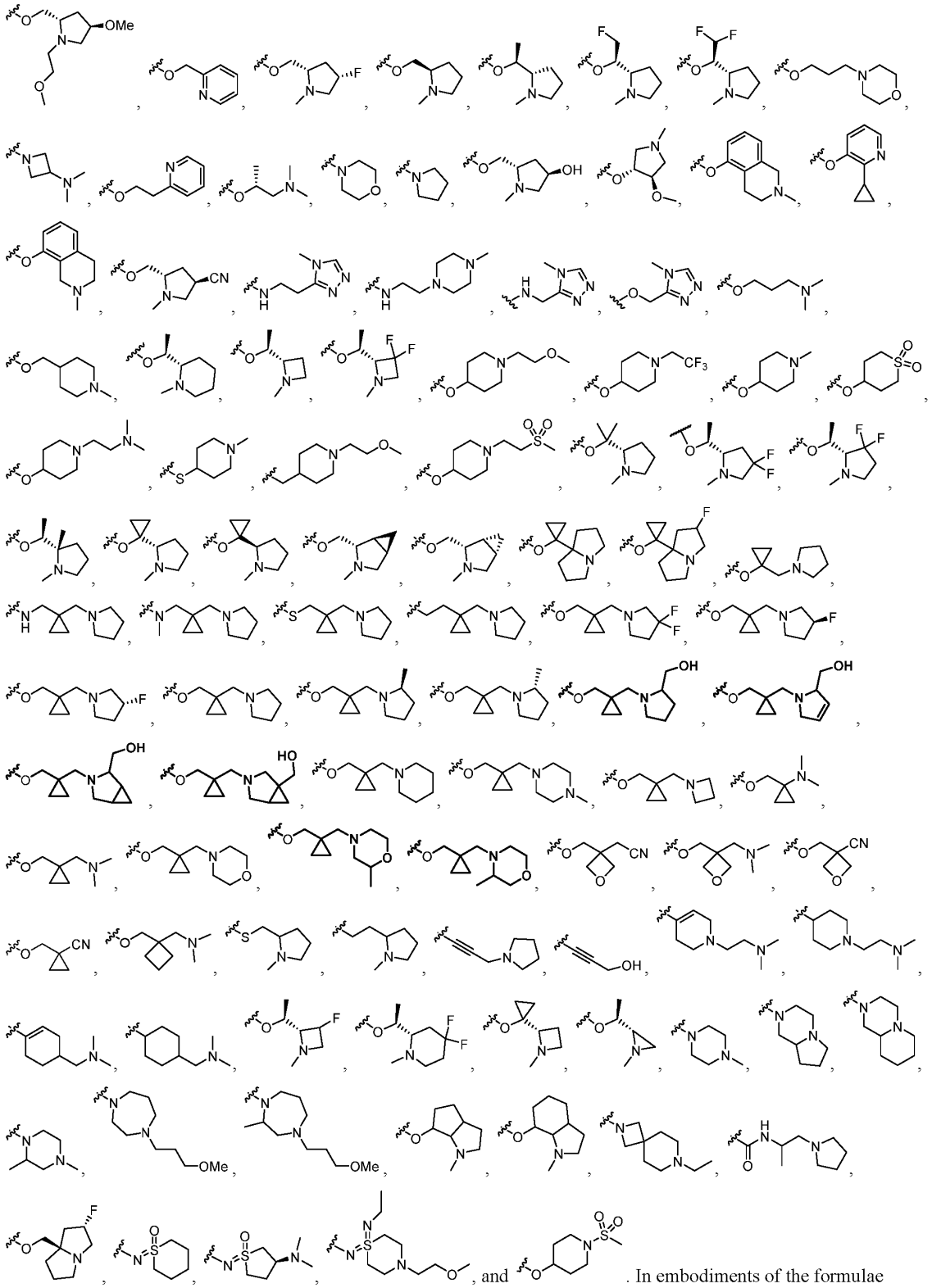


selected from  . In embodiments of the formulae above, R^{19} is  . In embodiments of the formulae above, R^{19} is  . In embodiments of the formulae above, R^{19} is  . In embodiments of the formulae above, R^{19} is  . In embodiments of the formulae above, R^{19} is  . In embodiments of the formulae above, R^{19} is  . In embodiments of the formulae above, R^{19} is  . In embodiments of the

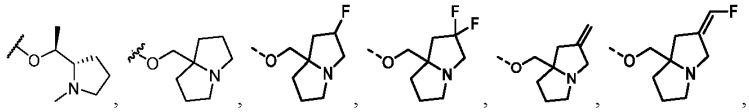
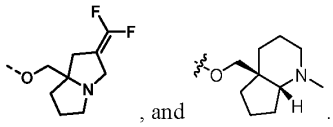
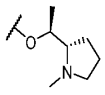
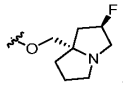
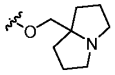
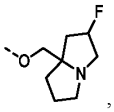
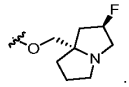
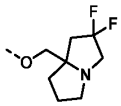
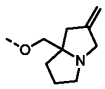
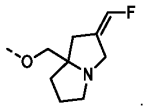
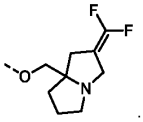
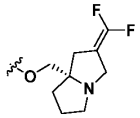
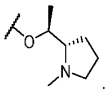
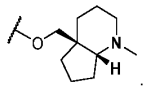
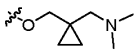
formulae above, R^{19} is  .

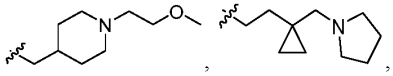
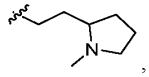
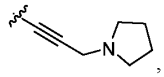
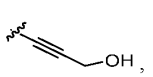
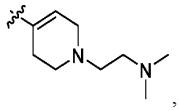
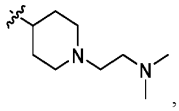
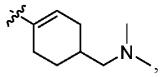
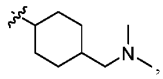
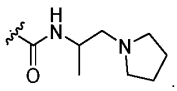
[468] In embodiments of the formulae above, R^2 is $-OR^{12'}$.

[469] In embodiments of the formulae above, R^2 is selected from 



. In embodiments of the formulae

above, R^2 is selected from  ,  , and . In embodiments of the formulae above, R^2 is selected from  and  . In embodiments of the formulae above, R^2 is  optionally substituted with one or more R^{20}. In embodiments of the formulae above, R^2 is  , such as  . In embodiments of the formulae above, R^2 is  . In embodiments of the formulae above, R^2 is  . In embodiments of the formulae above, R^2 is  . In embodiments of the formulae above, R^2 is  . In embodiments of the formulae above, R^2 is  . In embodiments of the formulae above, R^2 is  . In embodiments of the formulae above, R^2 is  . In embodiments of the formulae above, R^2 is  .

[470] In embodiments of the formulae above, R^{2b} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  .

[471] In embodiments of the formulae above, R^3 is hydrogen. In embodiments of the formulae above, R^3 is-CN. In embodiments of the formulae above, R^3 is $C_{1\text{-}6}$alkyl optionally substituted with one, two, or three R^{20b}. In embodiments of the formulae above, R^3 is $C_{2\text{-}6}$alkenyl optionally substituted with one, two, or three R^{20b}. In embodiments of the formulae above, R^3 is $C_{2\text{-}6}$alkynyl optionally substituted with one, two, or three R^{20b}. In embodiments of the formulae above, R^3 is $C_{3\text{-}10}$cycloalkyl optionally substituted with one, two, or three R^{20b}. In embodiments of the formulae above, R^3 is $C_{2\text{-}9}$heterocycloalkyl optionally substituted with one, two, or three R^{20b}. In embodiments of the formulae above, R^3 is $C_{6\text{-}10}$aryl optionally substituted with one, two, or three R^{20b}. In embodiments of the formulae above, R^3 is $C_{1\text{-}9}$heteroaryl optionally substituted with one, two, or three R^{20b}. In embodiments of the formulae above, R^3 is selected from $-OR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, halogen, and $-N(R^{12})(R^{13})$. In embodiments of the formulae

above, R^3 is $-NH_2$.

[472] In embodiments of the formulae above, R^8 is hydrogen. In embodiments of the formulae above, R^8 is halogen. In embodiments of the formulae above, R^8 is -CN. In embodiments of the formulae above, R^8 is C_{1-6}alkyl. In embodiments of the formulae above, R^8 is C_{2-6}alkenyl. In embodiments of the formulae above, R^8 is C_{2-6}alkynyl. In embodiments of the formulae above, R^8 is C_{3-10}cycloalkyl. In embodiments of the formulae above, R^8 is C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^8 is C_{6-10}aryl. In embodiments of the formulae above, R^8 is C_{1-9}heteroaryl. In embodiments of the formulae above, R^8 is CF_3.

[473] In embodiments of the formulae above, R^8 is C_{1-6}alkyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^8 is C_{2-6}alkenyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^8 is C_{2-6}alkynyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^8 is C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^8 is C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^8 is C_{6-10}aryl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^8 is C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20c}.

[474] In embodiments of the formulae above, R^{8a} is hydrogen.

[475] In embodiments of the formulae above, R^{8b} is hydrogen. In embodiments of the formulae above, R^{8b} is halogen. In embodiments of the formulae above, R^{8b} is -CN. In embodiments of the formulae above, R^{8b} is C_{1-6}alkyl. In embodiments of the formulae above, R^{8b} is C_{2-6}alkenyl. In embodiments of the formulae above, R^{8b} is C_{2-6}alkynyl. In embodiments of the formulae above, R^{8b} is C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{8b} is C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{8b} is C_{6-10}aryl. In embodiments of the formulae above, R^{8b} is C_{1-9}heteroaryl. In embodiments of the formulae above, R^{8b} is unsubstituted cyclopropyl.

[476] In embodiments of the formulae above, R^{8b} is C_{1-6}alkyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^{8b} is C_{2-6}alkenyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^{8b} is C_{2-6}alkynyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^{8b} is C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^{8b} is C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^{8b} is C_{6-10}aryl optionally substituted with one, two, or three R^{20c}. In embodiments of the formulae above, R^{8b} is C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20c}.

[477] In embodiments of the formulae above, R^{18} is hydrogen. In embodiments of the formulae above, R^{18} is halogen. In embodiments of the formulae above, R^{18} is -CN. In embodiments of the formulae above, R^{18} is C_{1-6}alkyl. In embodiments of the formulae above, R^{18} is C_{2-6}alkenyl. In embodiments of the formulae above, R^{18} is C_{2-6}alkynyl. In embodiments of the formulae above, R^{18} is C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{18} is C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{18} is C_{6-10}aryl. In embodiments of the formulae above, R^{18} is C_{1-9}heteroaryl. In embodiments of the formulae above, R^{18} is F. In embodiments of the formulae above, R^{18} is Cl. In embodiments of the formulae above, R^{18} is Br. In embodiments of the formulae above, R^{18} is I. In embodiments of the formulae above, R^{18} is cyclopropyl. In embodiments of the formulae above, R^{18} is CN substituted C_{1-4}alkyl. In embodiments of the formulae above, R^{18} is CN substituted propyl. In embodiments of the formulae above, R^{18} is CN substituted ethyl. In embodiments of the formulae above, R^{18} is CN substituted butyl. In embodiments of the formulae above, R^{18} is CN substituted methyl.

[478] In embodiments of the formulae above, R^{18} is C_{1-6}alkyl optionally substituted with one, two, or three R^{20h}. In embodiments of the formulae above, R^{18} is C_{2-6}alkenyl optionally substituted with one, two, or three R^{20h}. In

embodiments of the formulae above, R^{18} is C_{2-6}alkynyl optionally substituted with one, two, or three R^{20h}. In embodiments of the formulae above, R^{18} is C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20h}. In embodiments of the formulae above, R^{18} is C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20h}. In embodiments of the formulae above, R^{18} is C_{6-10}aryl optionally substituted with one, two, or three R^{20h}. In embodiments of the formulae above, R^{18} is C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20h}.

[479] In embodiments of the formulae above, R^{18a} is hydrogen.

[480] In embodiments of the formulae above, R^{18b} is hydrogen. In embodiments of the formulae above, R^{18b} is halogen. In embodiments of the formulae above, R^{18b} is -CN. In embodiments of the formulae above, R^{18b} is C_{1-6}alkyl. In embodiments of the formulae above, R^{18b} is C_{2-6}alkenyl. In embodiments of the formulae above, R^{18b} is C_{2-6}alkynyl. In embodiments of the formulae above, R^{18b} is C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{18b} is C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{18b} is C_{6-10}aryl. In embodiments of the formulae above, R^{18b} is C_{1-9}heteroaryl.

[481] In embodiments of the formulae above, R^{16} is hydrogen. In embodiments of the formulae above, R^{16} is halogen. In embodiments of the formulae above, R^{16} is -CN. In embodiments of the formulae above, R^{16} is C_{1-6}alkyl. In embodiments of the formulae above, R^{16} is C_{2-6}alkenyl. In embodiments of the formulae above, R^{16} is C_{2-6}alkynyl. In embodiments of the formulae above, R^{16} is C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{16} is C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{16} is C_{6-10}aryl. In embodiments of the formulae above, R^{16} is C_{1-9}heteroaryl. In embodiments of the formulae above, R^{16} is F. In embodiments of the formulae above, R^{16} is Cl. In embodiments of the formulae above, R^{16} is Br. In embodiments of the formulae above, R^{16} is I.

[482] In embodiments of the formulae above, R^{16} is C_{1-6}alkyl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16} is C_{2-6}alkenyl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16} is C_{2-6}alkynyl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16} is C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16} is C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16} is C_{6-10}aryl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16} is C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20g}.

[483] In embodiments of the formulae above, R^{16} is independently selected from $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$.

[484] In embodiments of the formulae above, R^{16a} is hydrogen.

[485] In embodiments of the formulae above, R^{16b} is hydrogen. In embodiments of the formulae above, R^{16b} is halogen. In embodiments of the formulae above, R^{16b} is -CN. In embodiments of the formulae above, R^{16b} is C_{1-6}alkyl. In embodiments of the formulae above, R^{16b} is C_{2-6}alkenyl. In embodiments of the formulae above, R^{16b} is C_{2-6}alkynyl. In embodiments of the formulae above, R^{16b} is C_{3-10}cycloalkyl. In embodiments of the formulae above, R^{16b} is C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^{16b} is C_{6-10}aryl. In embodiments of the formulae above, R^{16b} is C_{1-9}heteroaryl.

[486] In embodiments of the formulae above, R^{16b} is C_{1-6}alkyl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16b} is C_{2-6}alkenyl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16b} is C_{2-6}alkynyl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16b} is C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20g}. In

embodiments of the formulae above, R^{16b} is C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16b} is C_{6-10}aryl optionally substituted with one, two, or three R^{20g}. In embodiments of the formulae above, R^{16b} is C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20g}.

[487] In select embodiments, R^2 is independently C_{1-6}alkyl. In embodiments of the formulae above, R^2 is independently C_{2-6}alkenyl. In embodiments of the formulae above, R^2 is independently C_{2-6}alkynyl. In embodiments of the formulae above, R^2 is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, R^2 is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, R^2 is independently C_{6-10}aryl. In embodiments of the formulae above, R^2 is independently C_{1-9}heteroaryl.

[488] In embodiments of the formulae above, R^2 is independently C_{1-6}alkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently methyl optionally substituted with one or two R^{20d}. In embodiments of the formulae above, R^2 is independently methyl. In embodiments of the formulae above, R^2 is independently ethyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently ethyl. In embodiments of the formulae above, R^2 is independently propyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently propyl. In embodiments of the formulae above, R^2 is independently C_{2-6}alkenyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently C_{2-6}alkynyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently C_{6-10}aryl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently and C_{1-9}heteroaryl optionally substituted with one, two, or three R^{20d}. .

[489] In additional embodiments, R^2 is independently halogen. In additional embodiments, R^2 is independently -CN. In embodiments of the formulae above, R^2 is $-OR^{12'}$. In embodiments of the formulae above, R^2 is $-SR^{12'}$. In embodiments of the formulae above, R^2 is $-N(R^{12''})(R^{13})$. In embodiments of the formulae above, R^2 is $-N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^2 is $-C(O)OR^{12'}$. In embodiments of the formulae above, R^2 is $-OC(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^2 is $-N(R^{14})C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^2 is $-N(R^{14})C(O)OR^{15}$. In embodiments of the formulae above, R^2 is $-N(R^{14})S(O)_2R^{15}$. In embodiments of the formulae above, R^2 is $-C(O)R^{15}$. In embodiments of the formulae above, R^2 is $-S(O)R^{15}$. In embodiments of the formulae above, R^2 is $-OC(O)R^{15}$. In embodiments of the formulae above, R^2 is $-C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^2 is $-C(O)C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^2 is $-N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^2 is $-S(O)_2R^{15}$. In embodiments of the formulae above, R^2 is $-S(O)_2N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^2 is $S(=O)(=NH)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^2 is $-CH_2C(O)N(R^{12'})(R^{13})$. In embodiments of the formulae above, R^2 is $-CH_2N(R^{14})C(O)R^{15}$. In embodiments of the formulae above, R^2 is $-CH_2S(O)_2R^{15}$. In embodiments of the formulae above, R^2 is $-CH_2S(O)_2N(R^{12'})(R^{13})$.

[490] In embodiments of the formulae above, R^2 is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently (monocyclic C_{2-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently (monocyclic C_{3-5}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently (spirocyclic C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently (spirocyclic C_{3-11}heterocycloalkyl) optionally substituted with

one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently (fused C_{2-11}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently (spirocyclic C_{6-8}heterocycloalkyl) optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently –(C_1-C_6alkyl)-R^{12b}. In embodiments of the formulae above, R^2 is independently, –(C_{2-6}alkenyl)-R^{12b}. In embodiments of the formulae above, R^2 is independently, –(C_{2-6}alkynyl)-R^{12b}. In embodiments of the formulae above, R^2 is independently, -(C_{3-10}cycloalkyl)-R^{12b}. In embodiments of the formulae above, R^2 is independently, -(C_{2-9}heterocycloalkyl)-R^{12b}. In embodiments of the formulae above, R^2 is independently, -(C_{6-10}aryl)-R^{12b}. In embodiments of the formulae above, R^2 is independently, or –(C_{1-9}heteroaryl)-R^{12b}. In embodiments of the formulae above, R^2 is independently –(C_1-C_6alkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently, –(C_{2-6}alkenyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently, –(C_{2-6}alkynyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently, -(C_{3-10}cycloalkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently, -(C_{2-9}heterocycloalkyl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently, -(C_{6-10}aryl)-R^{12b} optionally substituted with one, two, or three R^{20d}. In embodiments of the formulae above, R^2 is independently, –(C_{1-9}heteroaryl)-R^{12b} optionally substituted with one, two, or three R^{20d}.

[491] In embodiments of the formulae above, each R^{13} is independently hydrogen. In embodiments of the formulae above, each R^{13} is independently C_{1-6}alkyl. In embodiments of the formulae above, each R^{13} is independently C_{1-6}haloalkyl. In embodiments of the formulae above, each R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e}.

[492] In embodiments of the formulae above, each R^{14} is independently hydrogen. In embodiments of the formulae above, each R^{14} is independently C_{1-6}alkyl. In embodiments of the formulae above, each R^{14} is independently C_{1-6}haloalkyl.

[493] In embodiments of the formulae above, each R^{14a} is independently C_{1-6}alkyl. In embodiments of the formulae above, each R^{14a} is independently C_{1-6}haloalkyl.

[494] In embodiments of the formulae above, each R^{15} is independently C_{1-6}alkyl. In embodiments of the formulae above, each R^{15} is independently C_{2-6}alkenyl. In embodiments of the formulae above, each R^{15} is independently C_{2-6}alkynyl. In embodiments of the formulae above, each R^{15} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, each R^{15} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, each R^{15} is independently C_{6-10}aryl. In embodiments of the formulae above, each R^{15} is independently C_{1-9}heteroaryl.

[495] In embodiments of the formulae above, each R^{15} is independently C_{1-6}alkyl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently C_{2-6}alkenyl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently C_{2-6}alkynyl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently C_{3-10}cycloalkyl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently C_{2-9}heterocycloalkyl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently C_{6-10}aryl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently C_{1-9}heteroaryl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently ethenyl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently propenyl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently butenyl substituted with one, two, or three R^{20f}. In embodiments of the formulae above, each R^{15} is independently ethenyl. In embodiments of the formulae

above, each R^{15} is independently propenyl. In embodiments of the formulae above, each R^{15} is independently butenyl.

[496] In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently halogen. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently oxo. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently -CN. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{1\text{-}6}$alkyl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{2\text{-}6}$alkenyl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{2\text{-}6}$alkynyl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{3\text{-}10}$cycloalkyl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently -CH_2-$C_{3\text{-}10}$cycloalkyl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{2\text{-}9}$heterocycloalkyl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently -CH_2-$C_{2\text{-}9}$heterocycloalkyl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{6\text{-}10}$aryl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently -CH_2-$C_{6\text{-}10}$aryl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently -CH_2-$C_{1\text{-}9}$heteroaryl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{1\text{-}9}$heteroaryl. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently -OR^{21}. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently -SR^{21}. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently -$N(R^{22})(R^{23})$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently selected from -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{1\text{-}6}$alkyl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{2\text{-}6}$alkenyl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $C_{2\text{-}6}$alkynyl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$. In embodiments of the

formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently C_{3-10}cycloalkyl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $-CH_2-C_{3-10}$cycloalkyl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently C_{2-9}heterocycloalkyl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $-CH_2-C_{2-9}$heterocycloalkyl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently C_{6-10}aryl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $-CH_2-C_{6-10}$aryl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently $-CH_2-C_{1-9}$heteroaryl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$. In embodiments of the formulae above, each occurence of an R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, or R^{20m} is independently C_{1-9}heteroaryl optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, and $-OC(O)R^{25}$.

[497] In embodiments of the formulae above, each R^{21} is independently H. In embodiments of the formulae above, each R^{21} is independently C_{1-6}alkyl. In embodiments of the formulae above, each R^{21} is independently C_{1-6}haloalkyl. In

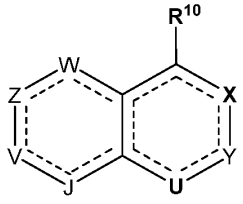
embodiments of the formulae above, each R^{21} is independently C_{2-6}alkenyl. In embodiments of the formulae above, each R^{21} is independently C_{2-6}alkynyl. In embodiments of the formulae above, each R^{21} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, each R^{21} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, each R^{21} is independently C_{6-10}aryl. In embodiments of the formulae above, each R^{21} is independently C_{1-9}heteroaryl.

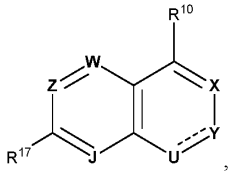
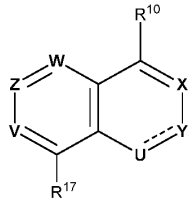
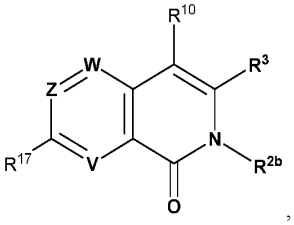
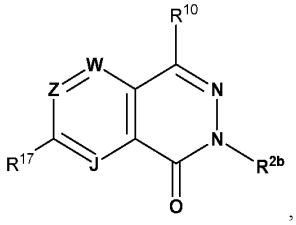
[498] In embodiments of the formulae above, each R^{22} is independently H. In embodiments of the formulae above, each R^{22} is independently C_{1-6}alkyl. In embodiments of the formulae above, each R^{22} is independently C_{1-6}haloalkyl. In embodiments of the formulae above, each R^{22} is independently C_{2-6}alkenyl. In embodiments of the formulae above, each R^{22} is independently C_{2-6}alkynyl. In embodiments of the formulae above, each R^{22} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, each R^{22} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, each R^{22} is independently C_{6-10}aryl. In embodiments of the formulae above, each R^{22} is independently C_{1-9}heteroaryl.

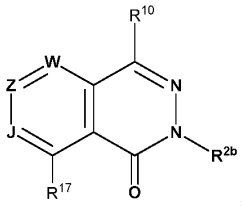
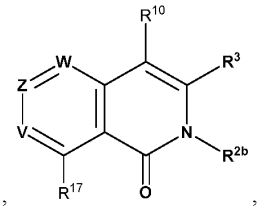
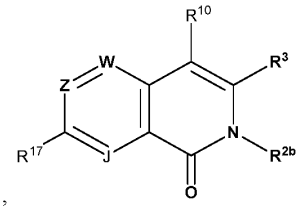
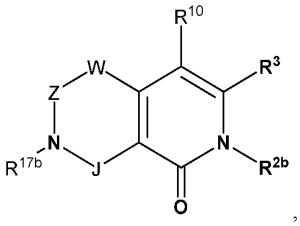
[499] In embodiments of the formulae above, each R^{23} is independently H. In embodiments of the formulae above, each R^{23} is independently C_{1-6}alkyl.

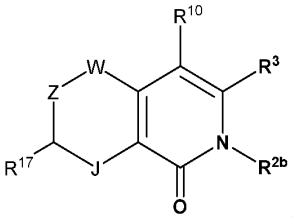
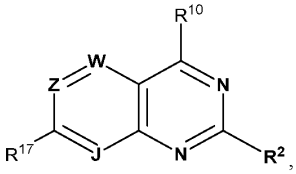
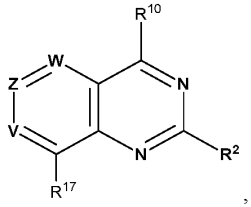
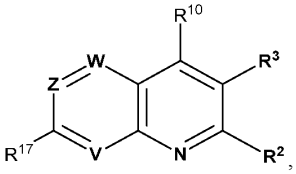
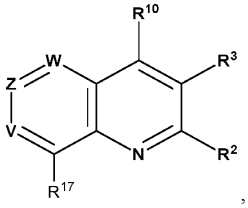
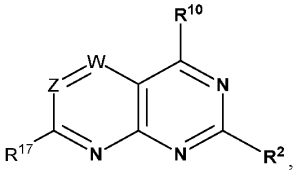
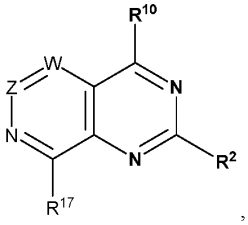
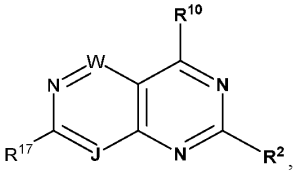
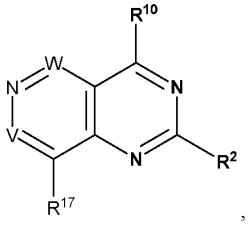
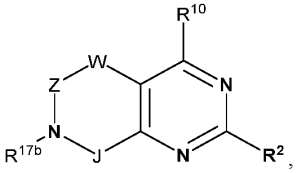
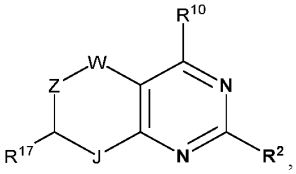
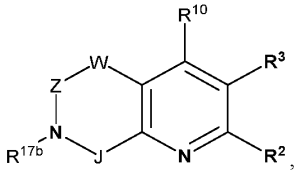
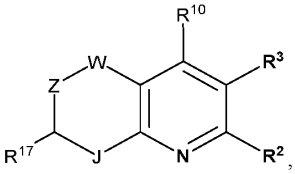
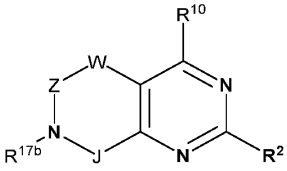
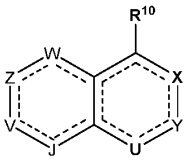
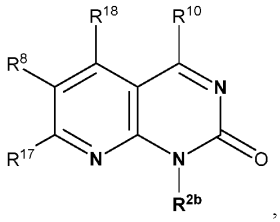
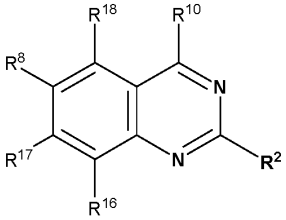
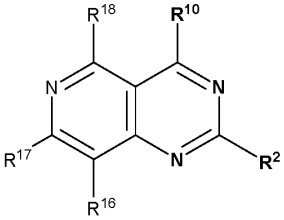
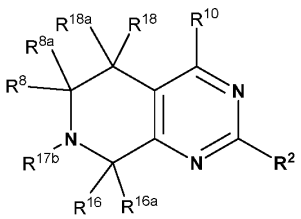
[500] In embodiments of the formulae above, each R^{24} is independently H. In embodiments of the formulae above, each R^{24} is independently C_{1-6}alkyl.

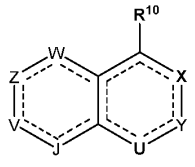
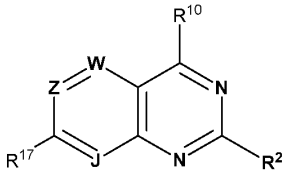
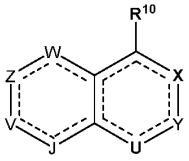
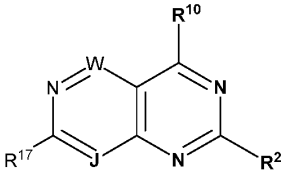
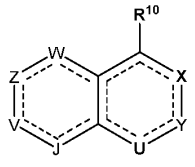
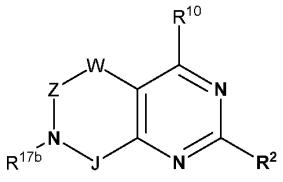
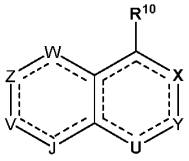
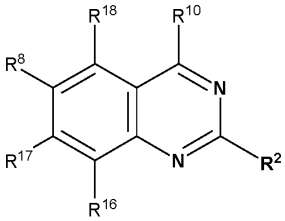
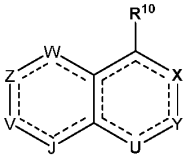
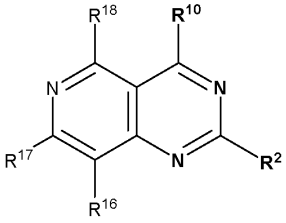
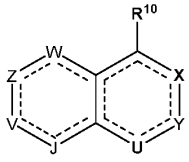
[501] In embodiments of the formulae above, each R^{25} is independently C_{1-6}alkyl. In embodiments of the formulae above, each R^{25} is independently C_{2-6}alkenyl. In embodiments of the formulae above, each R^{25} is independently C_{2-6}alkynyl. In embodiments of the formulae above, each R^{25} is independently C_{3-10}cycloalkyl. In embodiments of the formulae above, each R^{25} is independently C_{2-9}heterocycloalkyl. In embodiments of the formulae above, each R^{25} is independently C_{6-10}aryl. In embodiments of the formulae above, each R^{25} is independently C_{1-9}heteroaryl.

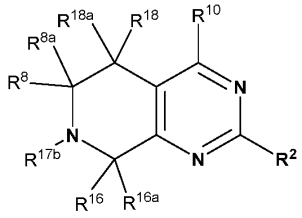
[502] In embodiments of the formulae above, the formula  is selected from

 ,  ,  ,  ,

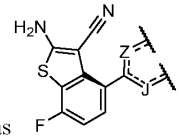
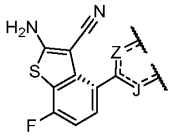
 ,  ,  ,  .

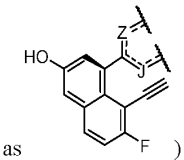














wherein X, Y, U, W, Z, V, J, R^2, R^{2b}, R^3, R^{10}, R^{17}, and R^{17b} are as described herein. In embodiments of the formulae above, the formula  is selected from  ,  ,  , and  wherein X, Y, U, W, Z, V, J, R^2, R^{2b}, R^{10}, R^8, R^{8a}, R^{16}, R^{16a}, R^{18}, R^{18a}, R^{17}, and R^{17b} are as described herein. In embodiments of the formulae

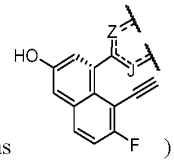
above, the formula  is  wherein W, Z, J, R^2, R^{10}, and R^{17} are as described herein. In embodiments of the formulae above, the formula  is  wherein W, J, R^2, R^{10}, and R^{17} are as described herein. In embodiments of the formulae above, the formula  is  wherein W, Z, J, R^2, R^{10}, and R^{17b} are as described herein. In embodiments of the formulae above, the formula  is  wherein R^2, R^{10}, R^8, R^{16}, R^{18}, and R^{17} are as described herein. In embodiments of the formulae above, the formula  is  wherein R^2, R^{10}, R^{16}, R^{18}, and R^{17} are as described herein. In embodiments of the formulae above, the formula  is



wherein R^2, R^{10}, R^8, R^{8a}, R^{16}, R^{16a}, R^{18}, R^{18a}, and R^{17b} are as described herein.

[503] In embodiments of the compounds recited above, each compound is a substantially pure single regioisomer at the positions corresponding to the attachment points of R^5 to L^2 and R^5 to R^{20k} in Formula (I) The single regioisomer shown in the compounds above is merely for simplicity of representation and it will be understood that in one embodiment, each compound is the regioisomer shown and in additional embodiments, the regioisomer is each of the alternative regioisomers. In embodiments of the compounds recited in the paragraph immediately above, each compound is a mixture of regioisomers at the positions corresponding to the attachment points of R^5 to L^2 and R^5 to R^{20k} in Formula (I). The single regioisomer shown in the compounds above is merely for simplicity of representation and it will be understood that embodiments, the compound is mixture of all possible regioisomers. In embodiments of the compounds recited in the paragraph immediately above, each compound is a partially purified mixture of regioisomers at the positions corresponding to the attachment points of R^5 to L^2 and R^5 to R^{20k} in Formula (I) (i.e., some but not all regioisomers are provided). In embodiments of the compounds recited in the paragraph immediately above, each compound is a single atropisomer (e.g., equivalent to R atropisomer) at the atom corresponding to the V atom bonded to R^{17} of Formula (I) and may optionally be a single, substantially single, partially purified, or mixture of regioisomers at the positions corresponding to the attachment points of R^5 to L^2 and R^5 to R^{20k} in Formula (I). In embodiments of the compounds recited in the paragraph immediately above, each compound is a single atropisomer (e.g., equivalent to S atropisomer) at the atom corresponding to the V atom bonded to R^{17} of Formula (I) and may optionally be a single, substantially single, partially purified, or mixture of regioisomers at the positions corresponding to the attachment points of R^5 to L^2 and R^5 to R^{20k} in Formula (I). In embodiments of the compounds recited in the paragraph immediately above, wherein atropisomers may be present, each compound is a single atropisomer (e.g., having the equivalent orientation as ) at the atom corresponding to the V atom bonded to R^{17} of Formula (I) and may optionally be a single, substantially single, partially purified, or mixture of regioisomers at the positions corresponding to the attachment points of R^5 to L^2 and R^5 to R^{20k} in Formula (I). In embodiments of the compounds recited in the paragraph immediately above, wherein atropisomers may be present, each compound is a single atropisomer (e.g., having the equivalent orientation as ) at the atom corresponding to the V atom bonded to R^{17} of Formula (I) and may optionally be a single, substantially single, partially purified, or mixture of regioisomers at the positions corresponding to the attachment points of R^5 to L^2 and R^5 to R^{20k} in Formula (I). In embodiments of the compounds recited in the paragraph immediately above, wherein atropisomers may be present, each

compound is a single atropisomer (e.g., having the equivalent orientation as 

) at the atom corresponding to the V atom bonded to R^{17} of Formula (I) and may optionally be a single, substantially single, partially purified, or mixture of regioisomers at the positions corresponding to the attachment points of R^5 to L^2 and R^5 to R^{20k} in Formula (I). In embodiments of the compounds recited in the paragraph immediately above, wherein atropisomers may be present, each compound is a single atropisomer (e.g., having the equivalent orientation as 

) at the atom corresponding to the V atom bonded to R^{17} of Formula (I) and may optionally be a single, substantially single, partially purified, or mixture of regioisomers at the positions corresponding to the attachment points of R^5 to L^2 and R^5 to R^{20k} in Formula (I). In embodiments, the compound is a compound described herein, including in an aspect, embodiment, example, table, scheme, method, or composition.

[504] In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (I), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (I-1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (I-2), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (II), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (II-1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (II-2), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (II-3), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (IV), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (IV-1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (IV-2), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (A), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (B), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (C), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate

thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (D), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (E), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (F), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (G), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Formula (H), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof.

[505] In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Table 1a, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the KRAS inhibitor is a compound of Table 1b, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, and the KRAS inhibitor is a compound described herein, or a pharmaceutically acceptable salt or solvate thereof.

[506] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

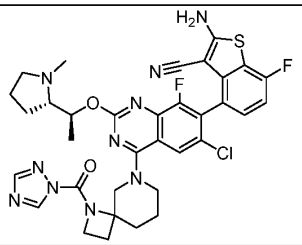
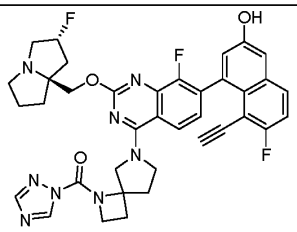
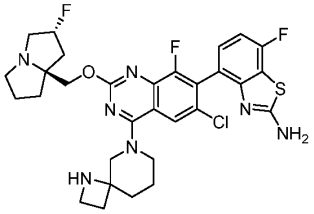
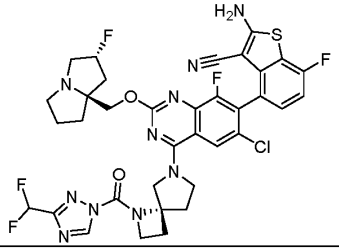
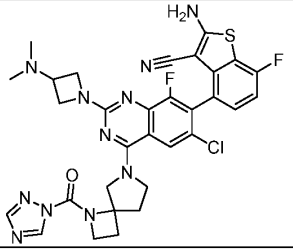
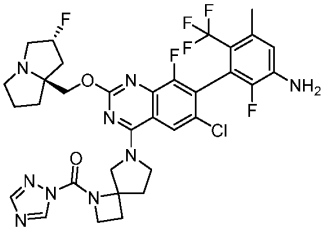
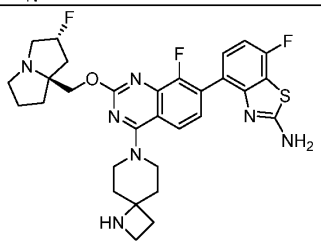
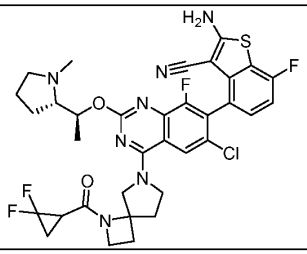
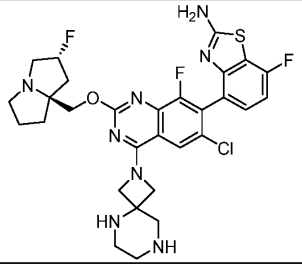
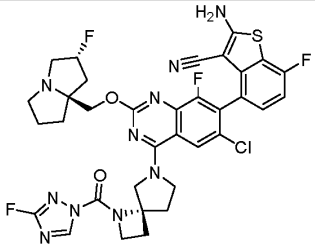
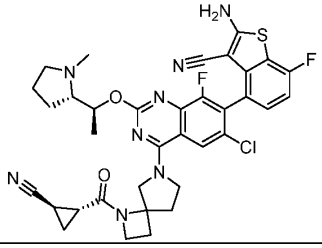
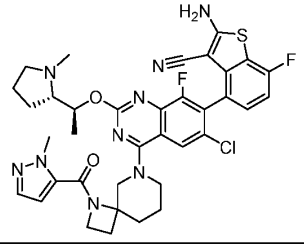
[507] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases or inorganic or organic acids to form a pharmaceutically acceptable salt. In some embodiments, such salts are prepared in situ during the final isolation and purification of the compounds described herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

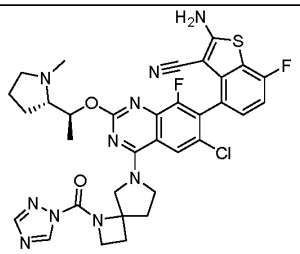
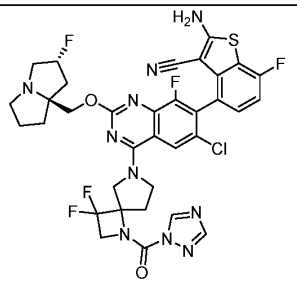
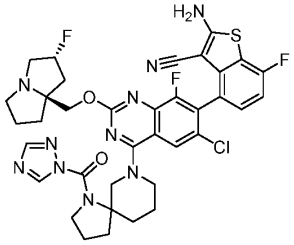
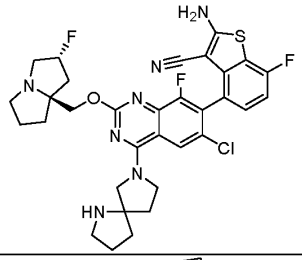
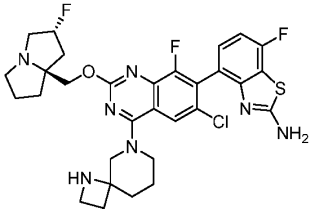
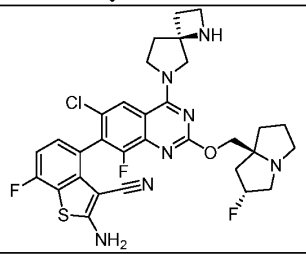
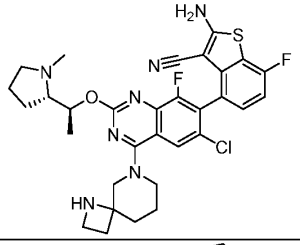
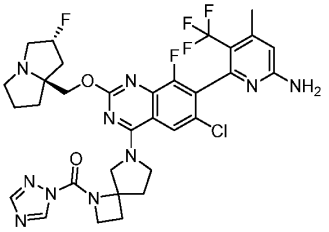
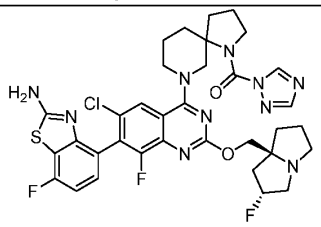
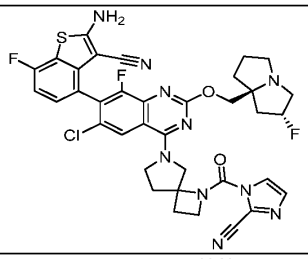
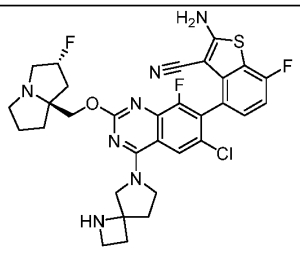
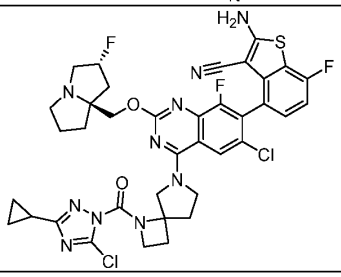
[508] In some embodiments, the compounds described herein exist as solvates. In some embodiments are methods of treating diseases by administering such solvates. Further described herein are methods of treating diseases by administering such solvates as pharmaceutical compositions.

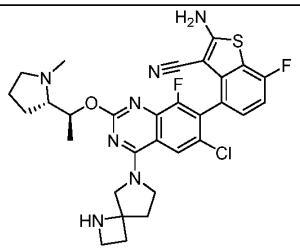
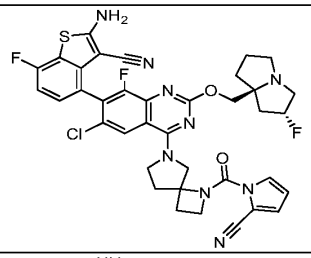
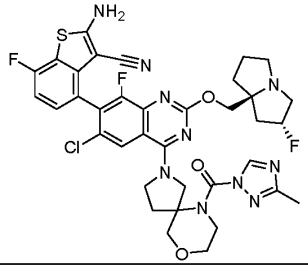
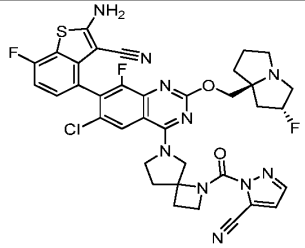
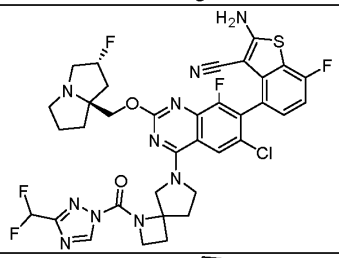
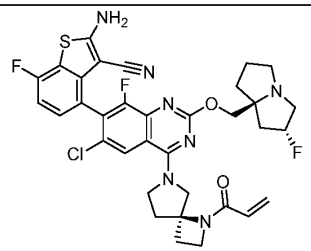
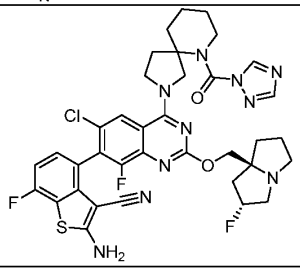
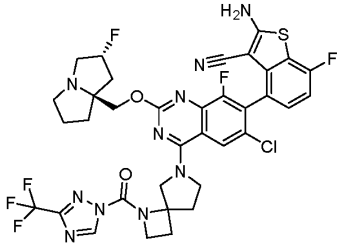
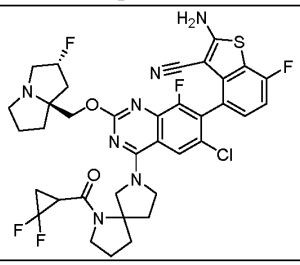
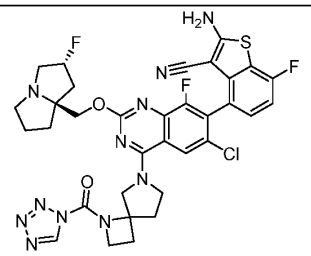
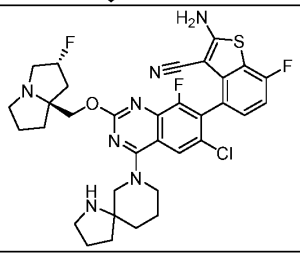
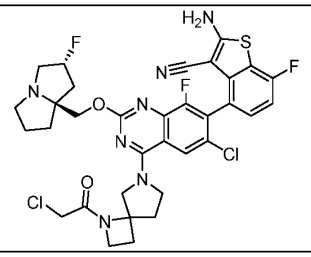
[509] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran, or MeOH. In addition, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

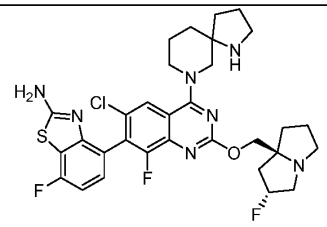
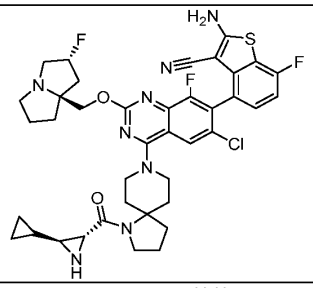
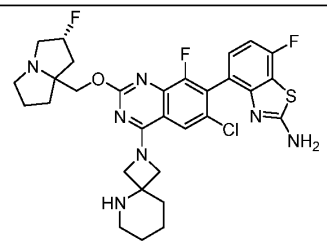
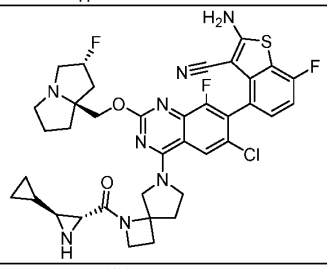
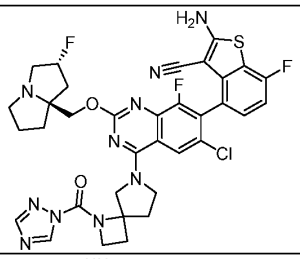
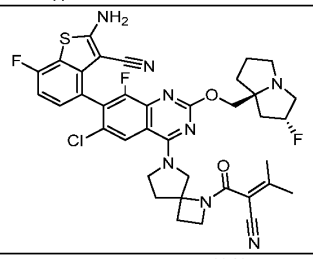
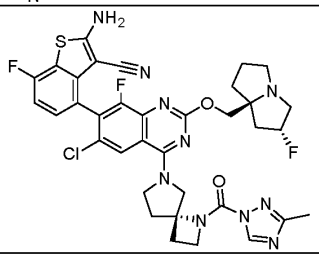
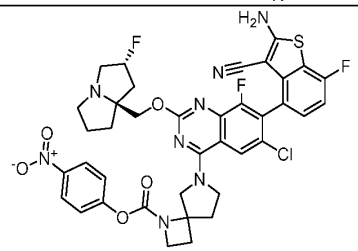
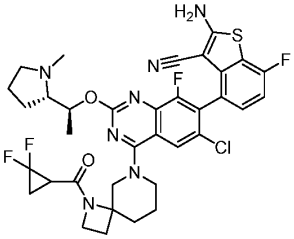
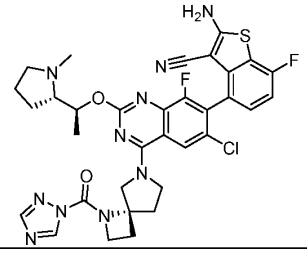
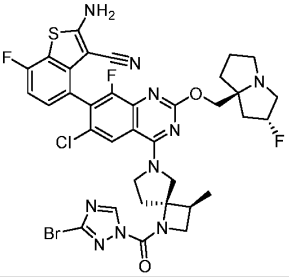
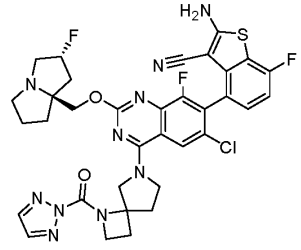
Table 1a: Compounds

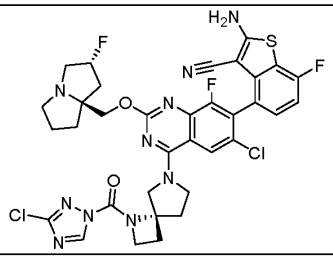
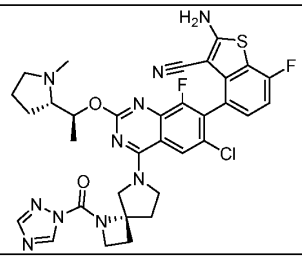
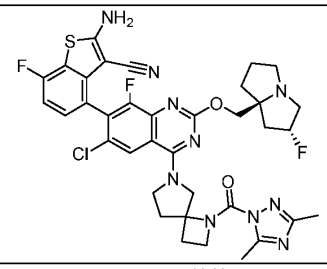
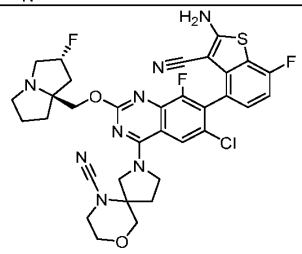
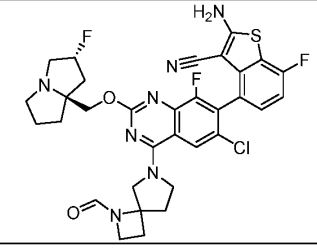
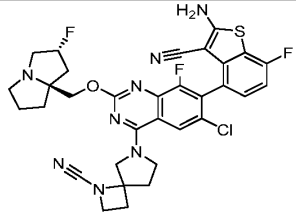
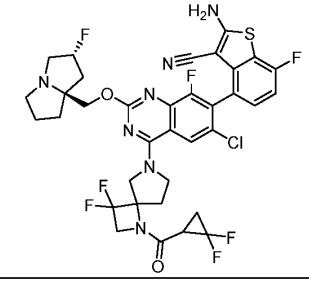
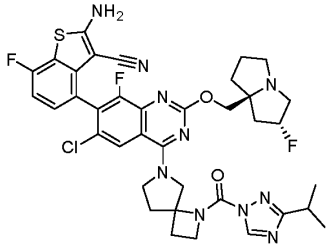
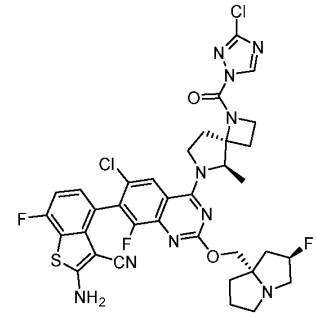
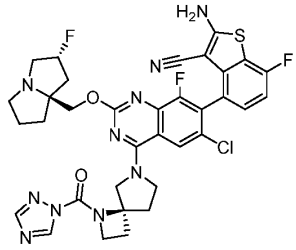
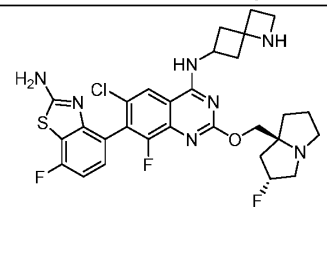
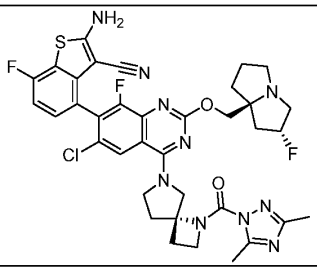
No.	Structure	$[M+H]^+$	No.	Structure	$[M+H]^+$

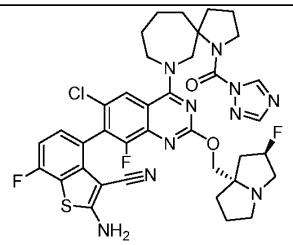
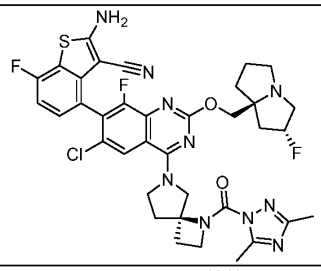
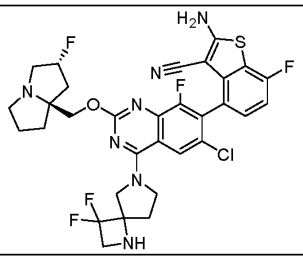
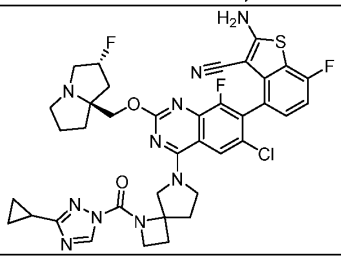
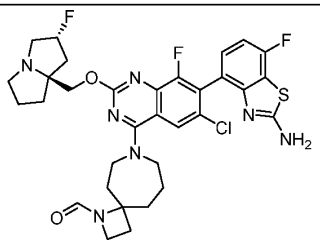
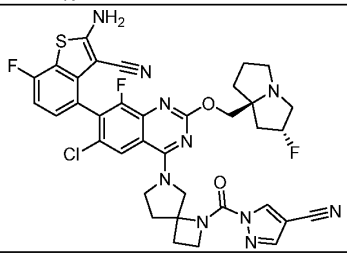
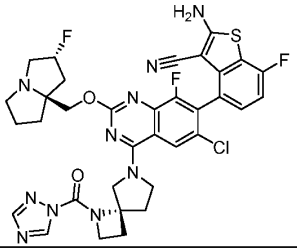
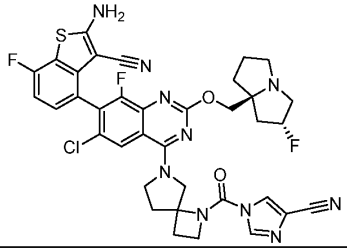
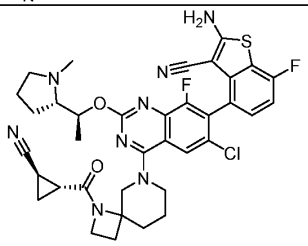
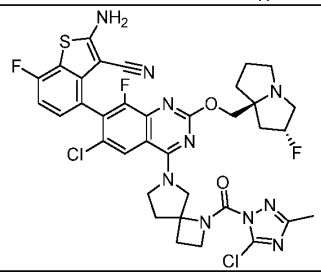
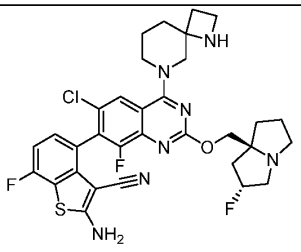
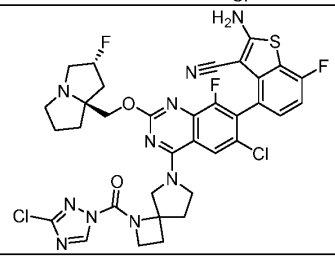
201		719.3	277		695.3
202		630.14	278 [2]		785.2
203		676.2	279		736.3
204		596.3	280		714.2
205		631.2	281 [2]		753.1
206		703.3	282		732.24

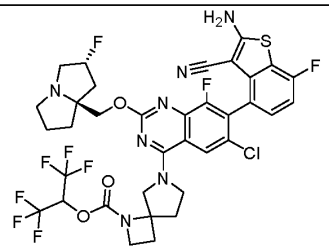
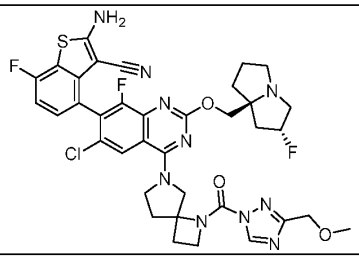
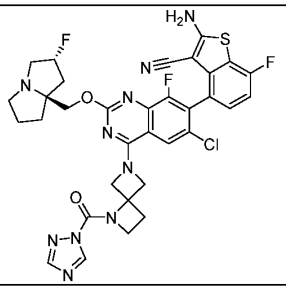
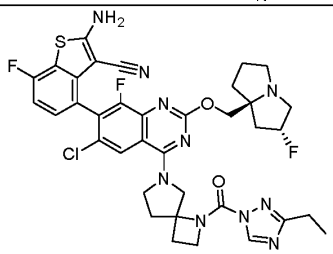
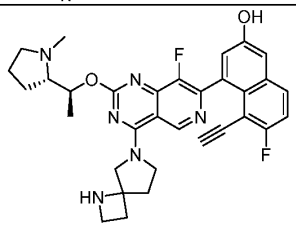
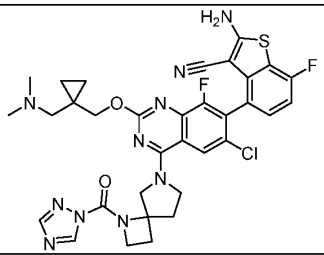
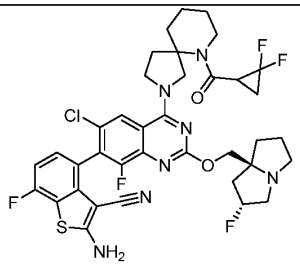
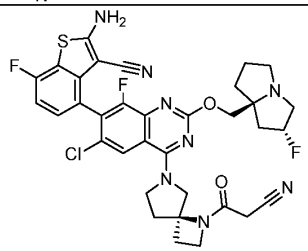
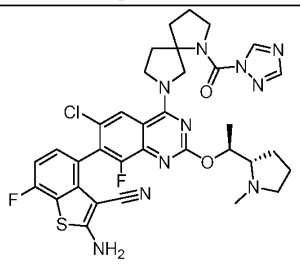
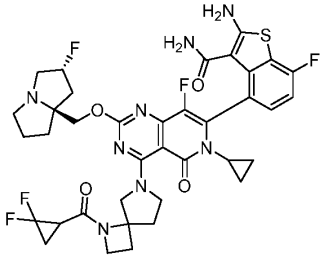
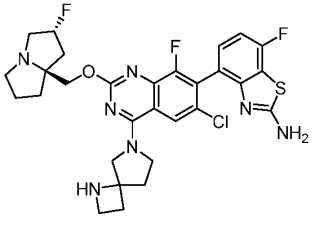
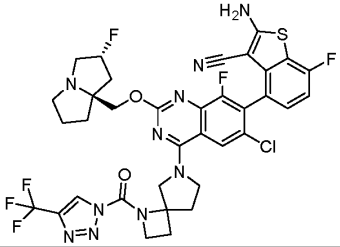
207		705.1	283		771.2
208 [1]		763.4	284		654.5
209		630.3	285 [2]		640.3
210		624.5	286		719.4
211		739.3	287		759.4
212		640.2	288 [5]		809.5

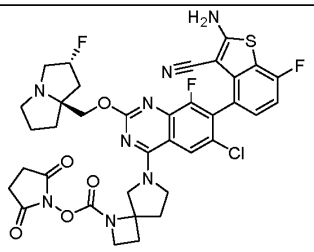
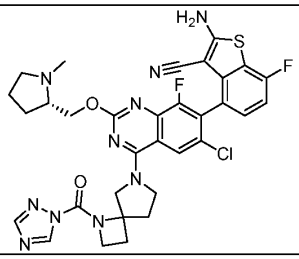
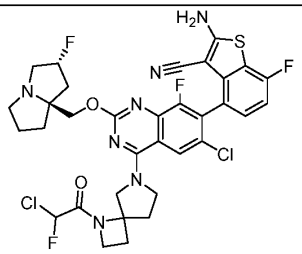
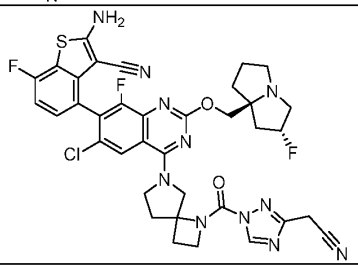
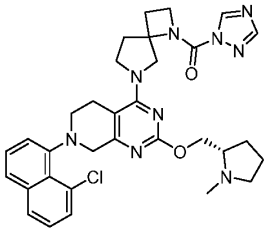
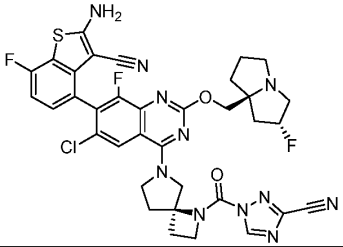
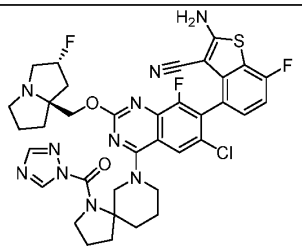
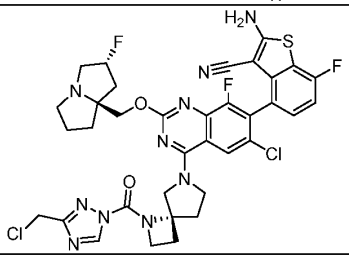
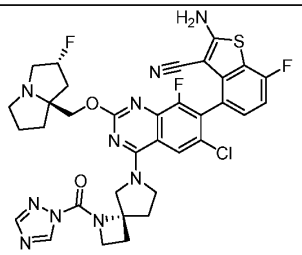
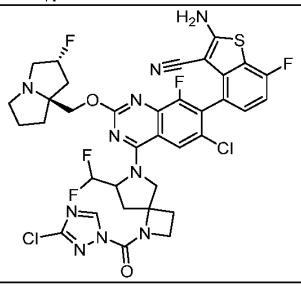
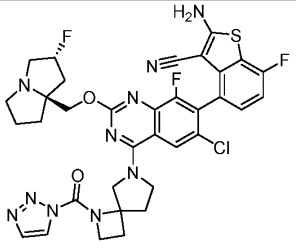
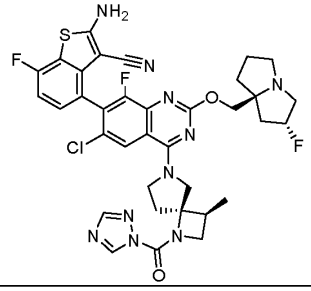
213		610.3	289		758.2
214 [4]		779.3	290 [5]		759.2
215		785.5	291 [2]		694.2
216		763.3	292		803.4
217		758.1	293 [5]		736.2
218 [1]		668.3	294		716.4

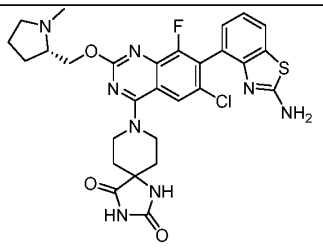
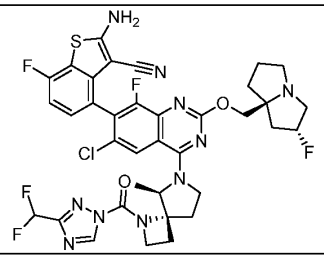
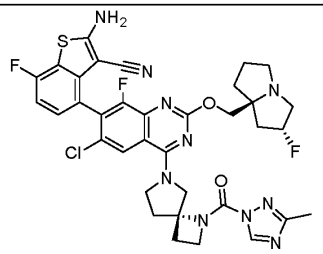
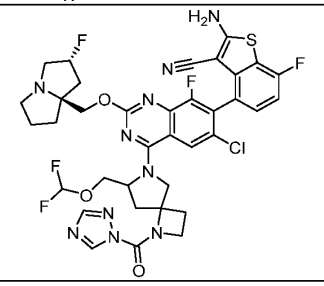
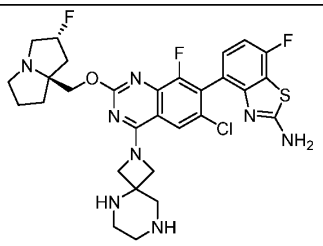
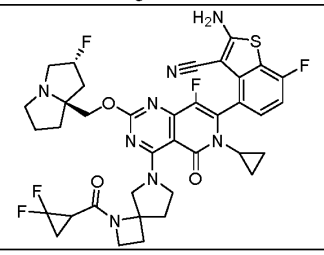
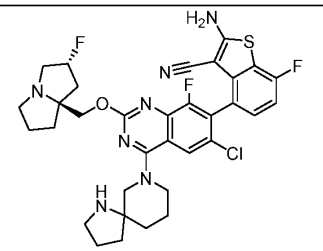
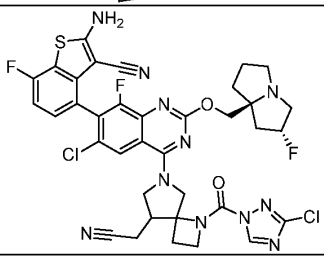
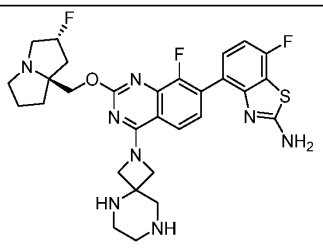
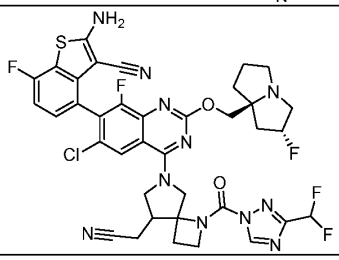
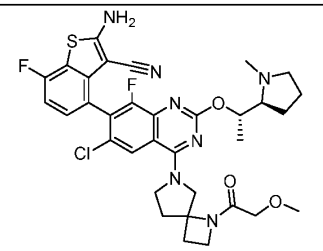
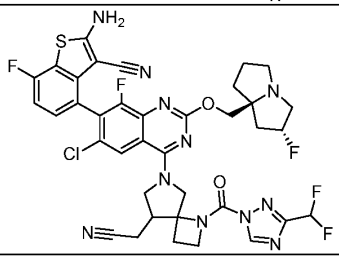
219		644.1	295		777.4
220		630.12	296		749.7
221 [2]		735.2	297		747.3
222 [3,4] (3/1 mix)		749.1	298		805.2
223		728.2	299 [2]		705.2
224		828.2	300 [4]		735.5

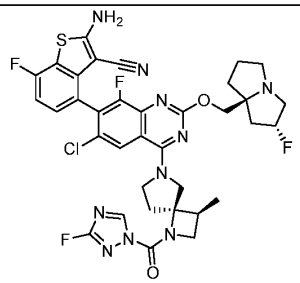
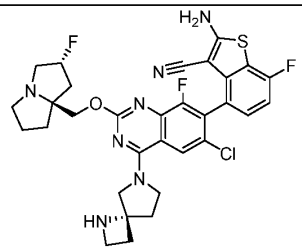
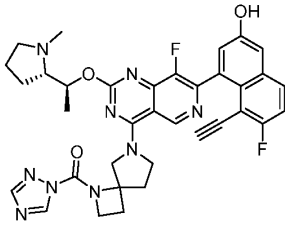
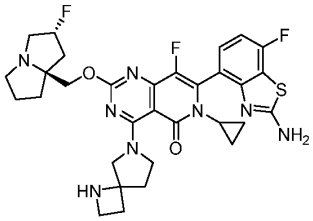
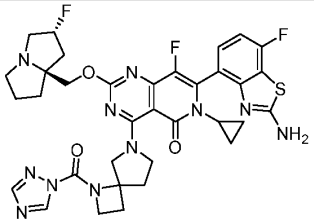
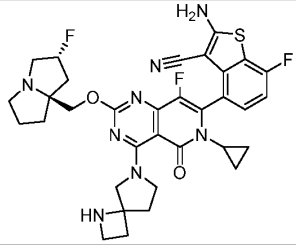
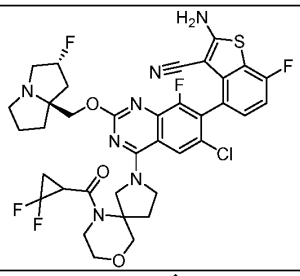
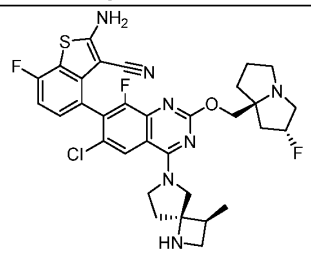
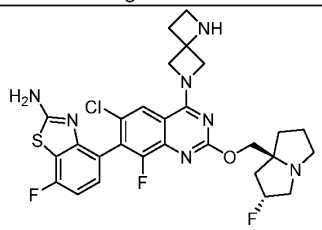
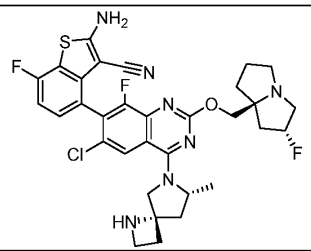
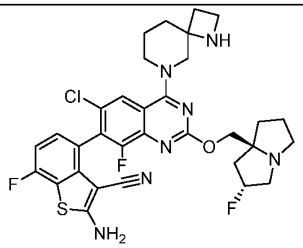
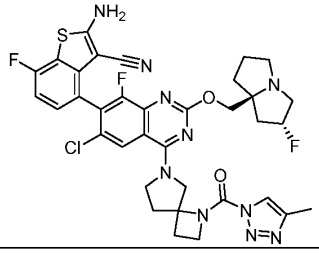
225 [2]		770.4	301 [3]		705.2
226		763.5	302		695.4
227		668.4	303		665.4
228		780.5	304		777.4
229 [2]		783.4	305 [2]		735.5
230		616.19	306 [2]		763.3

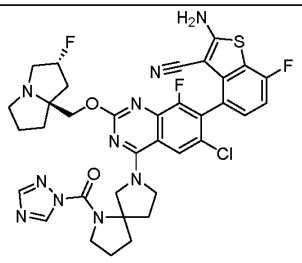
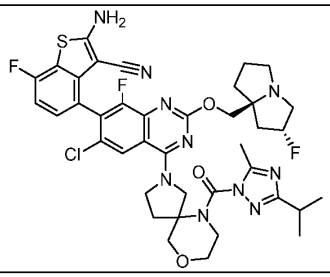
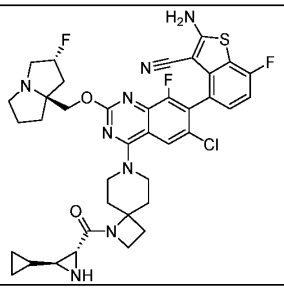
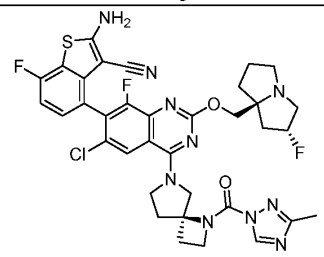
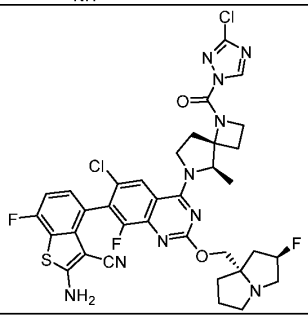
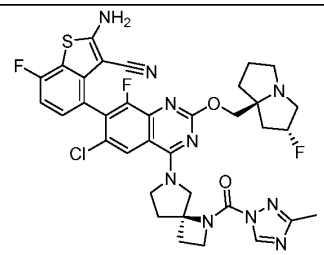
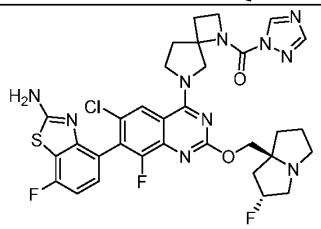
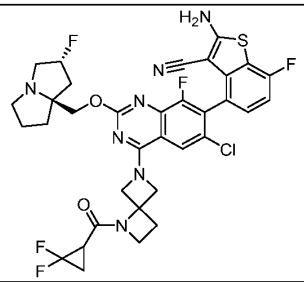
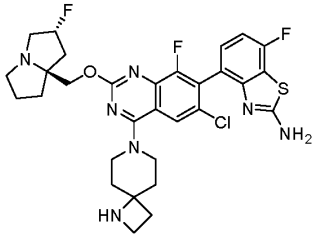
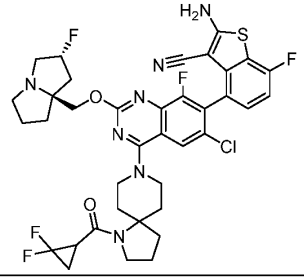
231 [1]		777.5	307		763.4
232		676.2	308		775.3
233		672.2	309		759.2
234 [2]		735.3	310 [5]		759.2
235		717.3	311 [5]		783.6
236 [1]		654.3	312		769.2

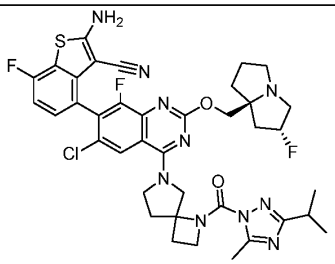
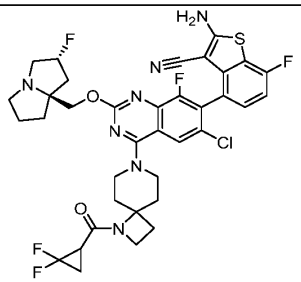
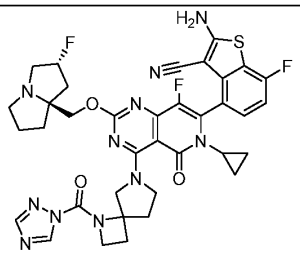
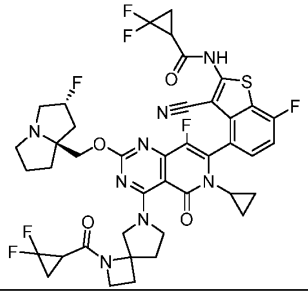
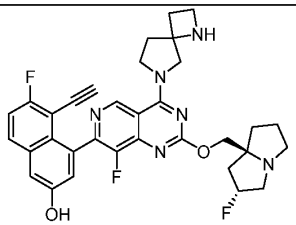
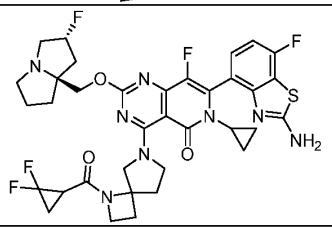
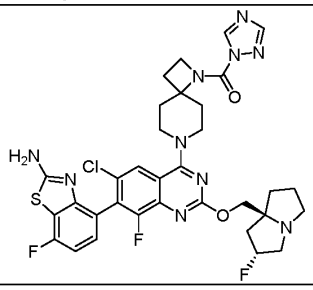
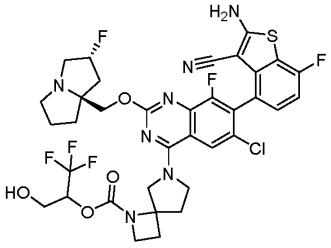
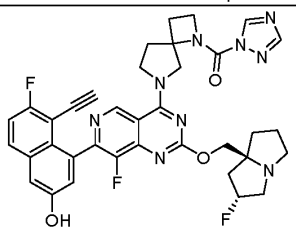
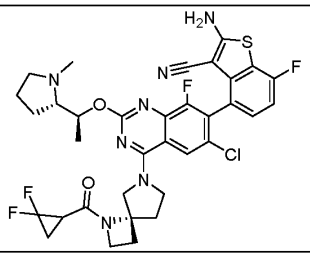
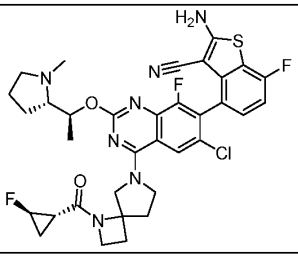
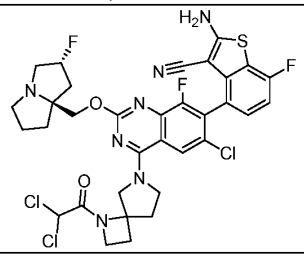
237		834.4	313		779.2
238		721.3	314		763.3
239		571.3	315		705.2
240		772.3	316 [2]		707.3
241		719.2	317 [6]		784.4
242		616.1	318 [4]		803.2

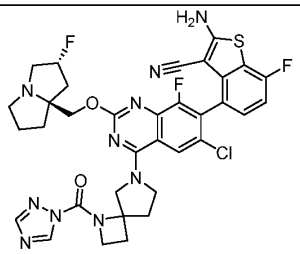
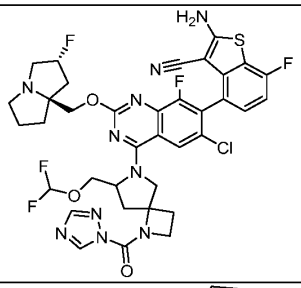
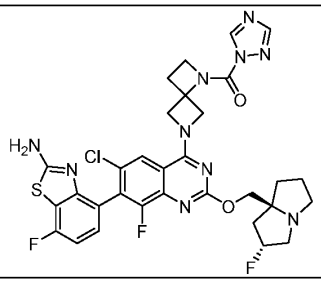
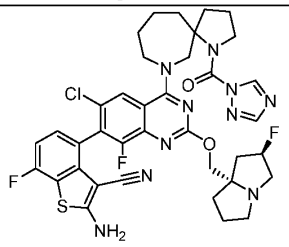
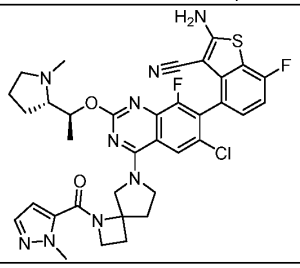
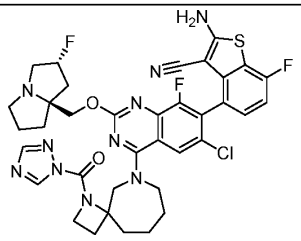
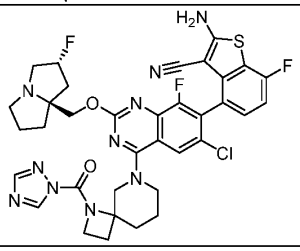
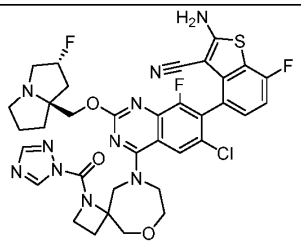
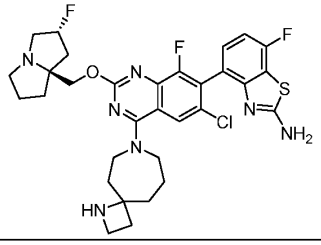
243		781.1	319		691.2
244		735.2	320		774.3
245		614.2	321 [2]		760.2
246 [1]		763.4	322 [2]		783.4
247 [3]		735.3	323 [2,6]		819.4
248 [4] (1/4 mix)		735.1	324 [2]		749.4

249		611.1	325 [2,6]		799.1
250 [2,4] (3/1 mix)		749.2	326 [6]		815.3
251		631.31	327		766.5
252 [1]		668.3	328 [2]		808.5
253		597.1	329 [2, 6]		824.1
254		682.1	330 [2, 6]		824.2

255 [2]		767.4	331 [2]		640.5
256		666.5	332		638.4
257		734.3	333		662.4
258		774.4	334 [2]		654.2
259		602.4	335 [2]		654.2
260 [1]		654.1	336 [4]		749.2

261		749.1	337 [5]		821.4
262		763.4	338 [2,4]		749.4
263 [2]		783.4	339 [3,4]		749.2
264		711.5	340		730.3
265		630.2	341		772.3

266 [5]		791.7	342		758.3
267		760.2	343		870.5
268		601.2	344		742.4
269		725.2	345		796.2
270		696.1	346 [3]		714.3
271		696.4	347		751.1

272		735.2	348 [6]		815.2
273		697.2	349 [6]		777.2
274		718.4	350 [2]		763.1
275		749.2	351 [2]		765.2
276		644.4			

[1] Compound provided as a single spirocyclic stereoisomer and mixture of atropisomers

[2] Compound provided as a single atropisomer (R)

[3] Compound provided as a single atropisomer (S)

[4] Compound provided as a mixture of regioisomers (e.g., of optionally substituted imidazole, pyrazole, triazole, or tetrazole)

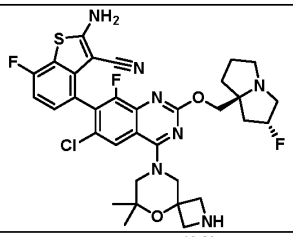
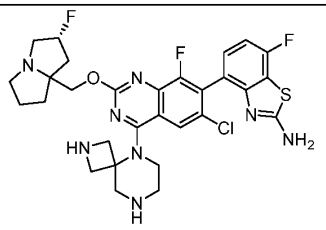
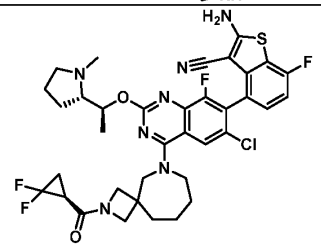
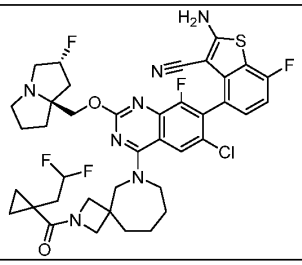
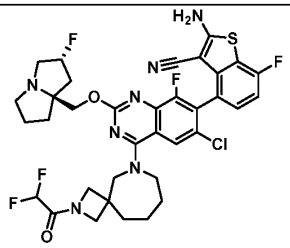
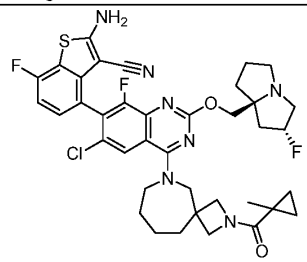
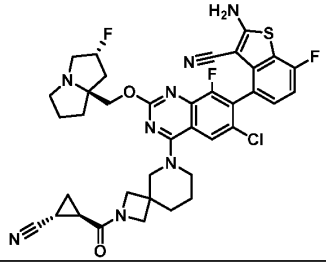
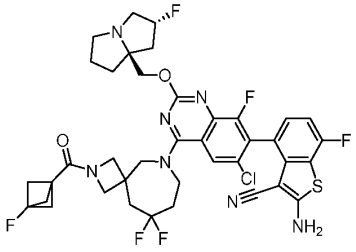
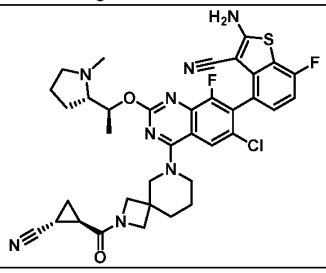
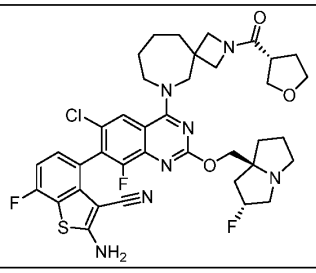
[5] Compound provided as a substantially pure single regioisomer (e.g., of optionally substituted imidazole, pyrazole, triazole, or tetrazole), though the structure provided has been tentatively assigned

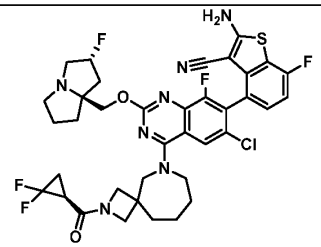
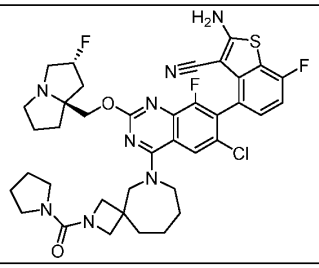
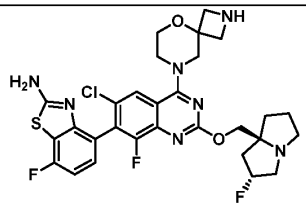
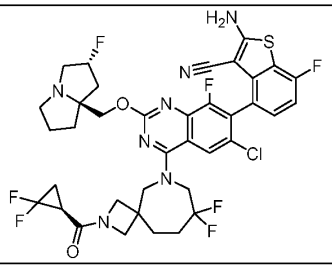
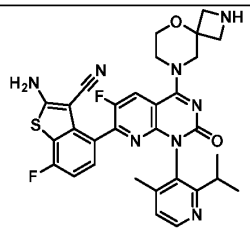
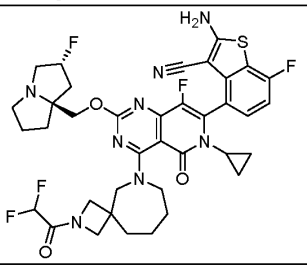
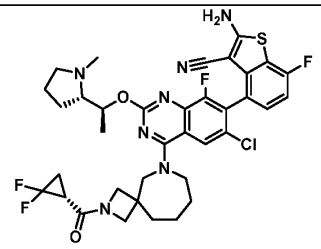
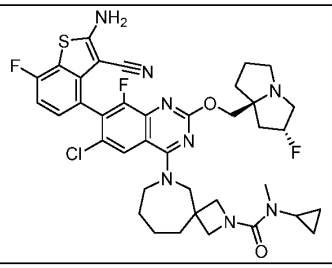
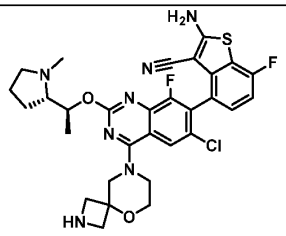
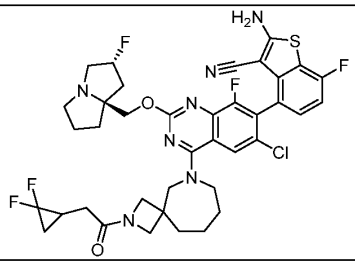
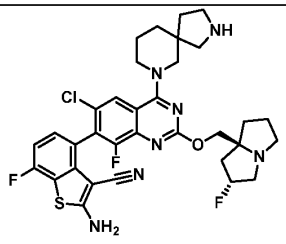
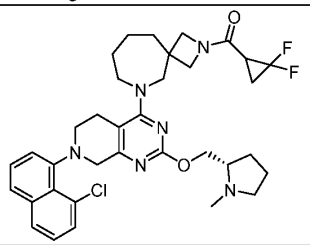
[6] Compound provided as partially purified mixture of diastereomers and atropisomers

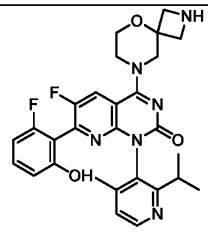
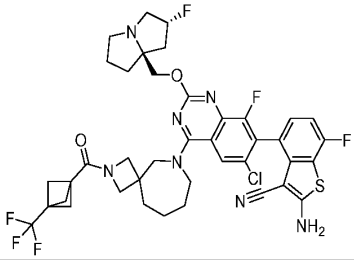
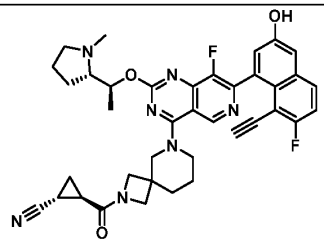
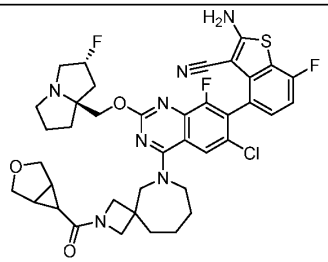
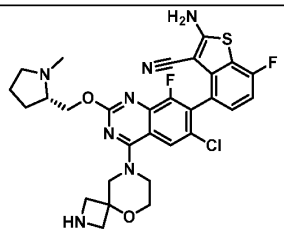
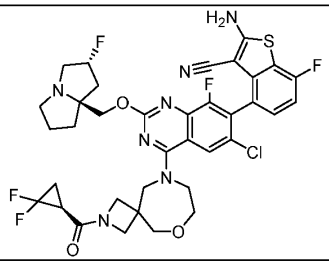
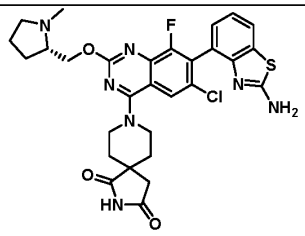
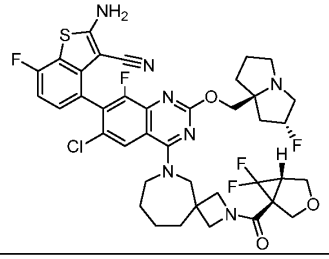
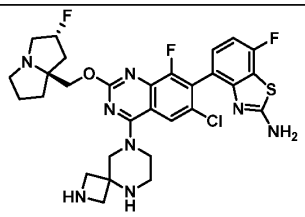
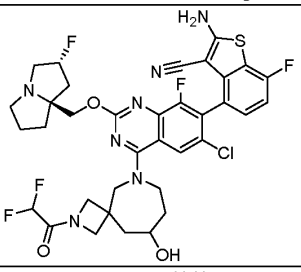
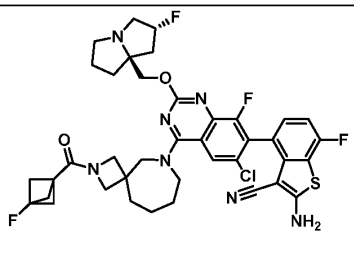
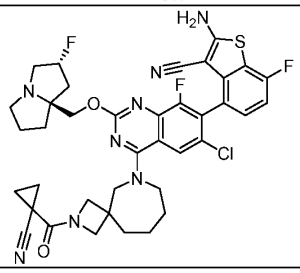
[7] Compound provided as tentatively assigned single diastereomer and single atropisomer

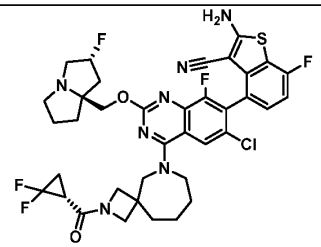
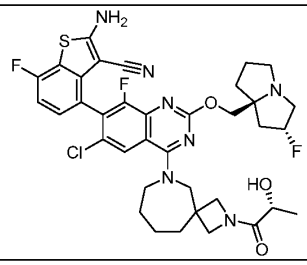
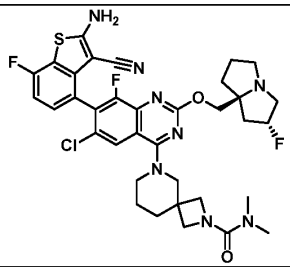
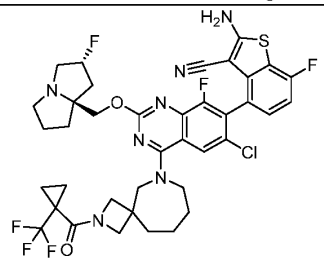
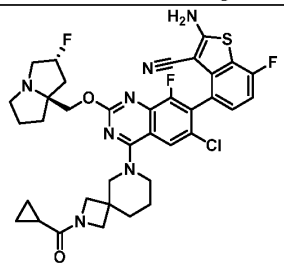
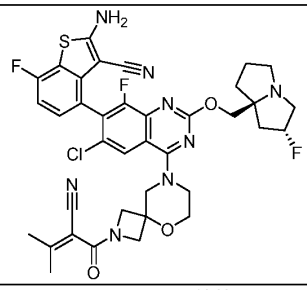
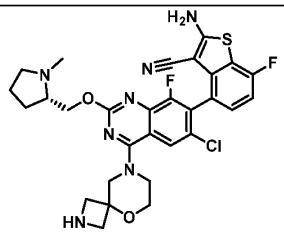
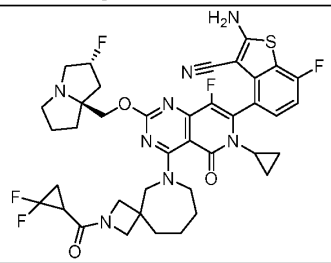
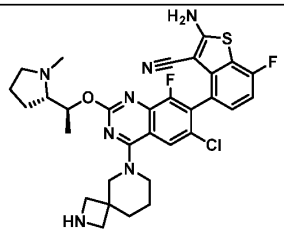
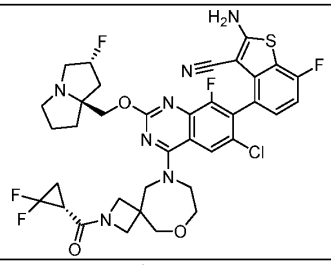
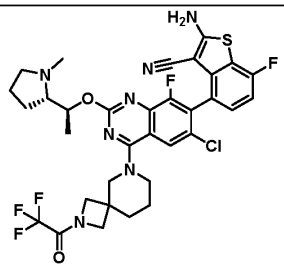
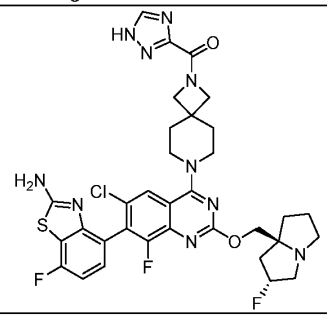
It will be understood that when referring to one or more atropisomers of the compounds in the table above, the atropisomer is in reference to the orientation of the bonds attached to the atom of the substituent corresponding to the R^{17}/R^{19} group of Formula (I) that is bonded to the V atom of Formula (I). It will be understood that when two superscripted numbers above (e.g, 2 and 6) apply to a single compound and both numbers limit the same characteristic (e.g., atropisomer), the number with greater specificity will apply. For example, when a compound is classified as 2 and 6, the compound is a partially purified mixture of diastereomers and a single R atropisomer.

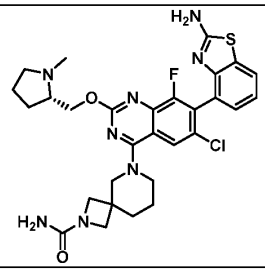
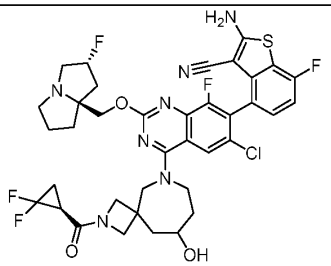
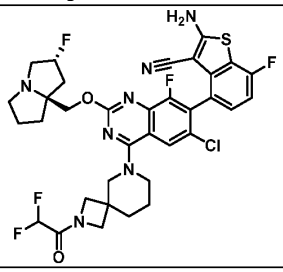
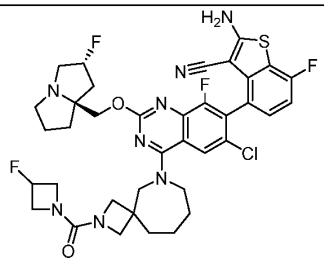
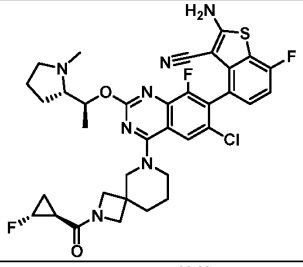
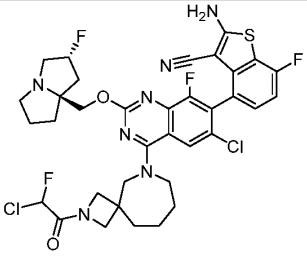
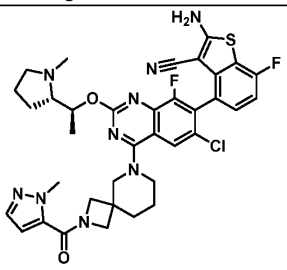
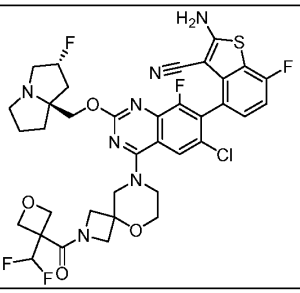
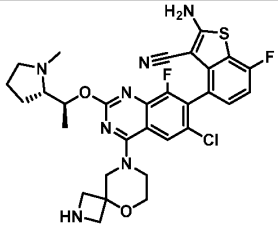
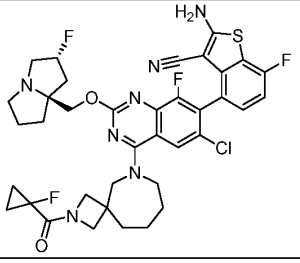
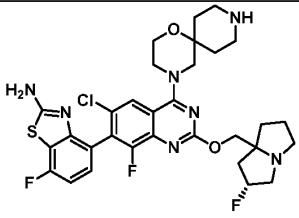
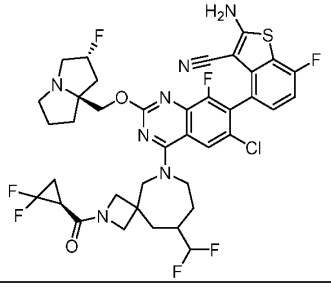
Table 1b: Compounds

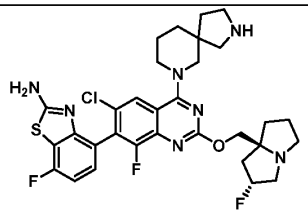
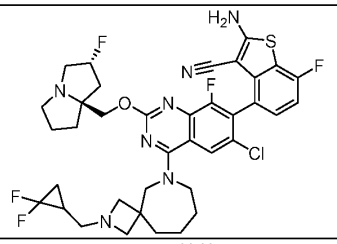
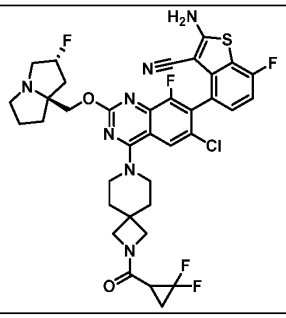
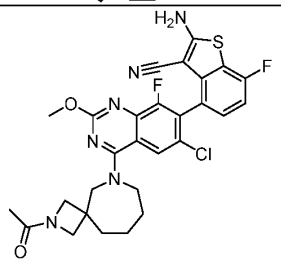
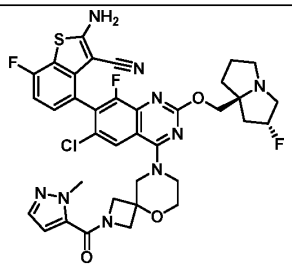
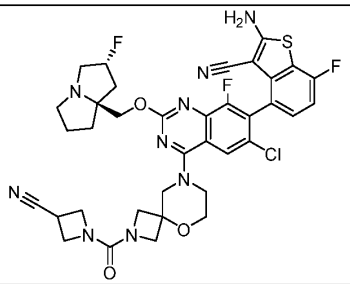
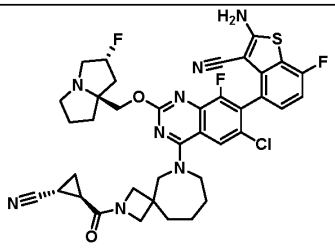
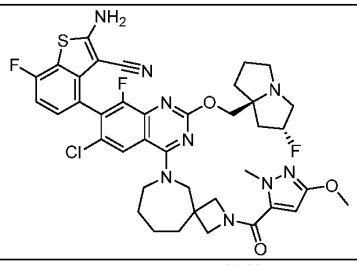
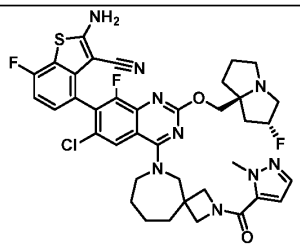
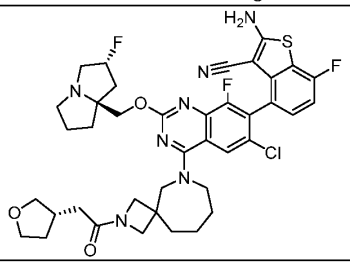
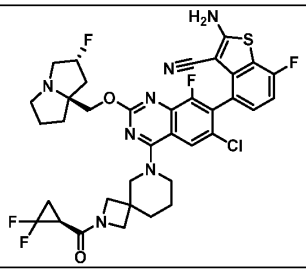
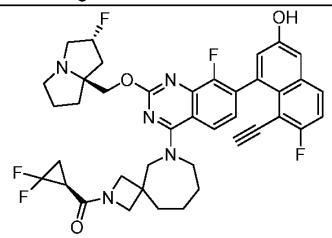
No.	Structure	$[M+H]^+$	No.	Structure	$[M+H]^+$
A101		684.19	A226		631.2
A102[2]		742.22	227		800.2
A103		746.24	A228		750.3
A104		747.3	A229		816.4
A105		717.33	A230		766.3

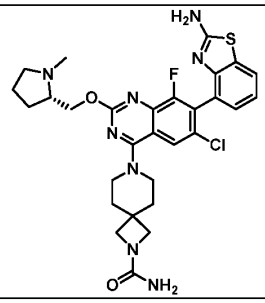
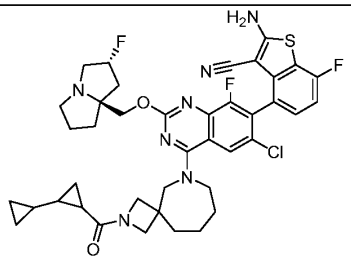
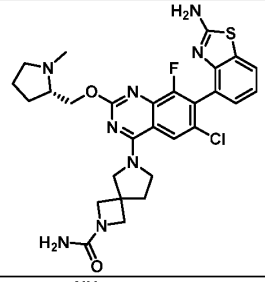
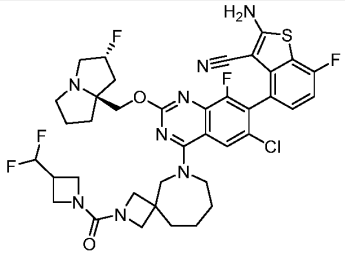
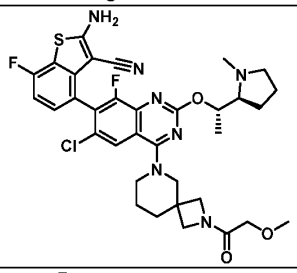
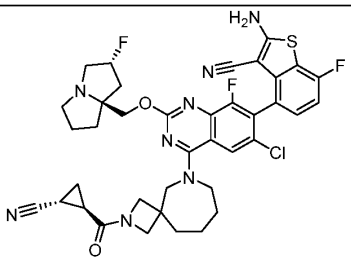
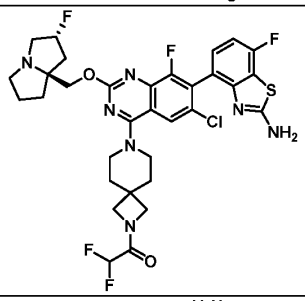
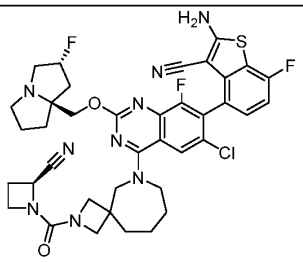
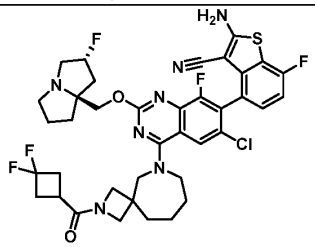
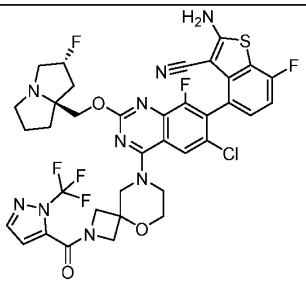
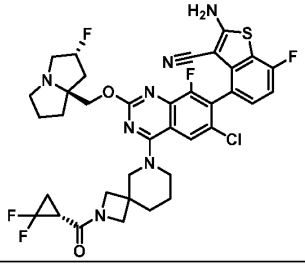
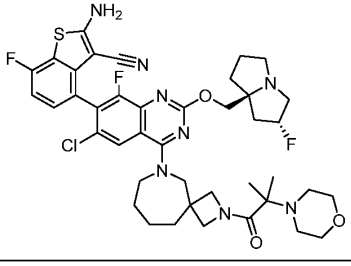
A106[2]		772.25	A231[2]		765.2
A107		632.15	A232[2]		808.3
A108		614.62	A233		769.3
A109[3]		742.15	A234		765.4
A110		626.11	A235[2]		786.3
A111		668.17	A236		651.4

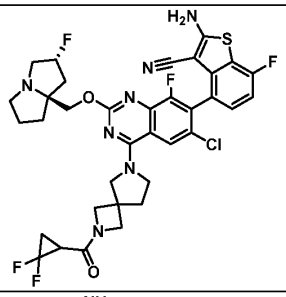
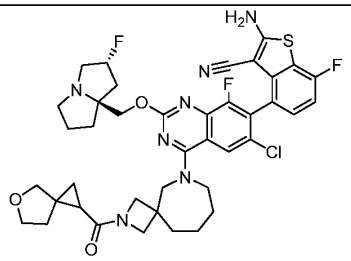
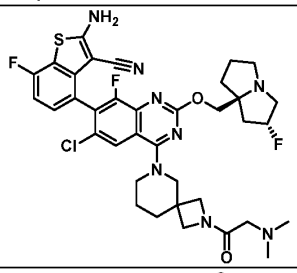
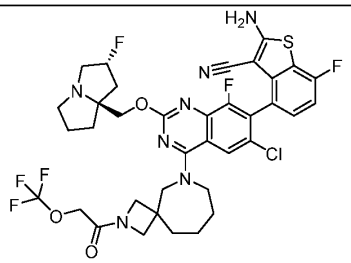
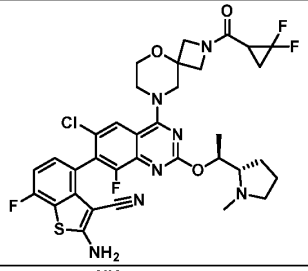
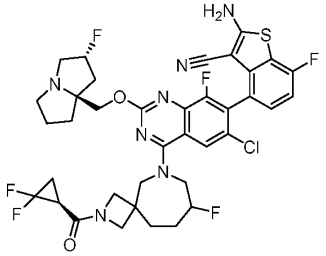
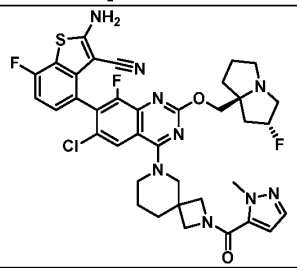
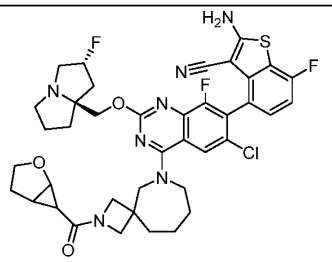
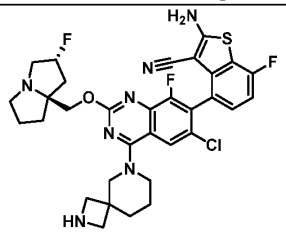
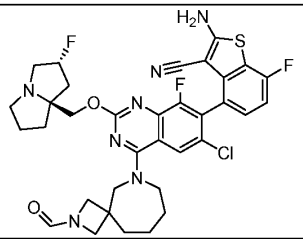
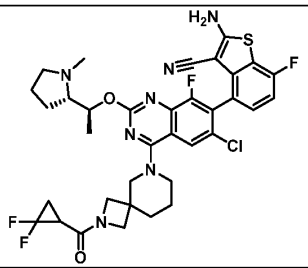
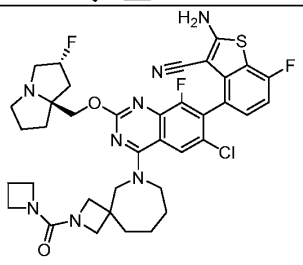
A112		534.55	A237		830.5
A113		677.55	A238 [2]		778.2
A114 [3]		612.11	A239		774.4
A115		612.1	A240 [2]		814.2
A116		631.12	A241		762.5
A117		780.22	A242		761.4

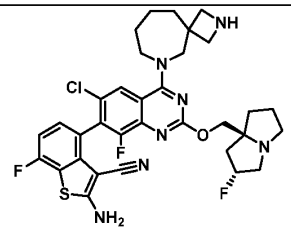
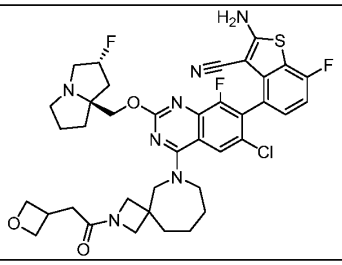
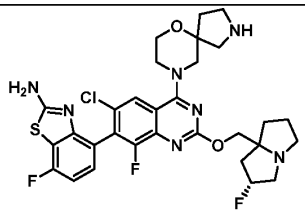
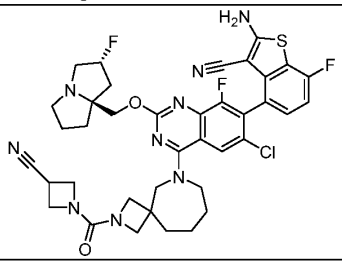
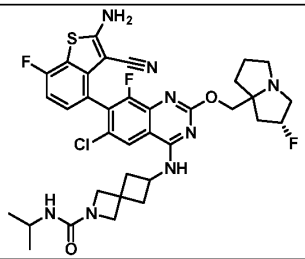
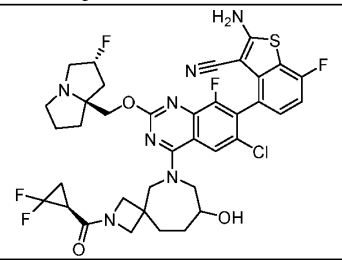
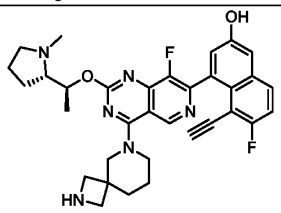
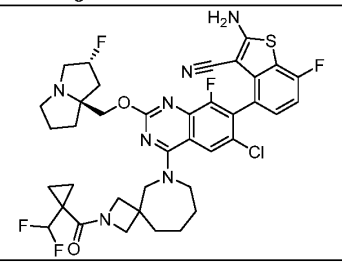
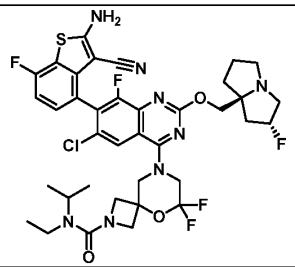
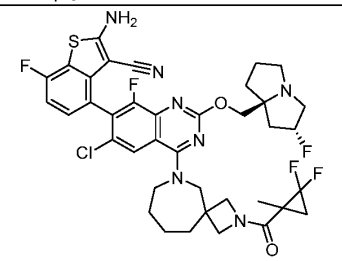
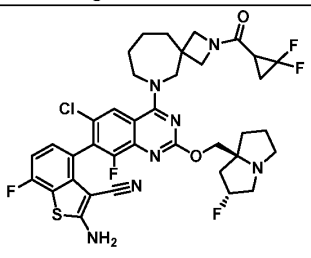
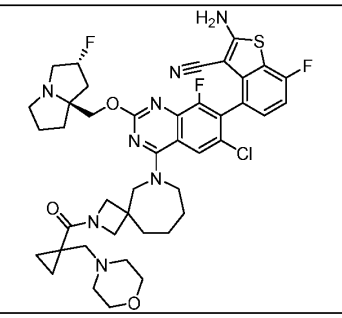
A118		772.21	A243		740.2
A119		725.19	A244		804.1
A120		722.25	A245 [2]		763.2
A121 [3]		612.18	A246		794.3
A122		624.11	A247		774.4
A123		720.18	A248		725.3

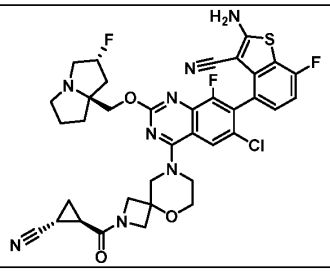
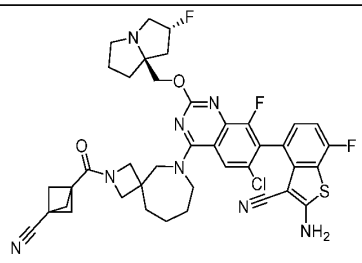
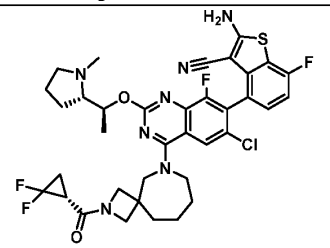
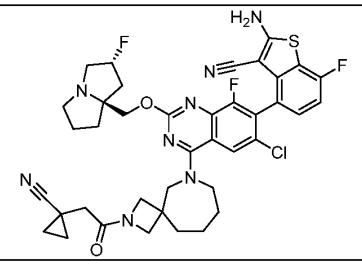
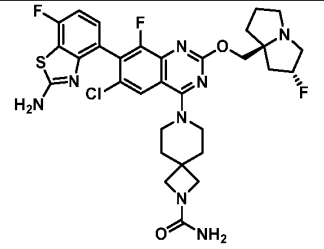
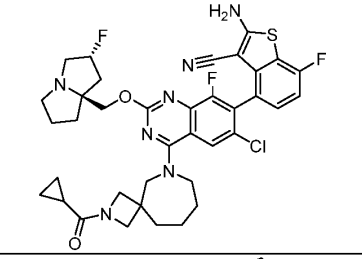
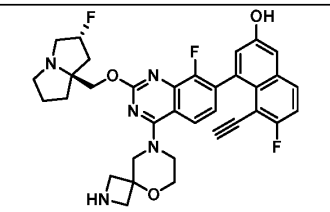
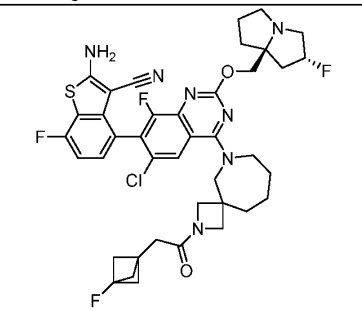
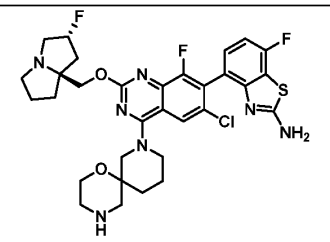
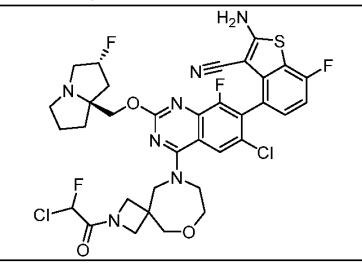
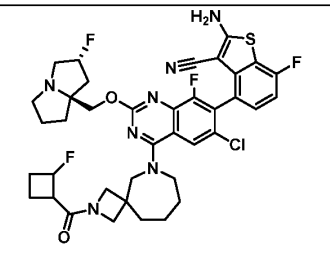
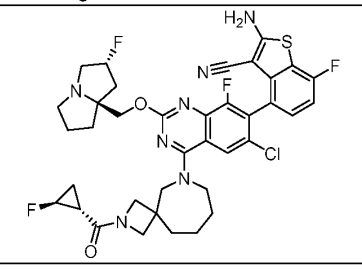
A124		611.2	A249		788.4
A125		732.18	A250		769.2
A126		710.3	A251		762.4
A127		732.22	A252		790.1
A128 [3]		626.19	A253		754.2
A129		660.15	A254 [2]		822.3

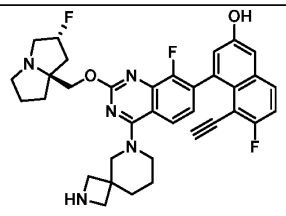
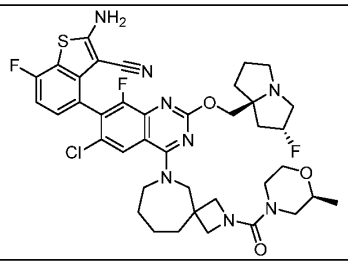
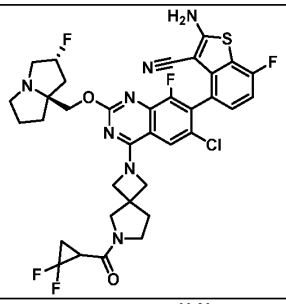
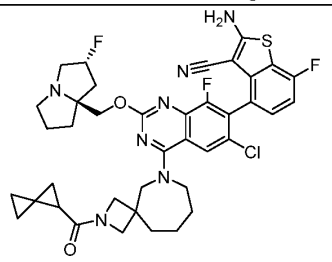
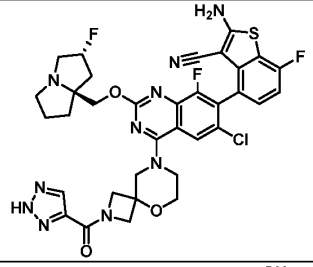
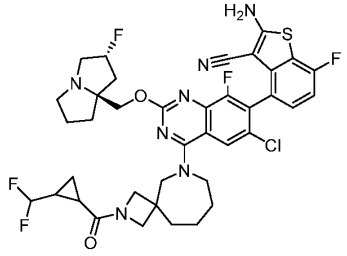
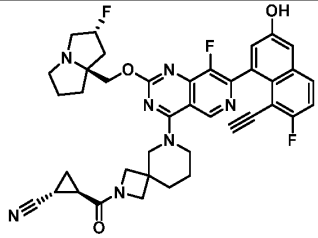
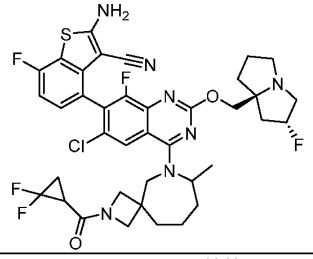
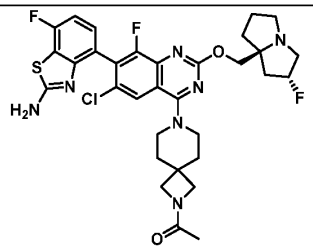
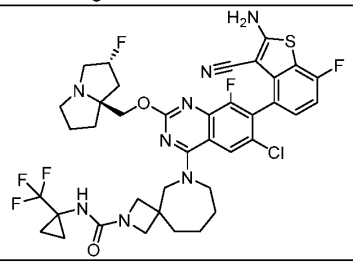
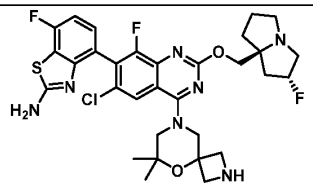
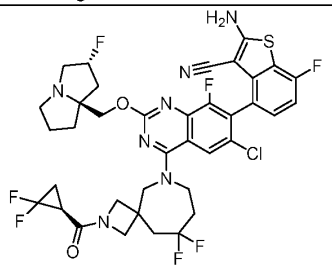
A130		644.18	A255		758.3
A131		758.24	A256		583.1
A132		764.26	A257		764.3
A133		761.24	A258		806.3
A134		776.3	A259		780.3
A135		758.3	A260		731.5

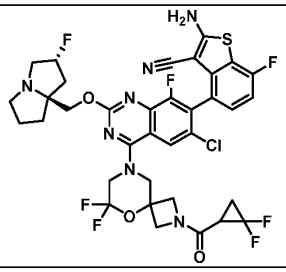
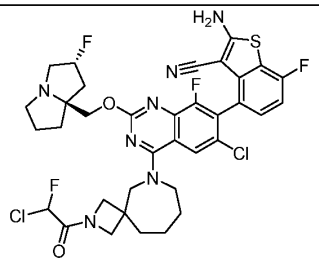
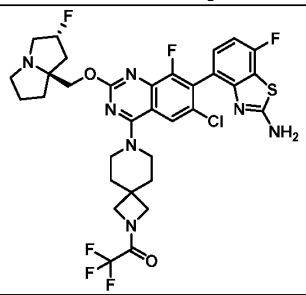
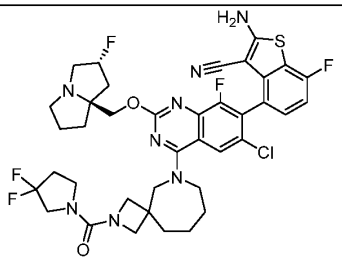
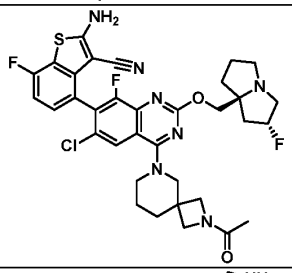
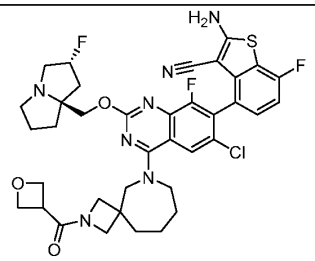
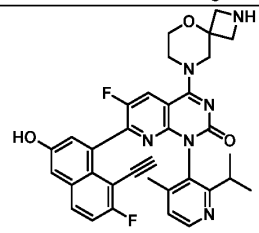
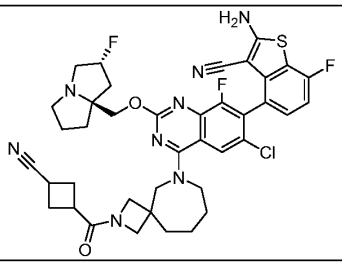
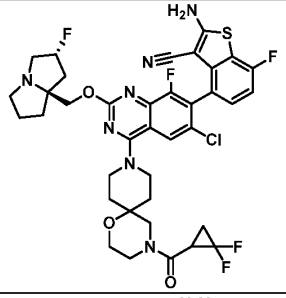
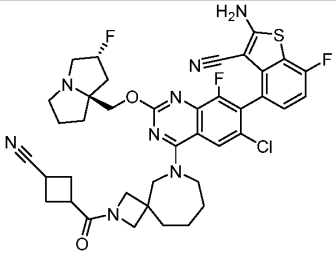
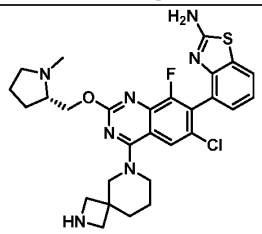
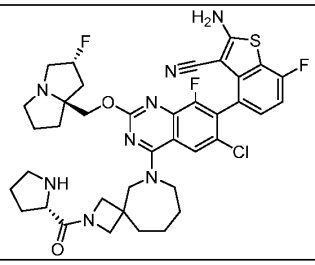
A136		611.2	A261		776.3
A137		597.2	A262		801.3
A138		696.23	A263 [2]		761.3
A139		708.18	A264		776.3
A140		786.24	A265 [2]		818.2
A142		758.23	A266		823.4

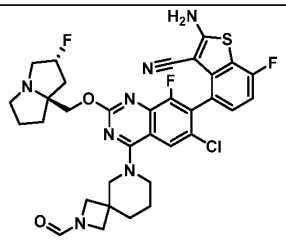
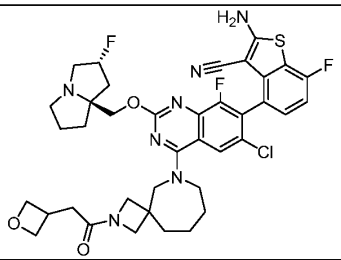
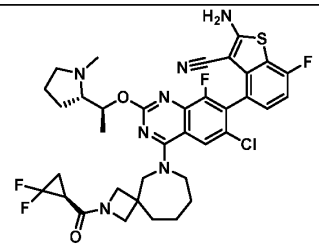
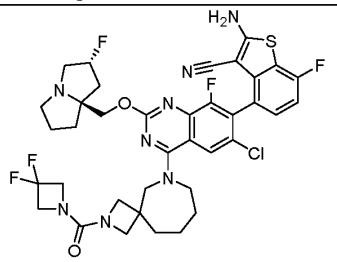
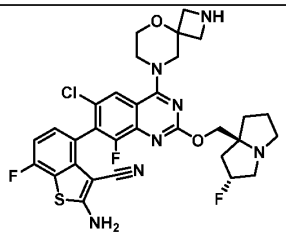
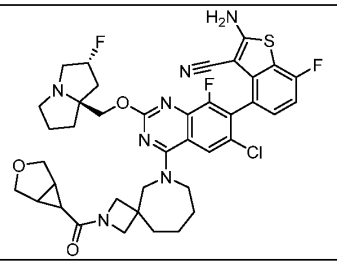
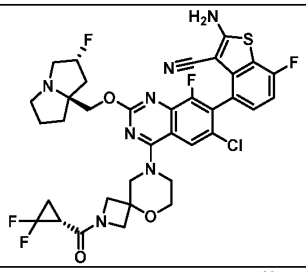
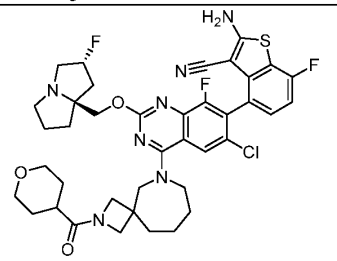
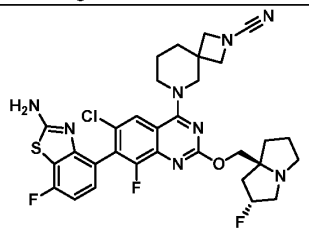
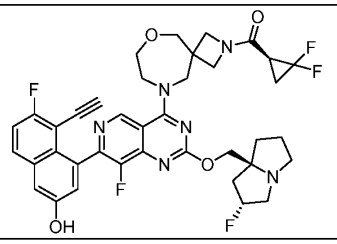
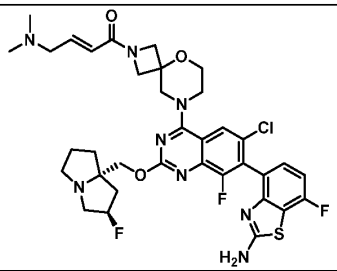
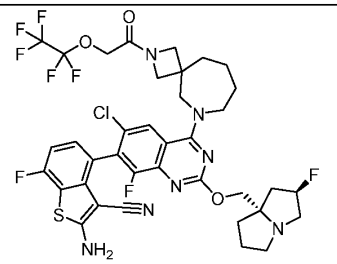
A143		744.15	A267		792.4
A144		739.3	A268 [2]		794.4
A145		730.11	A269 [2]		790.3
A146		762.23	A270		778.5
A147		654.17	A271 [2]		696.2
A148		728.25	A272		751.3

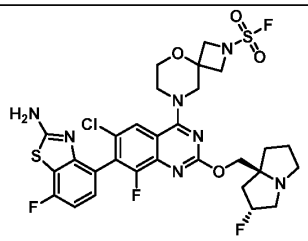
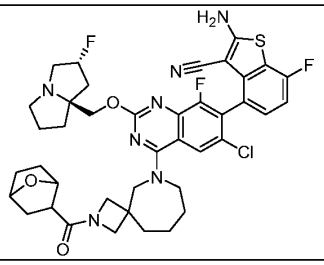
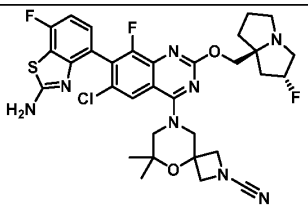
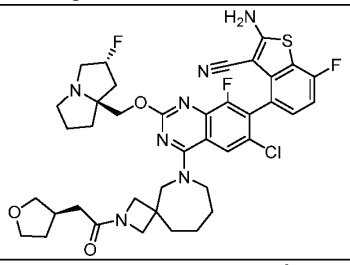
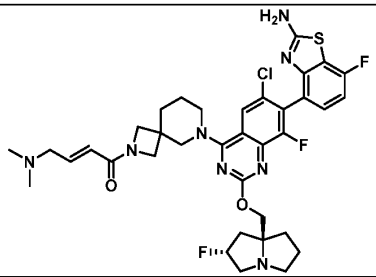
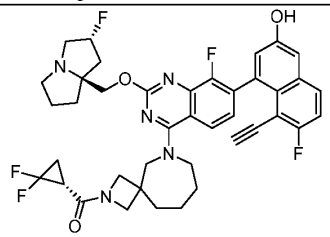
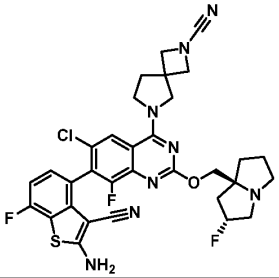
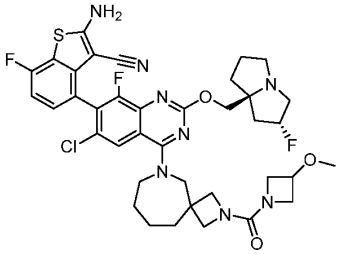
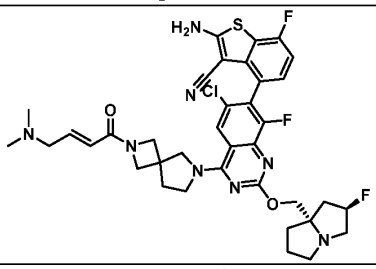
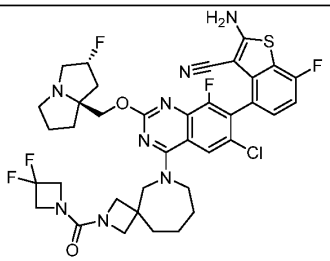
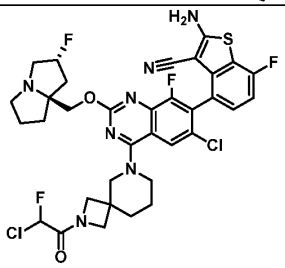
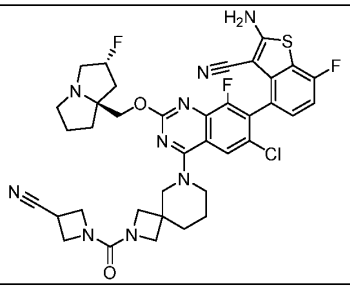
A149		668.2	A273		766.2
A150		646.18	A274 [2]		776.3
A151		725.4	A275		788.4
A152		584.59	A276		786.2
A153		805.3	A277		786.4
A154		772.22	A278 [2]		835.4

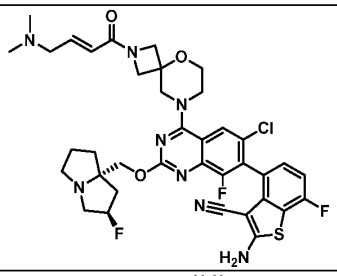
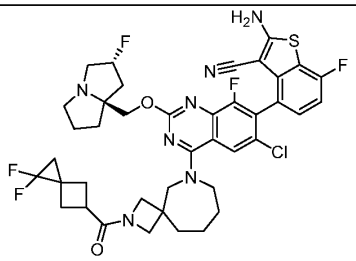
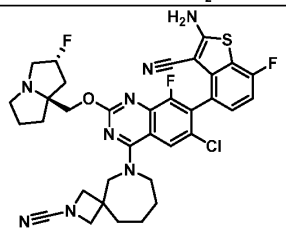
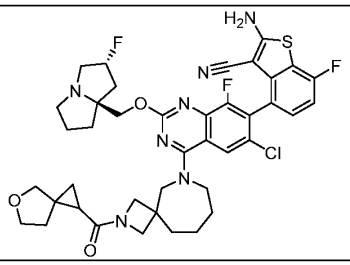
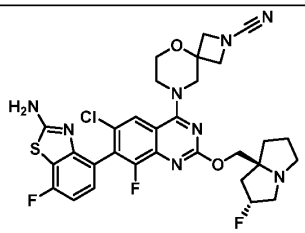
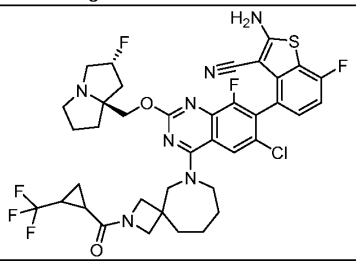
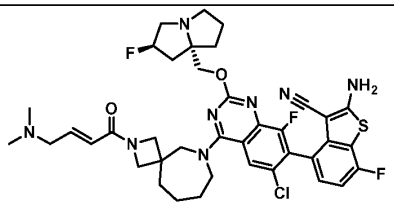
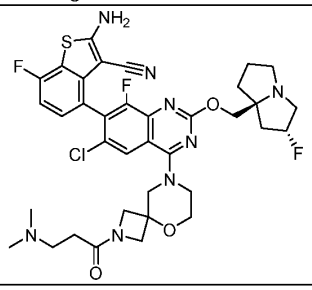
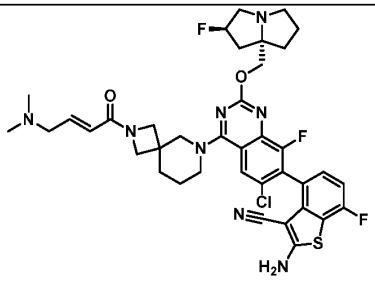
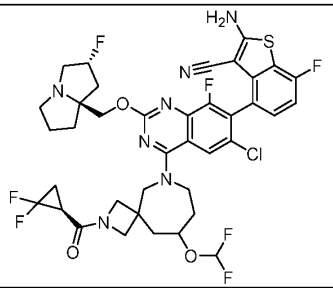
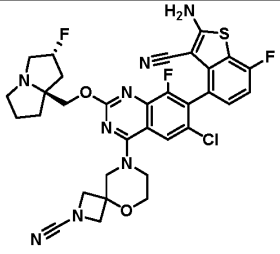
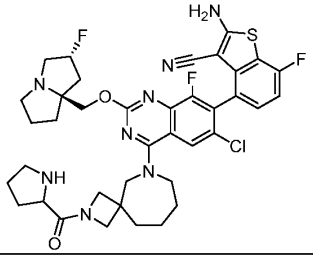
A155		749.23	A279		787.4
A156[2]		742.25	A280		775.3
A157		673.2	A281[2]		736.2
A158		615.6	A282		794.4
A159		660.13	A283		764.4
A160		768.19	A284		754.2

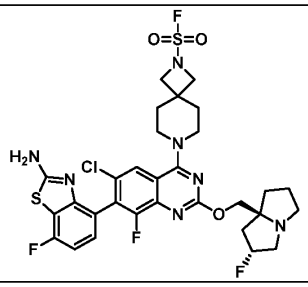
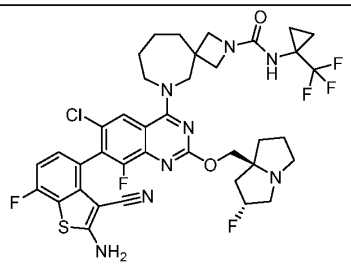
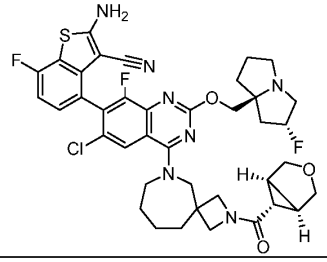
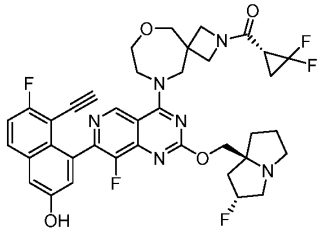
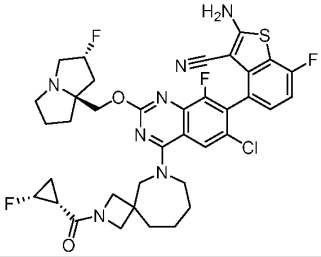
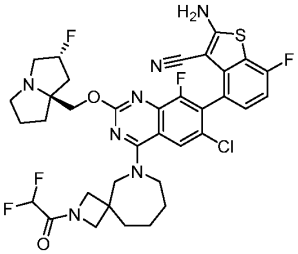
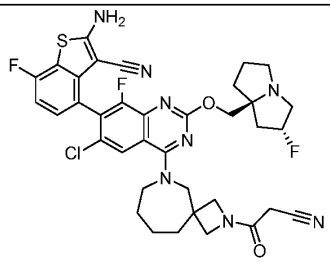
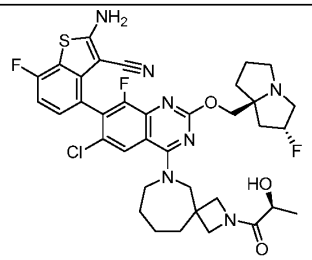
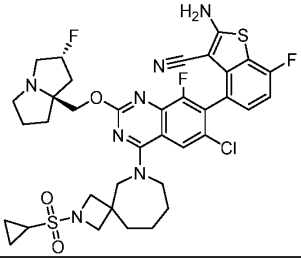
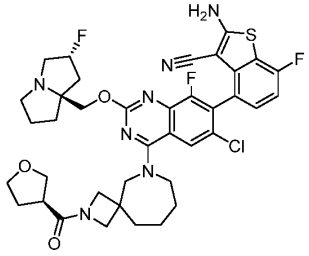
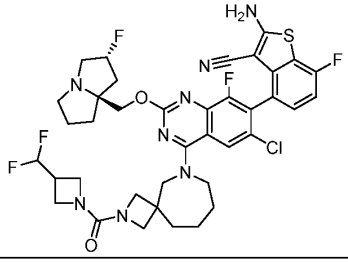
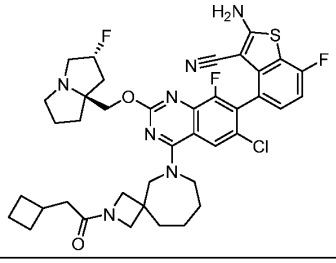
A161		613.66	A285 [2]		795.4
A162		744.23	A286		762.3
A163		751,16	A287		786.4
A164		707.75	A288 [4]		786.2
A165		672.5	A289		819.4
A166		660.12	A290 [2]		808.2

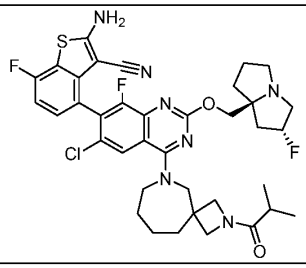
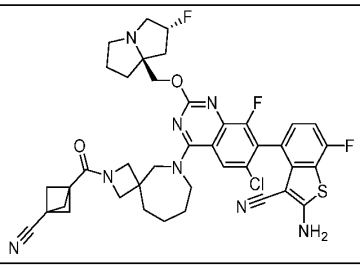
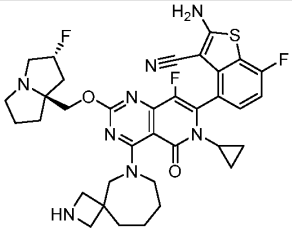
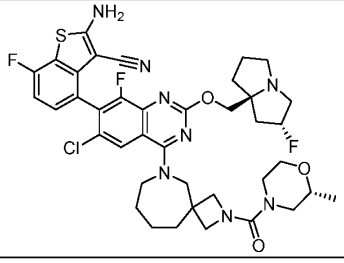
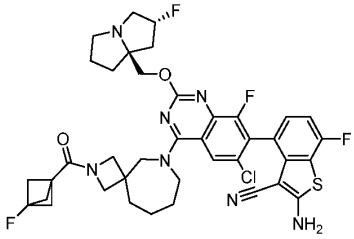
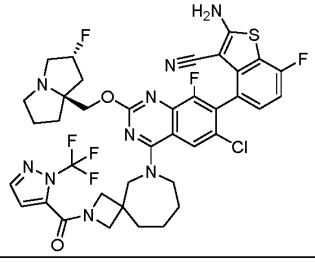
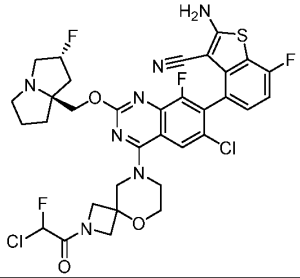
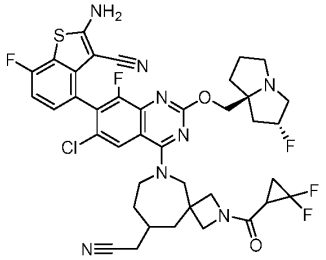
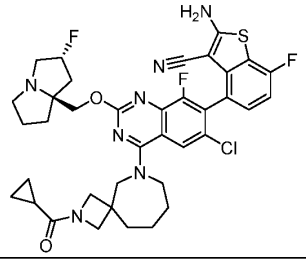
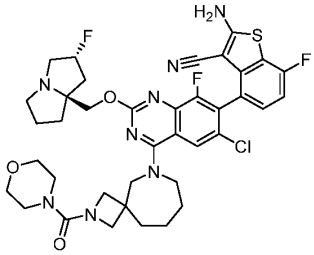
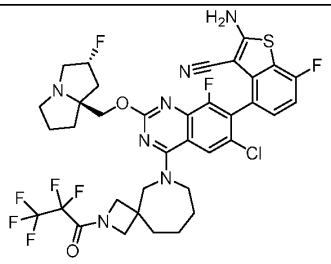
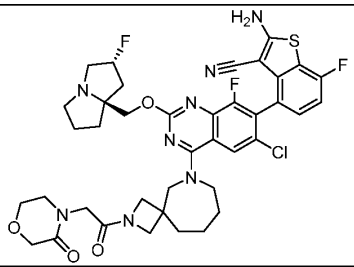
A167		796.18	A291 [2]		762.4
A168		726.2	A292		801.3
A169		696.3	A293		752.4
A170		608.6	A294 [2]		775.1
A171		788.21	A295		775.2
A172		568.2	A296		765.2

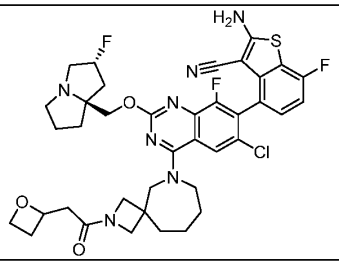
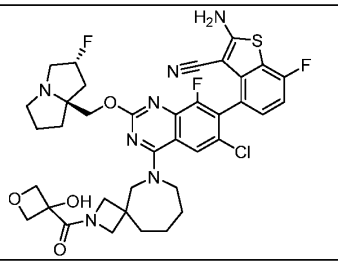
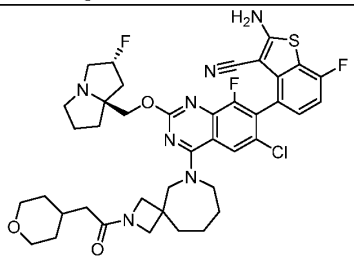
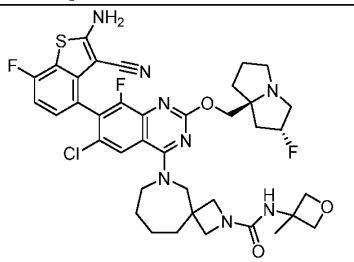
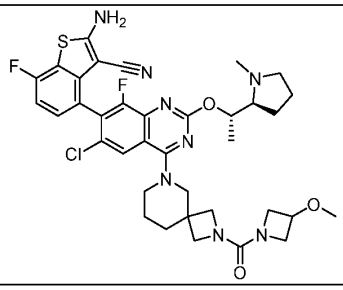
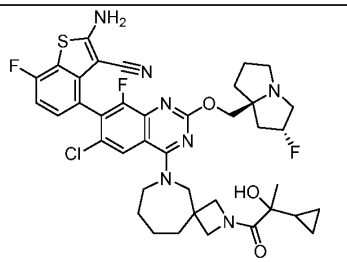
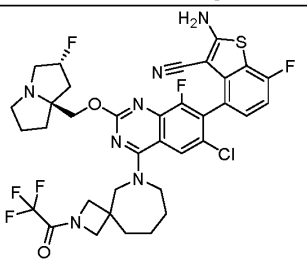
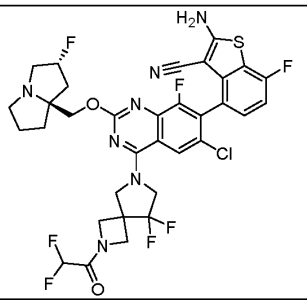
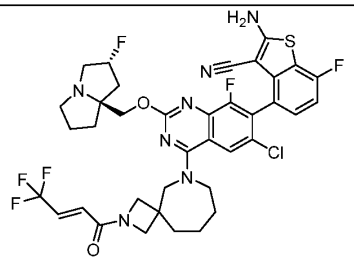
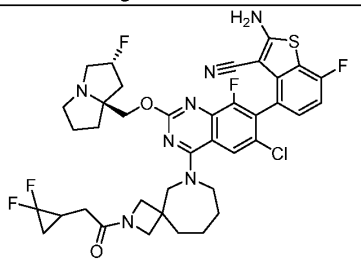
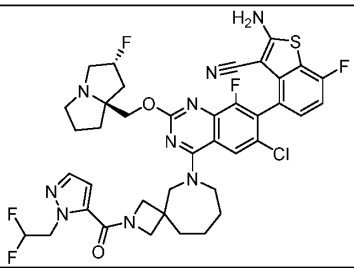
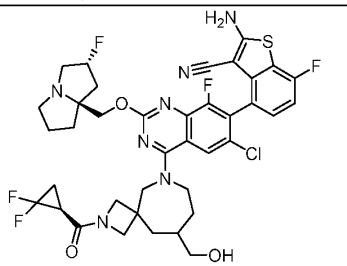
A173		682.11	A297 [2]		766.3
A174 [3]		742.25	A298		787.3
A175		656.17	A299		778.4
A176 [2]		760.12	A300 [2]		780.3
A177		655.18	A301		734.5
A178		743.3	A302		844.2

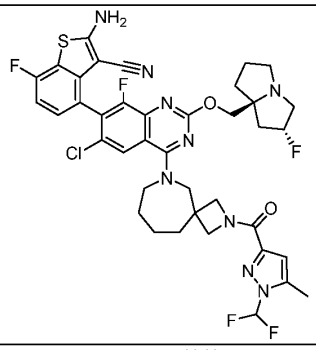
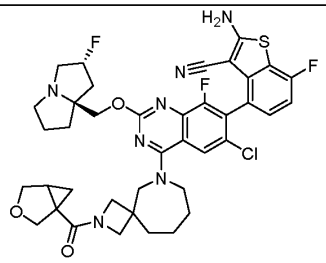
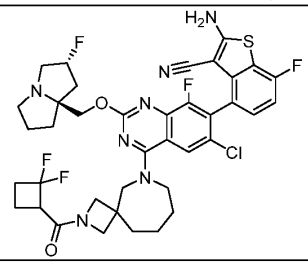
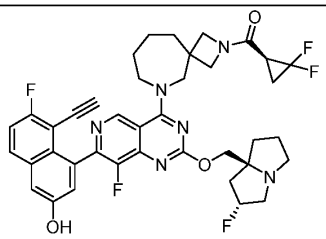
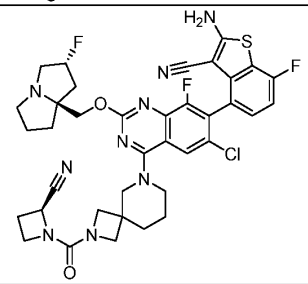
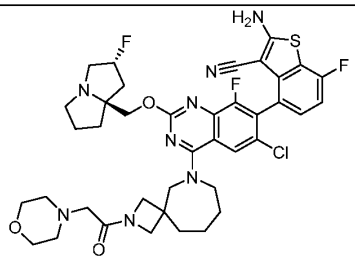
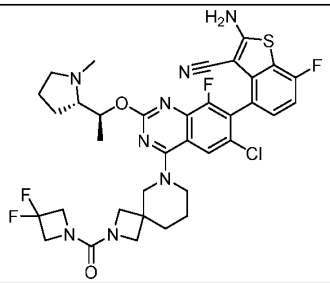
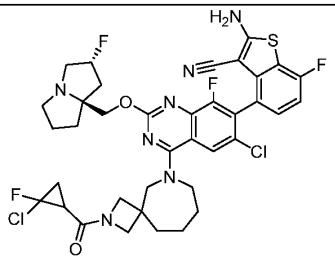
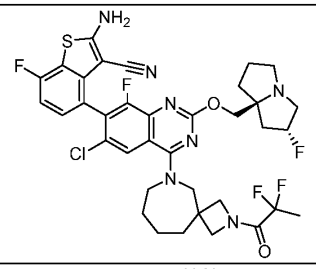
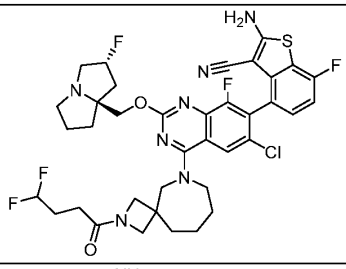
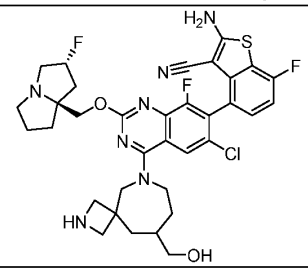
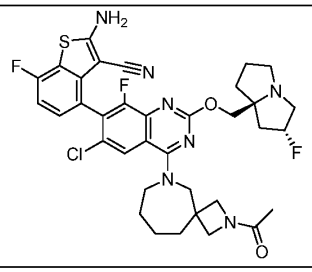
A179		714.16	A303		792.3
A180		685.17	A304		780.2
A181		741.3	A305		731.5
A182		665.15	A306		781.5
A183		751.22	A307 [2]		787.2
A184		748.6	A308		762.4

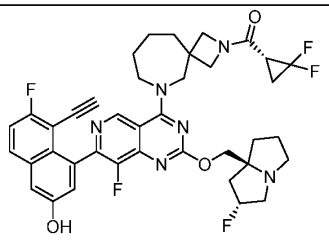
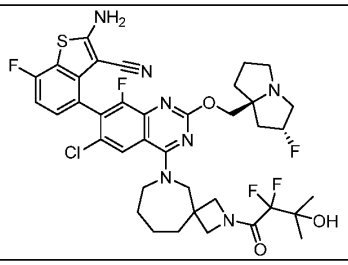
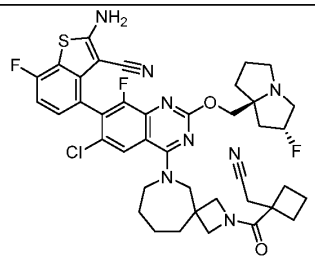
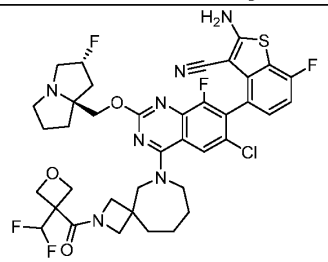
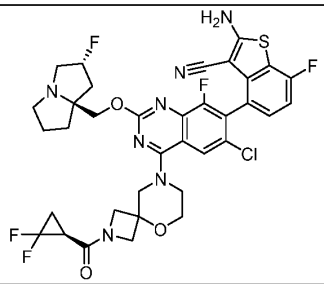
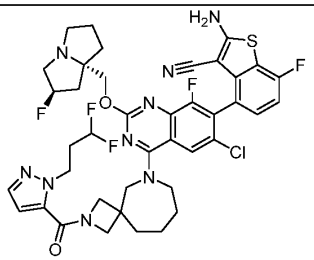
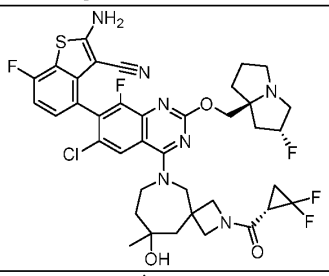
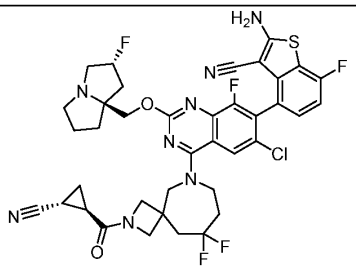
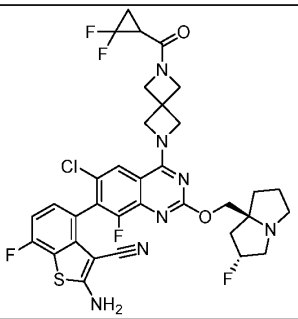
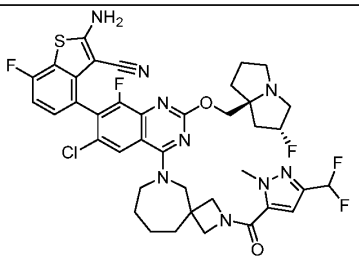
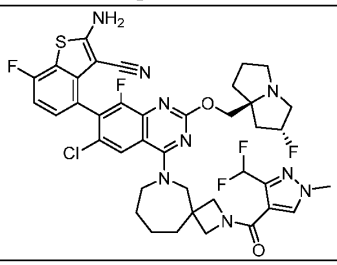
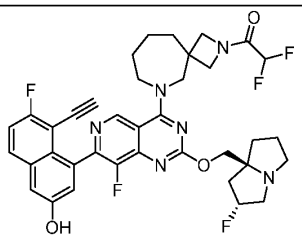
A185		767.24	A309		812.2
A186		693.2	A310 [2]		792.2
A187		657.12	A311		804.2
A188		779.3	A312 [2]		755.6
A189		765.33	A313		838.2
A190		681.22	A314		765.4

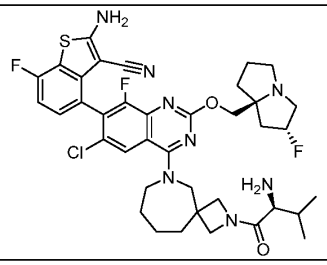
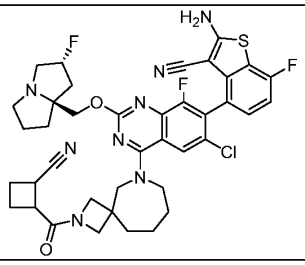
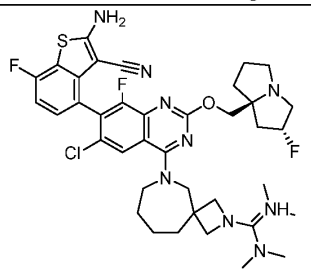
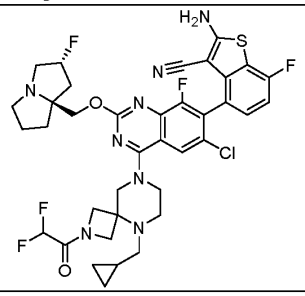
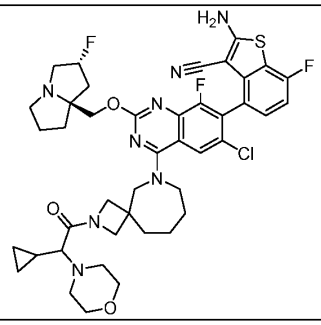
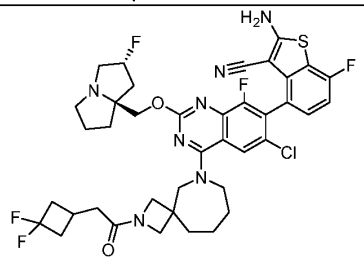
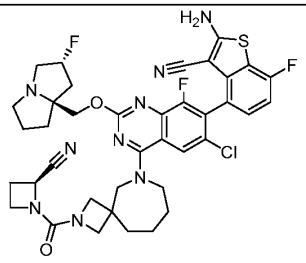
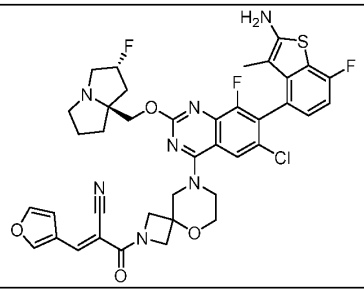
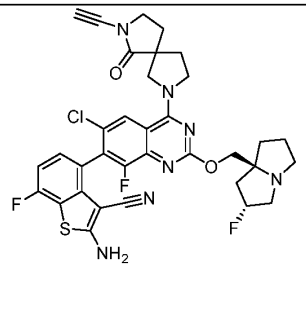
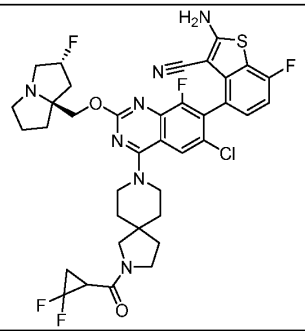
A191		712.21	A315[2]		819.2
A192[2]		778.4	A316		734.3
A193		754.2	A317[2]		746.2
A194		735.2	A318		740.2
A195		772.2	A319		766.2
A196[2]		801.4	A320		764.4

A197		738.4	A321 [2]		787.4
A198		691.4	A322 [2,] methyl R		795.5
A199 [2]		780.2	A323 [2]		830.3
A200		750.1	A324 [2]		811.4
A201		736.2	A325 [2]		781.2
A202 [2]		814.4	A326		809.4

A203		766.4	A327		768.2
A204		794.1	A328[2]		781.1
A205		737.3	A329		780.2
A206		764.2	A330		754.1
A207		790.2	A331		786.4
A208		826.3	A332[2]		802.2

A209		826.4	A333		778.6
A210		786.2	A334		732.2
A211		762.3	A335		795.4
A212		743.2	A336		788.5
A213		760.3	A337 [2]		774.3
A214 [2]		698.2	A338		710.3

A215		732.5	A339		804.3
A216		789.2	A340		802.2
A217 [2]		760.4	A341		840.2
A218 [2]		802.4	A342 [2]		797.3
A219		730.2	A343		826.2
A220		826.2	A344		706.4

A221		767.5	A345		775.4
A222[2]		767.5	A346		787.2
A223		835.4	A347		800.5
A224[2]		776.4	A348[2]		790.2
A225		692.4	A349		772.3

[1] Compound provided as a single spirocyclic stereoisomer and mixture of atropisomers

[2] Compound provided as a single atropisomer (R)

[3] Compound provided as a single atropisomer (S)

[4] Compound provided as a mixture of regioisomers (e.g., of optionally substituted imidazole, pyrazole, triazole, or tetrazole)

[5] Compound provided as a substantially pure single regioisomer (e.g., of optionally substituted imidazole, pyrazole, triazole, or tetrazole), though the structure provided has been tentatively assigned

[6] Compound provided as partially purified mixture of diastereomers and atropisomers

[7] Compound provided as tentatively assigned single diastereomer and single atropisomer

It will be understood that when referring to one or more atropisomers of the compounds in the table above, the atropisomer is in reference to the orientation of the bonds attached to the atom of the substituent corresponding to the R^{17}/R^{19} group of Formula (I) that is bonded to the V atom of Formula (I). It will be understood that when two superscripted numbers above (e.g, 2 and 6) apply to a single compound and both numbers limit the same characteristic (e.g., atropisomer), the number with greater specificity will apply. For example, when a compound is classified as 2 and 6, the compound is a partially purified mixture of diastereomers and a single R atropisomer.

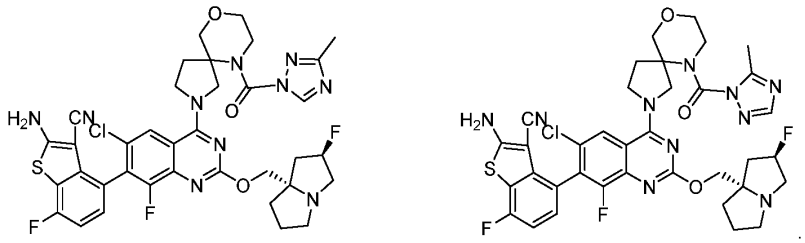
[510] Unless indicated otherwise, when a compound of Table 1a or 1b may exist as atropisomers or diastereomers and a single isomer or limited mixture of isomers is not described in the chemical structure, name, or superscripted notes of Table 1a or 1b, it will be understood that the compound may be provided as a mixture of two or more isomers. When two compounds are provided with identical chemical structures and/or names in Table 1a or 1b and the superscripted note for each compound indicates a single atropisomer or partially purified mixture of isomers (e.g., diastereomers) without identifying the exact atropisomer or isomer (e.g., diastereomer), it will be understood that the two compounds are provided as different atropisomers, isomers (e.g., diastereomers), or partially purified mixtures of isomers.

[511] In some instances, particularly for compounds denoted with [4], two or more regioisomers may exist and the compound structures and corresponding chemical names provided have been tentatively assigned. In the preparation of certain compounds herein, such as compounds comprising a pyrazolyl, imidazolyl, triazolyl, or tetrazolyl, the starting material may exist in two or more tautomeric forms, thus the products may be isolated from the respective reaction mixtures as a single regioisomer or as a mixture of regioisomers that result from reaction with the two or more tautomeric forms of the starting material.

[512] In some instances, particularly for compounds denoted with [5], one substantially pure regioisomer is provided and the compound structures and corresponding chemical names provided are tentatively assigned.

[513] Unless indicated otherwise, where atropisomers of a compound are possible, the compound may be provided as a mixture of atropisomers. Unless indicated otherwise, where a compound includes a possible stereocenter (e.g., spirocyclic stereocenter) and no specific stereoisomer(s) is depicted, the compound may be provided as a mixture of stereoisomers.

[514] For example, Compound 214 was isolated and screened as a mixture of the two regioisomers depicted below, though for convenience only one regioisomer is depicted in Table 1a:



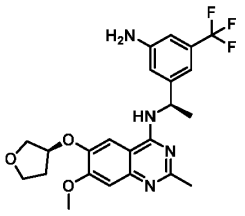
[515] KRAS inhibitors suitable for use in the subject methods—including the synergistic inhibition of proliferation of KRAS-mediated cancer cells in combination with a SOS1 inhibitor—include compounds of Formula (I), encompassing Compound K; Formula (I-1); Formula (I-2); Formula (II); Formula (II-1); Formula (II-2); Formula (II-3);

Formula (IV); Formula (IV-1); Formula (IV-2); Formula (A); Formula (B); Formula (C); Formula (D); Formula (E); Formula (F); Formula (G); and Formula (H). Exemplary KRAS inhibitors include, but are not limited to, compounds selected from Table 1a (including Compound K) and Table 1b, or a salt or solvate thereof.

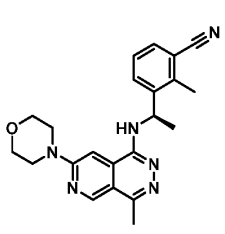
[516] A SOS1 inhibitor for use in the present disclosure can be any SOS1 inhibitor that is known in the art, and can include any entity that, upon administration to a subject, results in downregulation of SOS1 in the subject. For example, a suitable SOS1 inhibitor can be selected from a variety of types of molecules. In particular, the SOS1 inhibitor can be a biological or chemical compound, such as a simple or complex organic or inorganic molecule, peptide, peptido mimetic, protein (e.g., antibody), liposome, or a polynucleotide (e.g., small interfering RNA, short hairpin RNA, microRNA, antisense, aptamer, ribozyme, triple helix). In some embodiments, a method disclosed herein utilizes a small molecule SOS1 inhibitor. As used herein, the term "small molecule" refers to a low molecular weight organic compound, such as a compound having a molecular weight of less than 1500 g/mol, less than 1250 g/mol, less than 1000 g/mol, or less than 750 g/mol. Many compounds are known to inhibit SOS1 (e.g., compounds of WO 2005/097119, which is incorporated herein by reference in its entirety).

[517] In some embodiments, a small molecule SOS1 inhibitor may be conjugated to a degradation tag. A degradation tag may be configured to bind a degradation moiety having a capacity to degrade at least a portion of a target moiety that is bound by the degradation tag. In some embodiments, the target moiety is SOS1 or a substrate of SOS1.

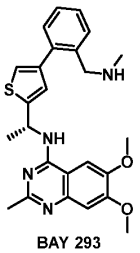
[518] In some embodiments, a subject SOS1 inhibitor disrupts the interaction between SOS1 and KRAS at an IC50 of less than about 20 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, 0.1 nM or even less, as ascertained utilizing the Ras-SOS interaction assay described in Example 6. In some embodiments, the SOS1 inhibitor is at least 5-times more potent than BI-3406, MRTX0902, BAY 293, RMC-5845, or BI-1701963, such as at least 10-times, 20-times, 30-times, 40-times, 50-times, 60-times, 70-times, 80-times, 90-times, or 100-times more potent, as ascertained utilizing the Ras-SOS interaction assay described in Example 6. In some embodiments, a subject SOS1 inhibitor inhibits growth of a cancer cell, such as a lung cancer cell line (e.g., NSCLC), colorectal cancer cell line, or pancreatic cancer cell line, with an IC50 less than about 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, or even less, as ascertained in a growth inhibition assay, optionally utilizing the lung cancer cell line (e.g., NSCLC), colorectal cancer cell line, or pancreatic cancer cell line. In some embodiments, the SOS1 inhibitor inhibits growth of a lung cancer cell line (e.g., NSCLC), colorectal cancer cell line, or pancreatic cancer cell line with an IC50 at least 10, 50, 100, 200, 300, 500, or 1000 times less than that of



BI-3406 ,



MRTX0902 ,

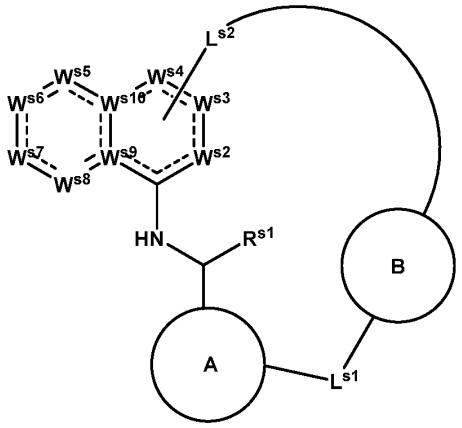


BAY 293 , RMC-5845, or BI-1701963. In some embodiments, the SOS1 inhibitor inhibits growth of a NSCLC cell line with an IC50 at least 10, 50, 100, 200, 300, 500, or 1000 times less than that of a SOS

inhibitor described in WO2021092115, WO2018172250, WO2019201848, WO2019122129, WO2018115380, WO2021127429, WO2020180768, or WO2020180770, each of which is herein incorporated by reference in its entirety for all purposes. In some embodiments, the SOS1 inhibitor synergistically inhibits growth of a cancer cell, such as a lung cancer cell line (e.g., NSCLC), colorectal cancer cell line, or pancreatic cancer cell line, in combination with a KRAS inhibitor. In some embodiments, the SOS1 inhibitor is characterized in that it synergistically increases percent of cell growth inhibition from about 10% to at least about 50%, when less than about 100 nM, 50 nM, 40 nM, 30 nM, 20 nM, or 10 nM, of the SOS1 inhibitor is applied in combination with the RAS inhibitor applied at its IC10 molarity, as ascertained in an in vitro growth inhibition assay using lung cancer cells (e.g., NSCLC), colorectal cancer cells, or pancreatic cancer cells.

[519] The compounds of Formula (SI) and (A) disclosed herein—including the compounds of Formula (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SII-B), (SII-C), (SIII), (A-1), and (Aa-1)—or a pharmaceutically acceptable salt or solvate thereof, are SOS modulators and have a wide range of applications in therapeutics, diagnostics, and other biomedical research.

[520] In certain aspects, the present disclosure provides a compound of Formula (SI):



(SI),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from C_{5-7} carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R^{s11};

is absent or selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7}; or L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s4} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

L^{s3} is selected from C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

D is absent or selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally

substituted with one or more R^{s11d};

L^{s4} is selected from C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

W^{s2} is selected from $N(R^{s2b})$, N, $C(R^{s2})$, $C(R^{s2})(R^{s2a})$, and C(O);

W^{s3} is selected from $N(R^{s3b})$, N, $C(R^{s3})$, $C(R^{s3})(R^{s3a})$, and C(O);

W^{s4} is selected from $N(R^{s4b})$, N, $C(R^{s4})$, $C(R^{s4})(R^{s4a})$, and C(O);

W^{s5} is selected from $N(R^{s5b})$, N, $C(R^{s5})$, $C(R^{s5})(R^{s5a})$, and C(O);

W^{s6} is selected from $N(R^{s6b})$, N, $C(R^{s6})$, $C(R^{s6})(R^{s6a})$, and C(O);

W^{s7} is selected from $N(R^{s7b})$, N, $C(R^{s7})$, $C(R^{s7})(R^{s7a})$, and C(O);

W^{s8} is selected from $N(R^{s8b})$, N, $C(R^{s8})$, $C(R^{s8})(R^{s8a})$, and C(O);

W^{s9} is selected from N, $C(R^{s9})$, and C;

W^{s10} is selected from N, $C(R^{s10})$, and C;

R^{s1} is C_{1-3} alkyl optionally substituted with one or more R^{s11c};

R^{s2}, R^{s2a}, R^{s3a}, R^{s4a}, R^{s5a}, R^{s6a}, R^{s7a}, R^{s8}, and R^{s8a} are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s2b} and R^{s8b} are each independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, R^{s5b}, R^{s6b}, and R^{s7b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s9} and R^{s10} are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle),

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) is independently optionally substituted with one, two, or three R^{s20};

R^{s11}, R^{s11a}, and R^{s11d} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, -OR^{s12}, -SR^{s12}, -$N(R^{s12})(R^{s13})$, -$C(O)OR^{s12}$, -$OC(O)N(R^{s12})(R^{s13})$, -$N(R^{s14})C(O)N(R^{s12})(R^{s13})$, -$N(R^{s14})C(O)OR^{s15}$, -$N(R^{s14})S(O)_2R^{s15}$, -$C(O)R^{s15}$, -$S(O)R^{s15}$, -$OC(O)R^{s15}$, -$C(O)N(R^{s12})(R^{s13})$, -$C(O)C(O)N(R^{s12})(R^{s13})$, -$N(R^{s14})C(O)R^{s15}$, -$S(O)_2R^{s15}$, -$S(O)_2N(R^{s12})(R^{s13})$, -$S(=O)(=NH)N(R^{s12})(R^{s13})$, -$CH_2C(O)N(R^{s12})(R^{s13})$, -$CH_2N(R^{s14})C(O)R^{s15}$, -$CH_2S(O)_2R^{s15}$, -$CH_2S(O)_2N(R^{s12})(R^{s13})$, -$CH_2N(R^{s12})S(O)_2(R^{s13})$, and -$P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, -OR^{s12}, -SR^{s12}, -$N(R^{s12})(R^{s13})$, -$C(O)OR^{s12}$, -$OC(O)N(R^{s12})(R^{s13})$, -$N(R^{s14})C(O)N(R^{s12})(R^{s13})$, -$N(R^{s14})C(O)OR^{s15}$, -$N(R^{s14})S(O)_2R^{s15}$, -$C(O)R^{s15}$, -$S(O)R^{s15}$, -$OC(O)R^{s15}$, -$C(O)N(R^{s12})(R^{s13})$, -$C(O)C(O)N(R^{s12})(R^{s13})$, -$N(R^{s14})C(O)R^{s15}$, -$S(O)_2R^{s15}$, -$S(O)_2N(R^{s12})(R^{s13})$, -$S(=O)(=NH)N(R^{s12})(R^{s13})$, -$CH_2C(O)N(R^{s12})(R^{s13})$, -$CH_2N(R^{s14})C(O)R^{s15}$, -$CH_2S(O)_2R^{s15}$, -$CH_2S(O)_2N(R^{s12})(R^{s13})$, -$CH_2N(R^{s12})S(O)_2(R^{s13})$, and -$P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11c} is independently selected at each occurrence from halogen, -OR^{s12}, and -$N(R^{s12})(R^{s13})$;

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, -CH_2-(3- to 10-membered heterocycle), -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, -$OCH_2C(O)OR^{s22}$, and -$OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, and -$OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

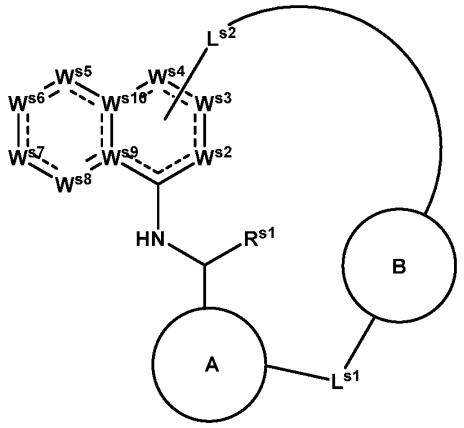
R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[521] In certain aspects, the present disclosure provides a compound of Formula (SI):



(SI),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from C_{5-7} carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R^{s11};

is absent or selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

W^{s2} is selected from $N(R^{s2b})$, N, $C(R^{s2})$, $C(R^{s2})(R^{s2a})$, and C(O);

W^{s3} is selected from $N(R^{s3b})$, N, $C(R^{s3})$, $C(R^{s3})(R^{s3a})$, and C(O);

W^{s4} is selected from $N(R^{s4b})$, N, $C(R^{s4})$, $C(R^{s4})(R^{s4a})$, and C(O);

W^{s5} is selected from $N(R^{s5b})$, N, $C(R^{s5})$, $C(R^{s5})(R^{s5a})$, and C(O);

W^{s6} is selected from $N(R^{s6b})$, N, $C(R^{s6})$, $C(R^{s6})(R^{s6a})$, and C(O);

W^{s7} is selected from $N(R^{s7b})$, N, $C(R^{s7})$, $C(R^{s7})(R^{s7a})$, and C(O);

W^{s8} is selected from $N(R^{s8b})$, N, $C(R^{s8})$, $C(R^{s8})(R^{s8a})$, and C(O);

W^{s9} is selected from N, $C(R^{s9})$, and C;

W^{s10} is selected from N, $C(R^{s10})$, and C;

R^{s1} is C_{1-3} alkyl optionally substituted with one or more R^{s11c};

R^{s2}, R^{s2a}, R^{s3a}, R^{s4a}, R^{s5a}, R^{s6a}, R^{s7a}, R^{s8}, and R^{s8a} are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s2b} and R^{s8b} are each independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, R^{s5b}, R^{s6b}, and R^{s7b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s9} and R^{s10} are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle), wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) is independently optionally substituted with one, two, or three R^{s20};

R^{s11} and R^{s11a} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, -

$S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11c} is independently selected at each occurrence from halogen, $-OR^{s12}$, and $-N(R^{s12})(R^{s13})$;

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6}alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6}alkyl;

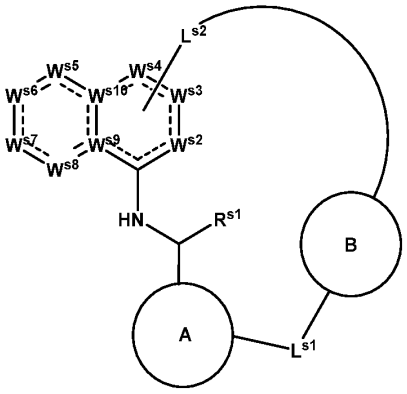
R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[522] In embodiments of the methods described herein, the SOS1 inhibitor is a compound of Formula (SI):



(SI),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from C_{5-7} carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R^{s11};

is absent or selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

W^{s2} is N;

W^{s3} is selected from $N(R^{s3b})$, N, $C(R^{s3})$, and C(O);

W^{s4} is selected from $N(R^{s4b})$, N, $C(R^{s4})$, and C(O);

W^{s5} is selected from $N(R^{s5b})$, N, and $C(R^{s5})$;

W^{s6} is selected from $C(R^{s6})$ and C(O);

W^{s7} is $C(R^{s7})$;

W^{s8} is $C(R^{s8})$;

W^{s9} and W^{s10} are each C;

R^{s1} is C_{1-3} alkyl optionally substituted with one or more R^{s11c};

R^{s8} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, -

$N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, and R^{s5b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s11} and R^{s11a} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11c} is independently selected at each occurrence from halogen, $-OR^{s12}$, and $-N(R^{s12})(R^{s13})$;

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-

membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

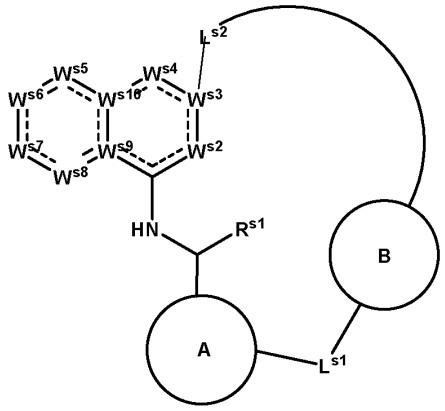
R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

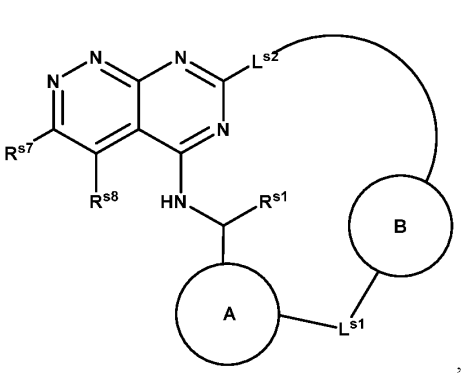
[523] In some embodiments, the compound of Formula (SI) is a compound of Formula (SI-A):



(SI-A),

or a pharmaceutically acceptable salt or solvate thereof.

[524] In some embodiments, the compound of Formula (SI-A) is a compound selected from: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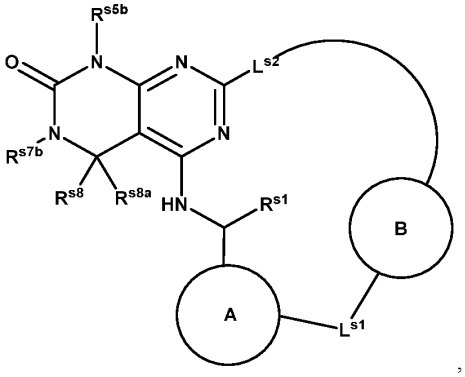
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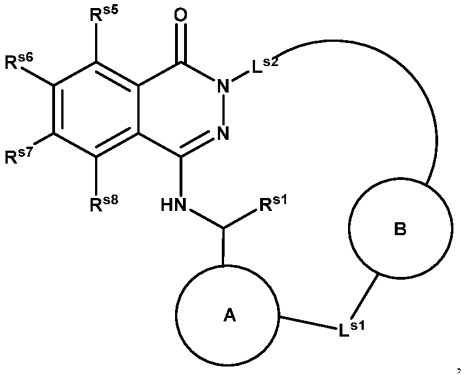
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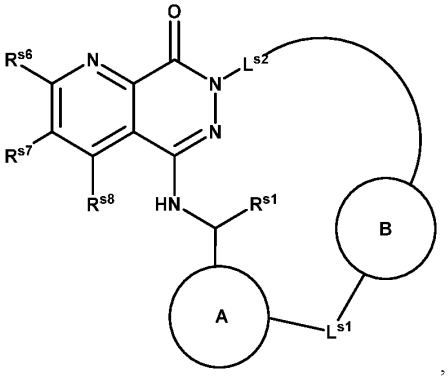
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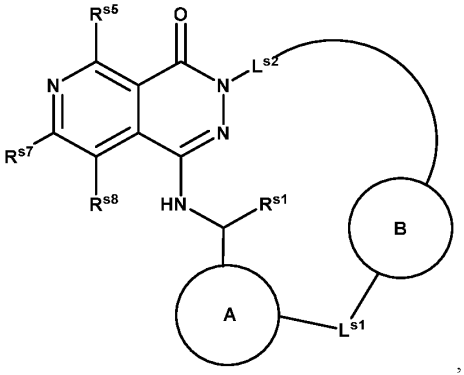
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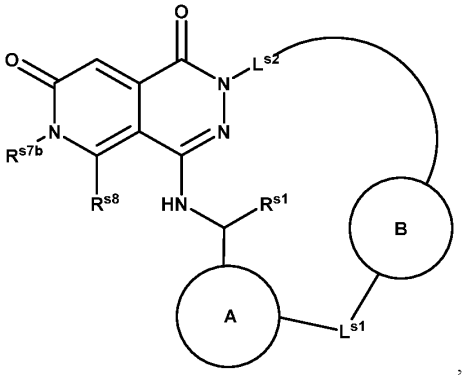
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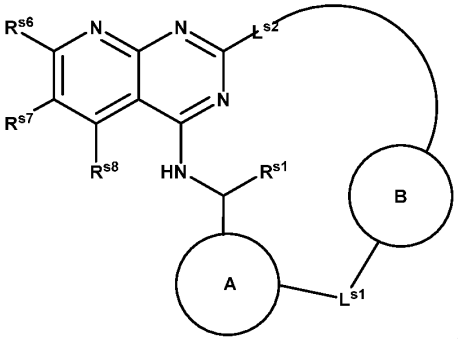
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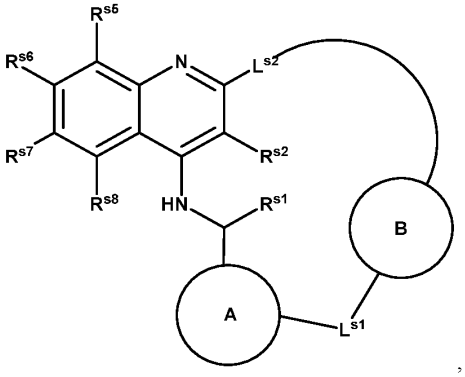
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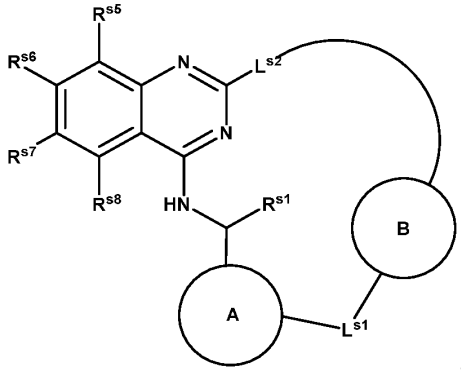
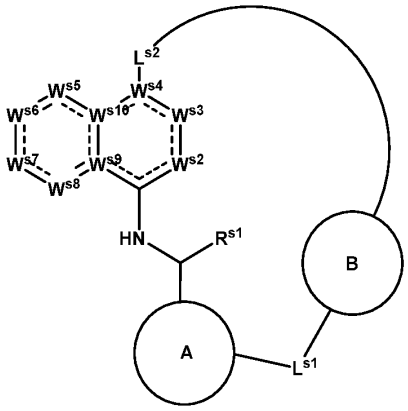
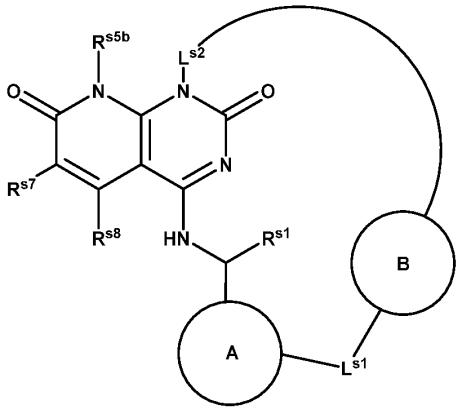


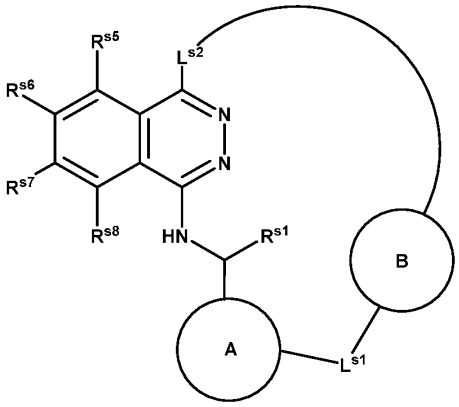
[525] In some embodiments, the compound of Formula (SI) is a compound of Formula (SI-B), such as a compound of Formula (SI-B1) or (SI-B2):



(SI-B),



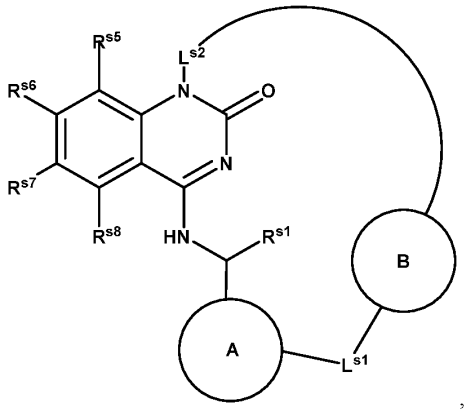
(SI-B1), or



(SI-B2),

or a pharmaceutically acceptable salt or solvate thereof.

[526] In some embodiments, the compound of Formula (SI-B) is a compound selected from:



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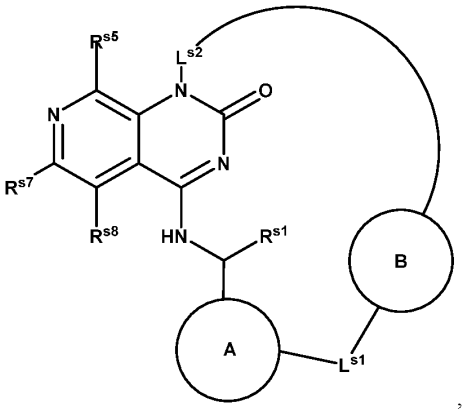

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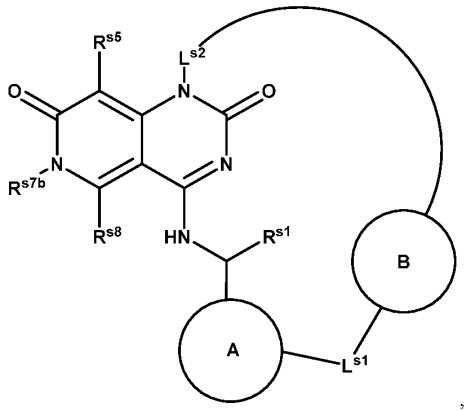
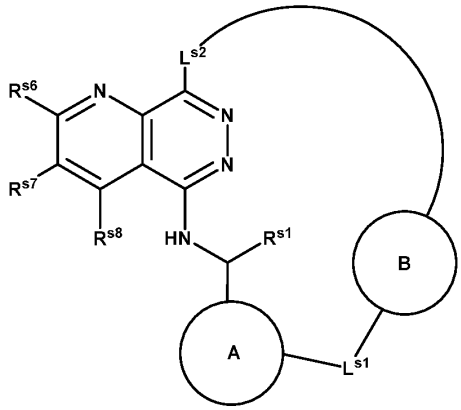
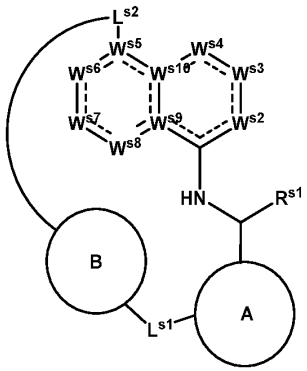


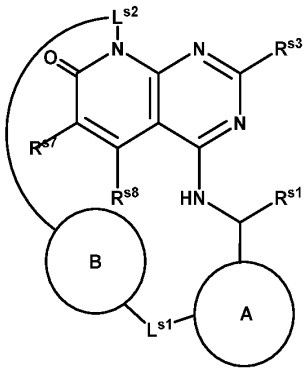


, and .

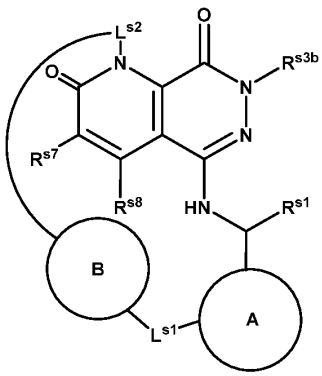
[527] In some embodiments, the compound of Formula (SI) is a compound of Formula (SI-C), such as a compound of Formula (SI-C1), (SI-C2), or (SI-C3):

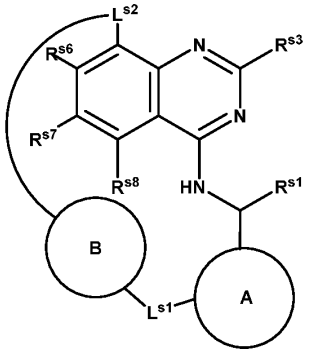


(SI-C),



(SI-C1),

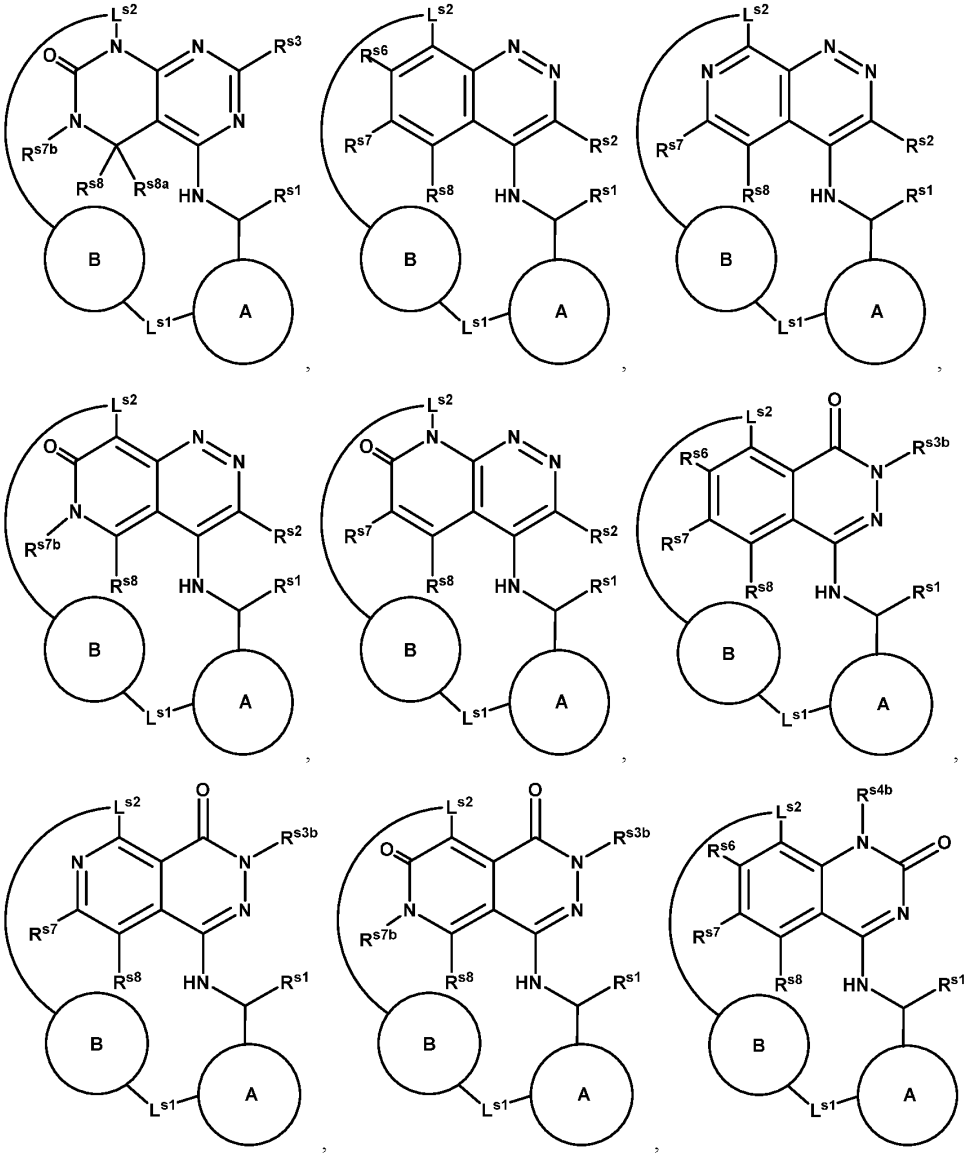


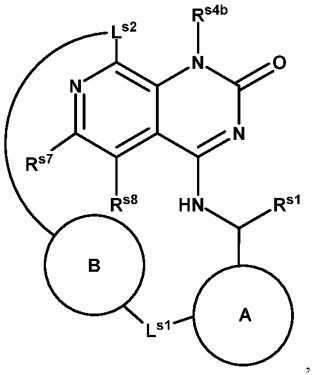


(SI-C2), or (SI-C3),

or a pharmaceutically acceptable salt or solvate thereof.

[528] In some embodiments, the compound of Formula (SI-C) is a compound selected from:





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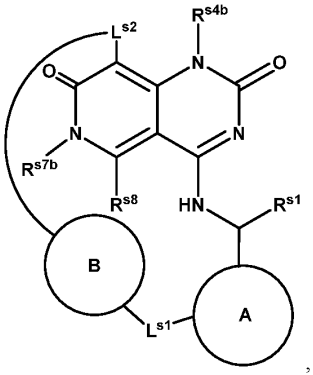

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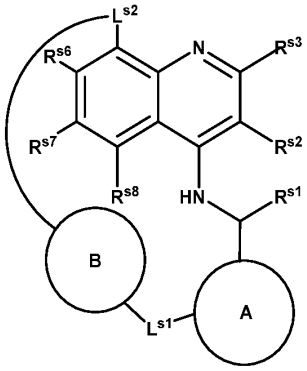
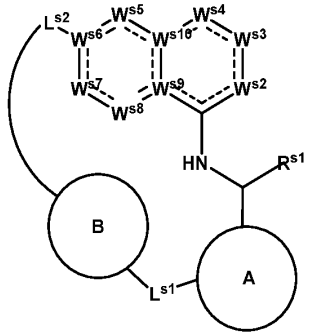
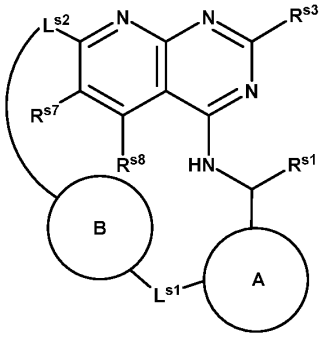
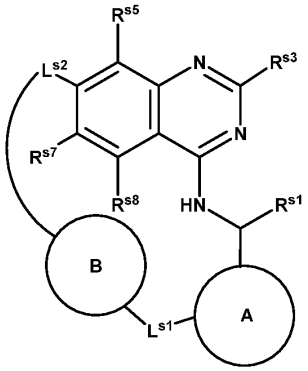


.

[529] In some embodiments, the compound of Formula (SI) is a compound of Formula (SI-D), such as a compound of Formula (SI-D1) or (SI-D2):



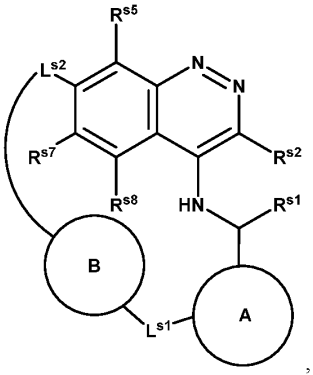
(SI-D),


(SI-D1), or


(SI-D2),

or a pharmaceutically acceptable salt or solvate thereof.

[530] In some embodiments, the compound of Formula (SI-D) is a compound selected from:



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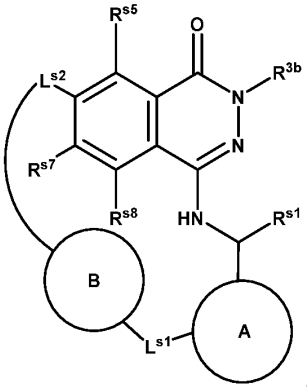

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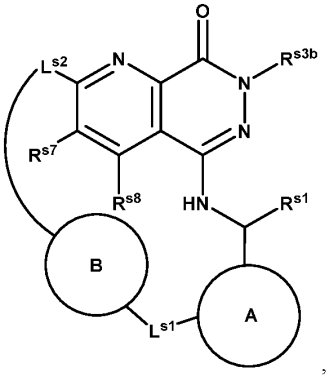

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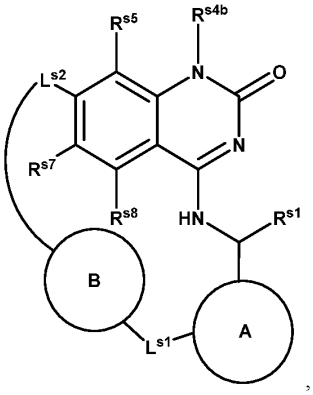

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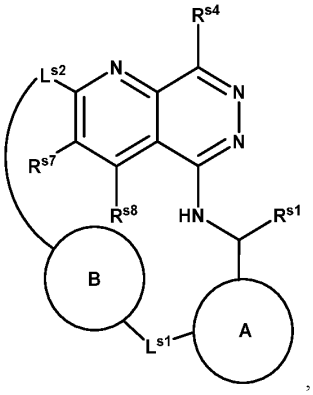

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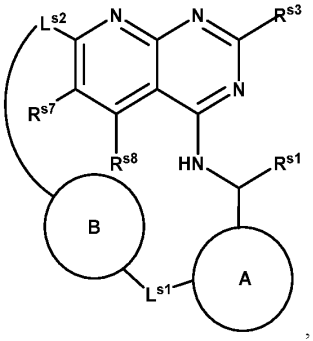

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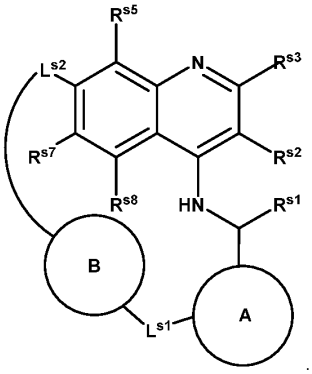

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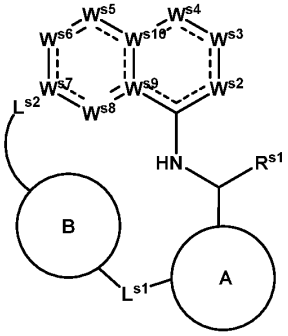
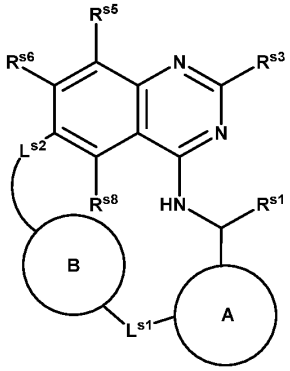
[531] In some embodiments, the compound of Formula (SI) is a compound of Formula (SI-E), such as a compound of Formula (SI-E1):



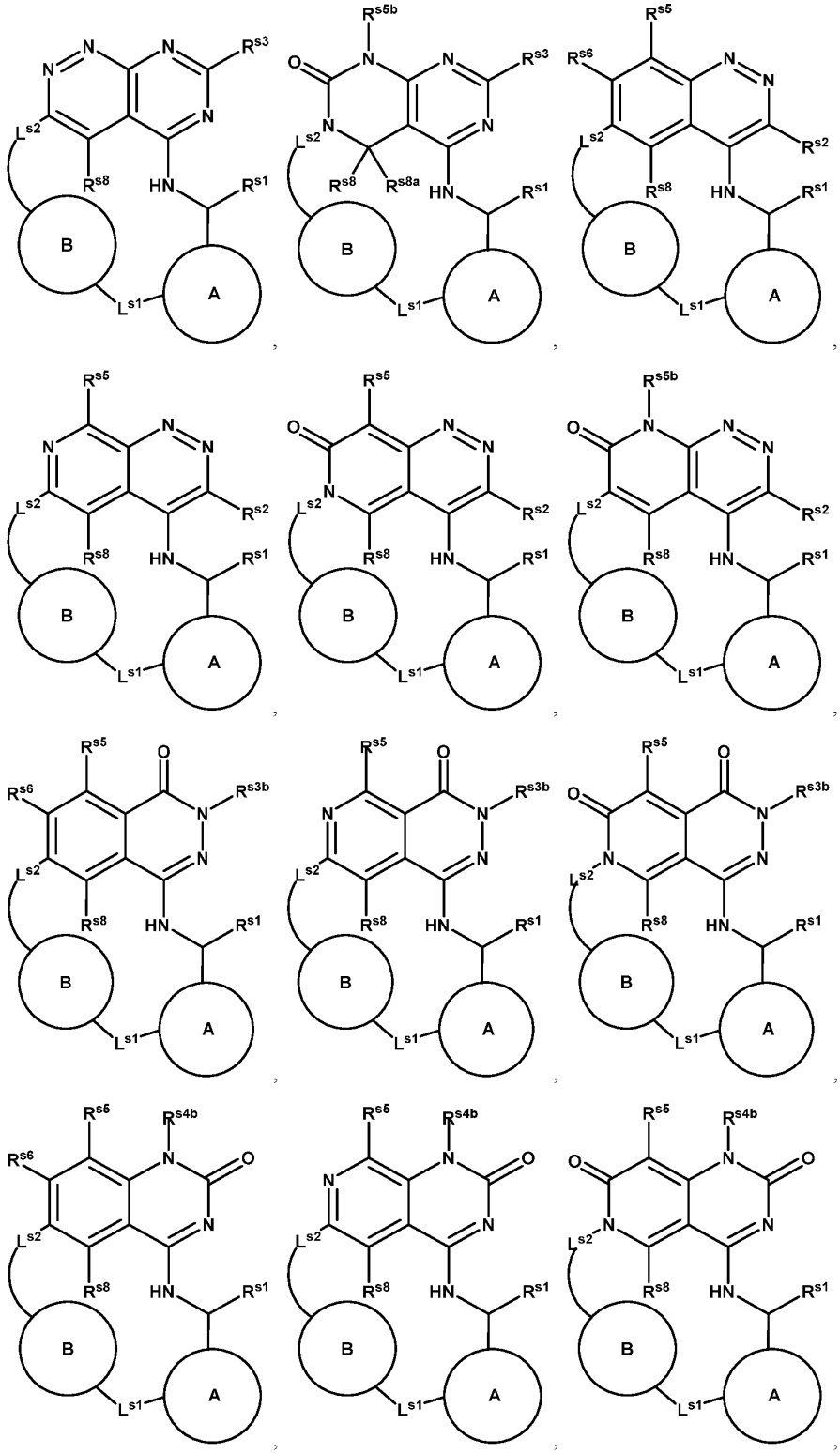
(SI-E) or

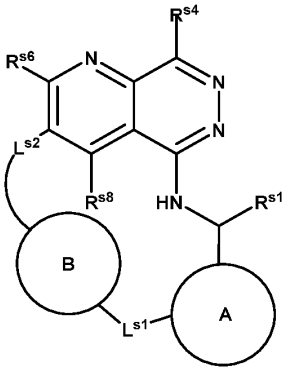


(SI-E1),

or a pharmaceutically acceptable salt or solvate thereof.

[532] In some embodiments, the compound of Formula (SI-E) is a compound selected from:





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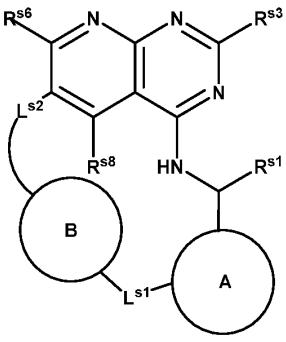

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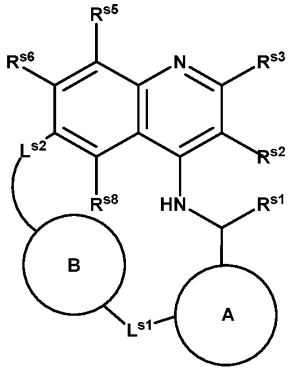
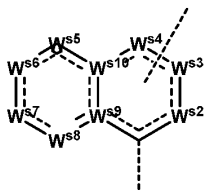


.

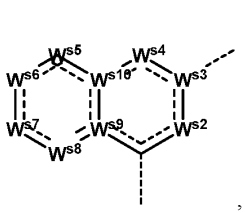
[533] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-C), (SI-D), or (SI-E), W^{s2} is N. In some embodiments, W^{s3} is selected from $N(R^{s3b})$, N, $C(R^{s3})$, and C(O), such as NCH_3, N, CH, CCH_3, and C(O). In some embodiments, W^{s3} is selected from $C(R^{s3})$ and C(O), such as CH, CCH_3 and C(O). In some embodiments, W^{s3} is CH. In some embodiments, W^{s3} is CCH_3. In some embodiments, W^{s4} is selected from $N(R^{s4b})$, N, $C(R^{s4})$, and C(O), such as $N(R^{s4b})$, N, $C(R^{s4})$, and C(O), wherein R^{s4b} and R^{s4} are each independently a bond to L^{s2}. In some embodiments, W^{s4} is selected from $N(R^{s4b})$ and N, such as $N(R^{s4b})$, wherein R^{s4b} is a bond to L^{s2}. In some embodiments, W^{s4} is N. In some embodiments, W^{s5} is selected from $N(R^{s5b})$, N, $C(R^{s5})$, and C(O), such as $N(R^{s5b})$, NCH_3, N, CH, $C(R^{s5})$, and C(O), wherein R^{s5b} and R^{s5} are each independently a bond to L^{s2}. In some embodiments, W^{s5} is selected from $N(R^{s5b})$, N, and $C(R^{s5})$, such as $N(R^{s5b})$, NCH_3, N, CH, and $C(R^{s5})$, wherein R^{s5b} and R^{s5} are each independently a bond to L^{s2}. In some embodiments, W^{s5} is selected from $N(R^{s5b})$ and $C(R^{s5})$, such as $N(R^{s5b})$, NCH_3, and CH, wherein R^{s5b} is a bond to L^{s2}. In some embodiments, W^{s5} is $N(R^{s5b})$. In some embodiments, W^{s6} is selected from $C(R^{s6})$ and C(O), such as $COCH_3$, CH, $C(R^{s6})$, and C(O), wherein R^{s6} is a bond to L^{s2}. In some embodiments, W^{s6} is C(O). In some embodiments, W^{s7} is $C(R^{s7})$, such as W^{s7} is $C(R^{s7})$ wherein R^{s7} is a bond to L^{s2}. In some embodiments, W^{s7} is $C(R^{s7})$, wherein R^{s7} is not hydrogen, such as R^{s7} is selected from $C_{3\text{-}10}$ cycloalkyl, 3- to 10-membered heterocycloalkyl, and $-OR^{s12}$, wherein $C_{3\text{-}10}$ cycloalkyl and 3- to 10-membered heterocycloalkyl are optionally substituted with one, two, or three R^{s20}. In some embodiments, W^{s8} is $C(R^{s8})$, such as W^{s8} is CH. In some embodiments, W^{s9} is C. In some embodiments, W^{s10} is C.

[534] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-C), (SI-D), or (SI-E), W^{s2} is N; W^{s3} is $N(R^{s3b})$; W^{s4} is C(O); and W^{s9} and W^{s10} are each C, such as W^{s2} is N; W^{s3} is NCH_3; W^{s4} is C(O); and W^{s9} and W^{s10} are each C. In some embodiments, for a compound of Formula (SI), (SI-B), (SI-C), (SI-D), or (SI-E),W^{s2} is N; W^{s3} is C(O); W^{s4} is $N(R^{s4b})$; and W^{s9} and W^{s10} are each C, such as W^{s2} is N; W^{s3} is C(O); W^{s4} is $N(R^{s4b})$, wherein R^{s4b} is a bond to L^{s2}; and W^{s9} and W^{s10} are each C. In some embodiments, for a compound of Formula (SI), (SI-A), (SI-C), (SI-D), or (SI-E), W^{s2} is N; W^{s3} is $C(R^{s3})$; W^{s4} is N; and W^{s9} and W^{s10} are each C, such as W^{s2} is N; W^{s3} is CH or CCH_3; W^{s4} is N; and W^{s9} and W^{s10} are each C. In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-C), (SI-D), or (SI-E), W^{s5} is $C(R^{s5})$; W^{s6} is $C(R^{s6})$; W^{s7} is $C(R^{s7})$; W^{s8} is $C(R^{s8})$; and W^{s9} and W^{s10} are each C, such as W^{s5} is CH or $C(R^{s5})$, wherein R^{s5} is a bond to L^{s2}; W^{s6} is CH or $C(R^{s6})$, wherein R^{s6} is a bond to L^{s2}; W^{s7} is $C(R^{s7})$; W^{s8} is CH; and W^{s9} and W^{s10} are each C. In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-C), or (SI-E), W^{s5} is $N(R^{s5b})$; W^{s6} is C(O); W^{s7} is $C(R^{s7})$; W^{s8} is $C(R^{s8})$; and W^{s9} and W^{s10} are each C, such as W^{s5} is NCH_3 or $N(R^{s5b})$, wherein R^{s5b} is a bond to L^{s2}; W^{s6} is C(O); W^{s7} is $C(R^{s7})$; W^{s8} is CH; and W^{s9} and W^{s10} are each C. In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-D), or (SI-E), W^{s5} is N; W^{s6} is $C(R^{s6})$; W^{s7} is $C(R^{s7})$; W^{s8} is $C(R^{s8})$; and W^{s9} and W^{s10} are each C, such as W^{s5} is N; W^{s6} is $COCH_3$, CH, or $C(R^{s6})$, wherein R^{s6} is a bond to L^{s2}; W^{s7} is $C(R^{s7})$; W^{s8} is CH; and W^{s9} and W^{s10} are each C. In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-C), (SI-D), or (SI-E), W^{s2} is N; W^{s3} is selected from $N(R^{s3b})$, N, $C(R^{s3})$, and C(O); W^{s4} is selected

from $N(R^{s4b})$, N, $C(R^{s4})$, and C(O); W^{s5} is selected from $N(R^{s5b})$, N, and $C(R^{s5})$; W^{s6} is selected from $C(R^{s6})$ and C(O); W^{s7} is $C(R^{s7})$; W^{s8} is $C(R^{s8})$; and W^{s9} and W^{s10} are each C, such as W^{s2} is N; W^{s3} is selected from NCH_3, N, CH, CCH_3, and C(O); W^{s4} is selected from $N(R^{s4b})$, N, $C(R^{s4})$, and C(O), wherein R^{s4b} and R^{s4} are each independently a bond to L^{s2}; W^{s5} is selected from $N(R^{s5b})$, NCH_3, N, CH, and $C(R^{s5})$, wherein R^{s5b} and R^{s5} are each independently a bond to L^{s2}; W^{s6} is selected from $COCH_3$, CH, $C(R^{s6})$, and C(O), wherein R^{s6} is a bond to L^{s2}; W^{s7} is $C(R^{s7})$; W^{s8} is CH; and W^{s9} and W^{s10} are each C. In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-C), (SI-D), or (SI-E), W^{s2} is N; W^{s3} is selected from $C(R^{s3})$ and C(O); W^{s4} is selected from $N(R^{s4b})$ and N; W^{s5} is selected from $N(R^{s5b})$ and $C(R^{s5})$; W^{s6} is selected from $C(R^{s6})$ and C(O); W^{s7} is $C(R^{s7})$; W^{s8} is CH; and W^{s9} and W^{s10} are each C, such as W^{s2} is N; W^{s3} is selected from CH, CCH_3, and C(O); W^{s4} is selected from $N(R^{s4b})$ and N, wherein R^{s4b} is a bond to L^{s2}; W^{s5} is selected from $N(R^{s5b})$, NCH_3, CH, and $C(R^{s5})$, wherein R^{s5b} and R^{s5} are each independently a bond to L^{s2}; W^{s6} is selected from $COCH_3$, CH, $C(R^{s6})$, and C(O), wherein R^{s6} is a bond to L^{s2}; W^{s7} is $C(R^{s7})$; W^{s8} is CH; and W^{s9} and W^{s10} are each C.



[535] In some embodiments, for a compound of Formula (SI), is selected from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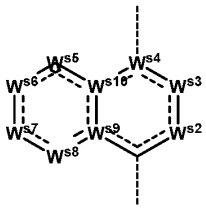
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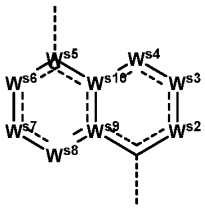
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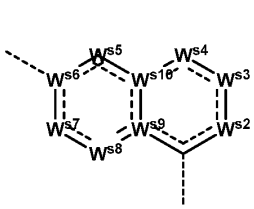
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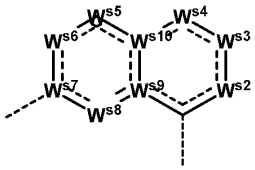
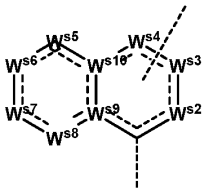
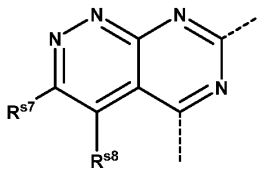

. In some embodiments, is selected from


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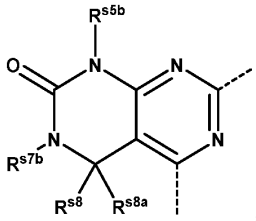
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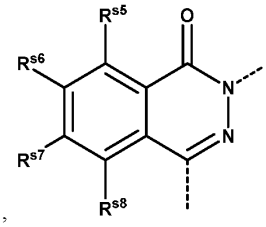
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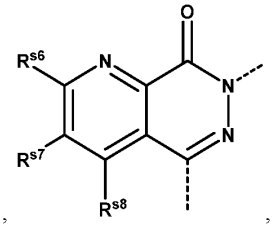
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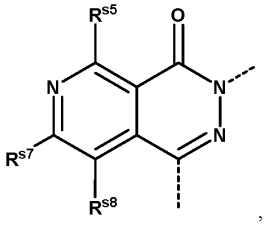
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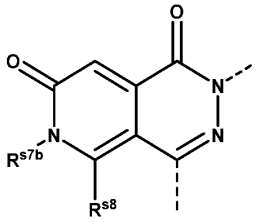
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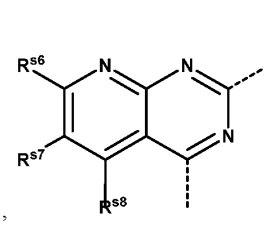
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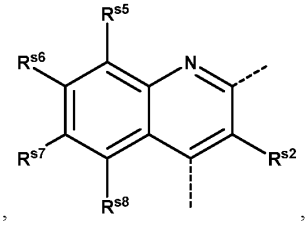
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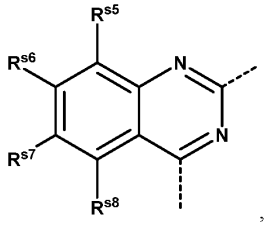
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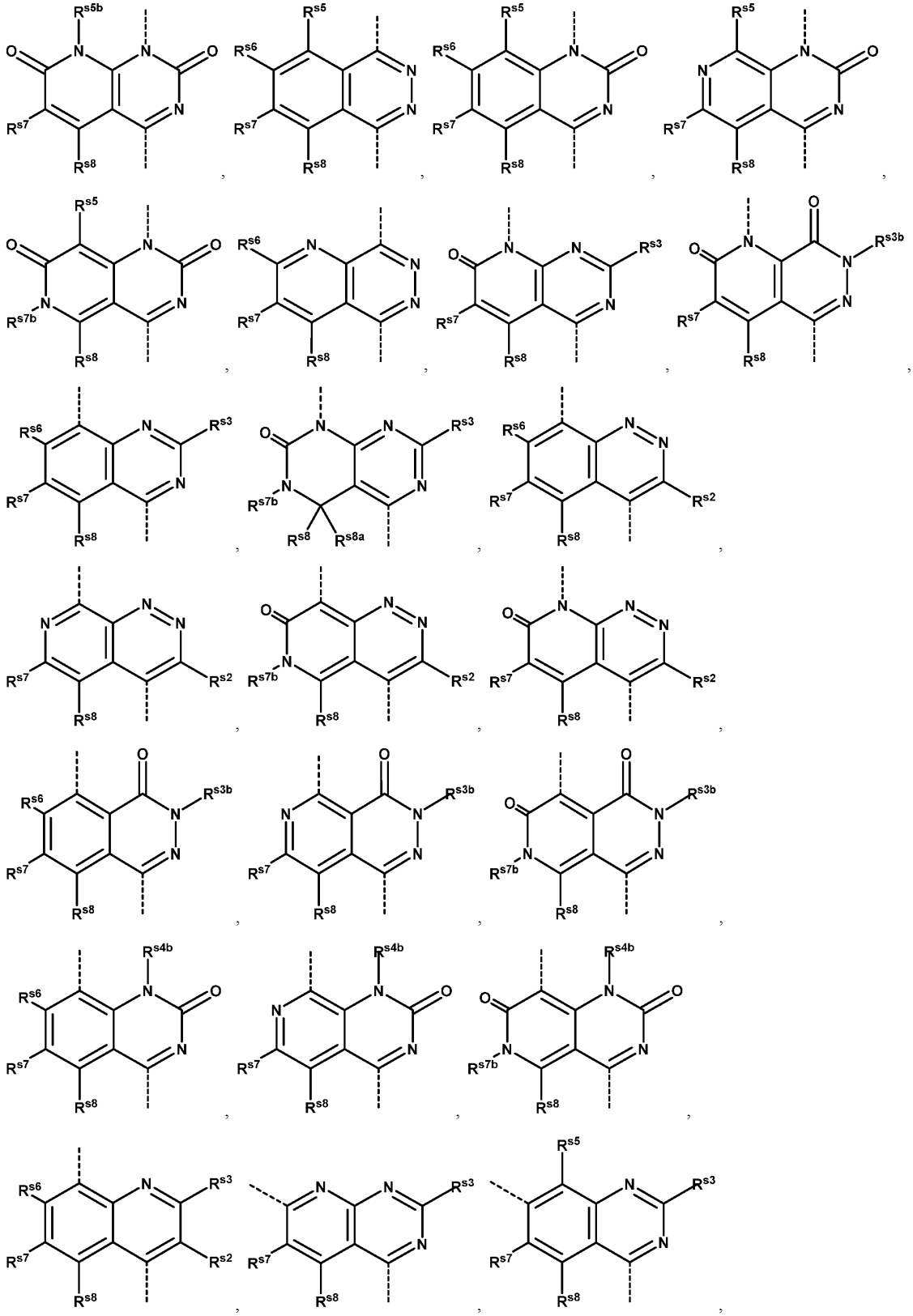

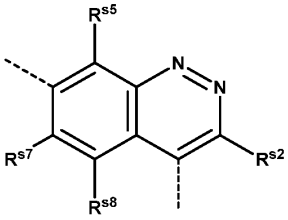
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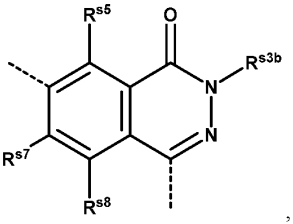
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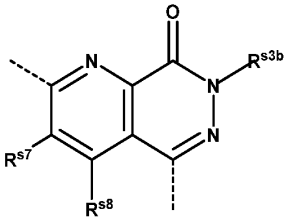
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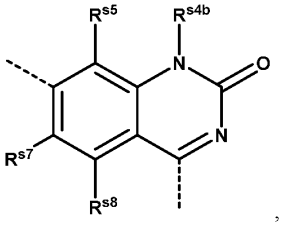
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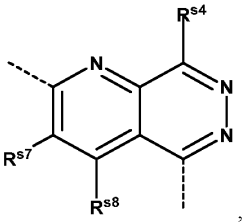
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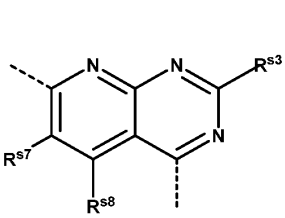
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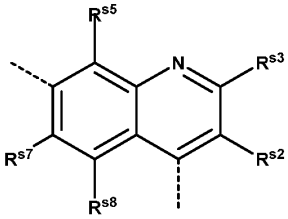
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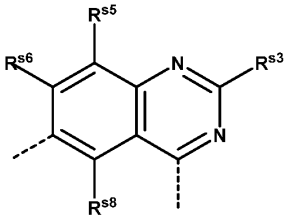
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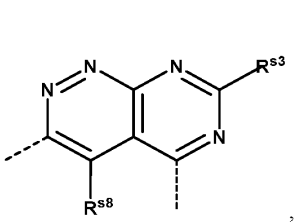
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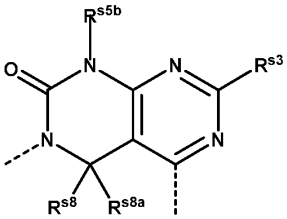
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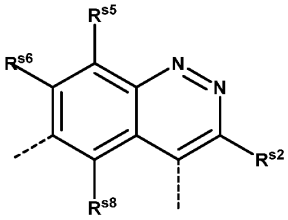
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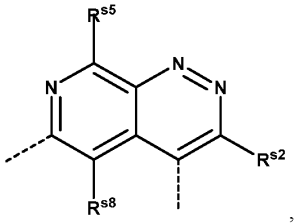
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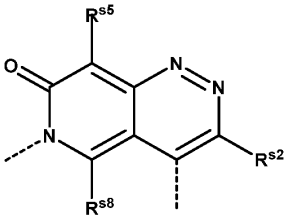
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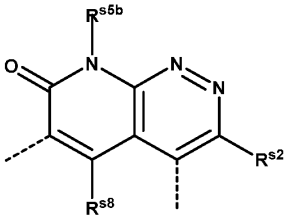
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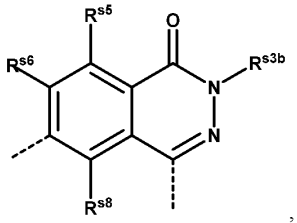
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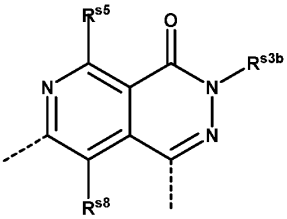
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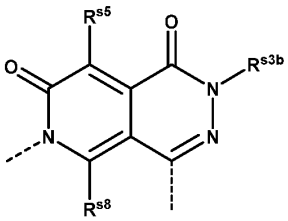
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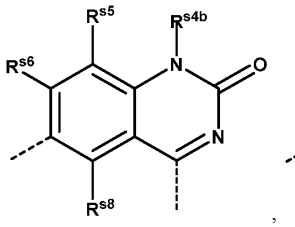
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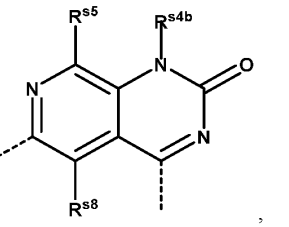
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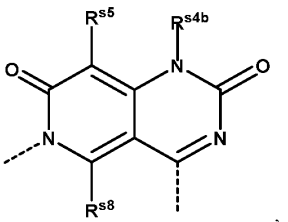
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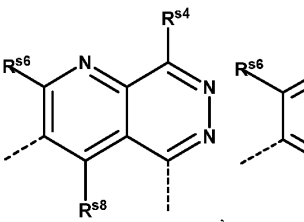
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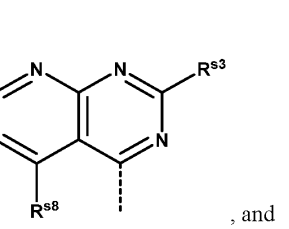
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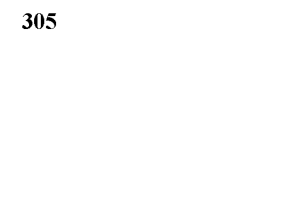
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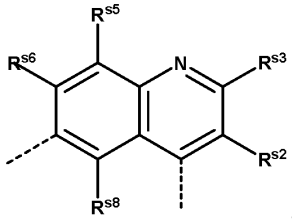
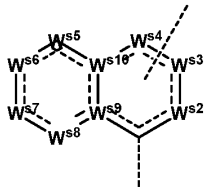

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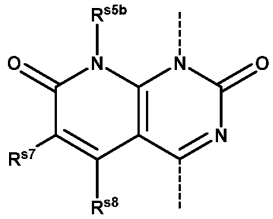
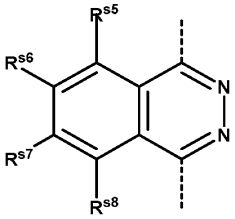
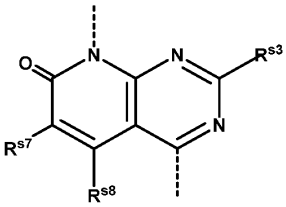
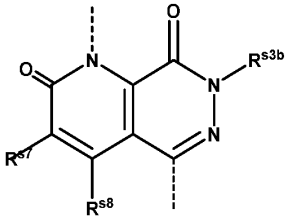

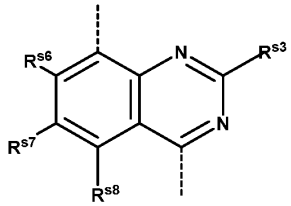
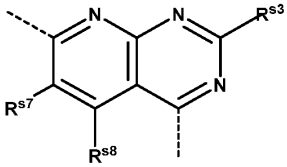
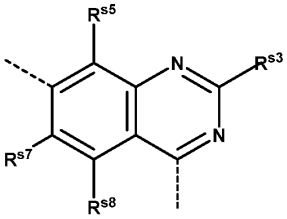

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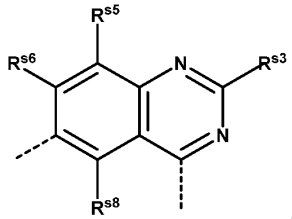
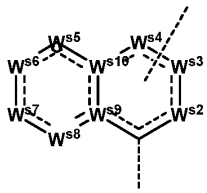

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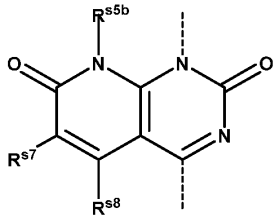
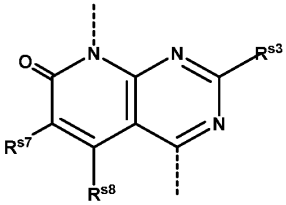
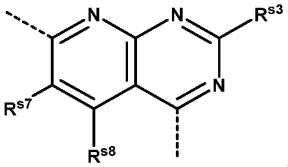

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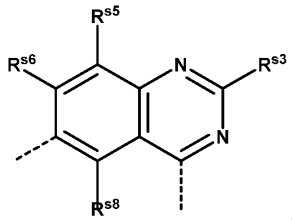
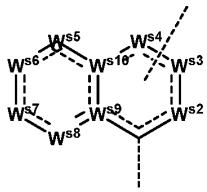
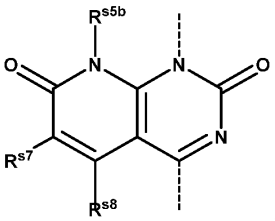

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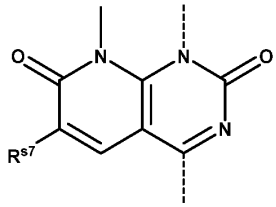
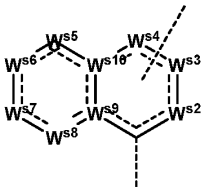
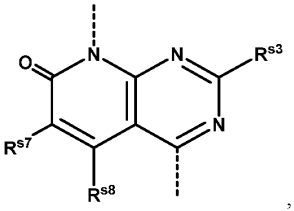

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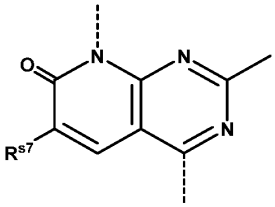
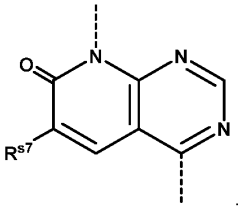
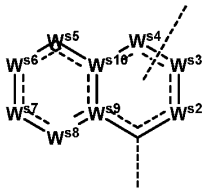
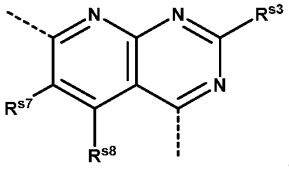
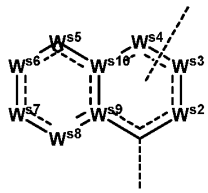
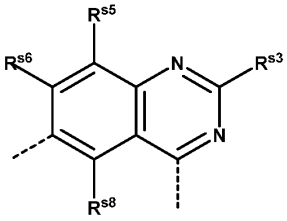
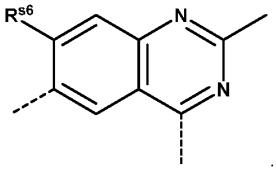
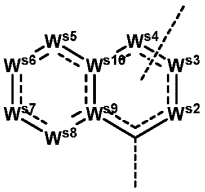
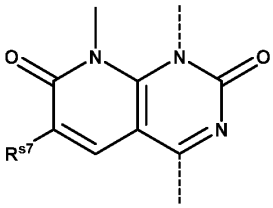
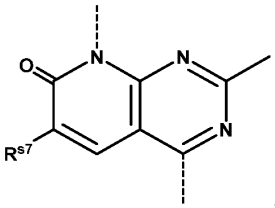
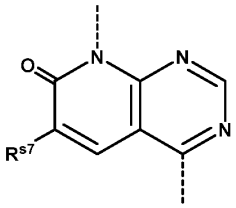
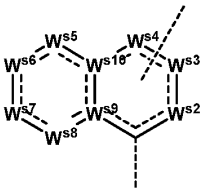
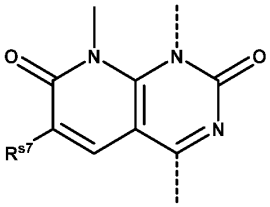
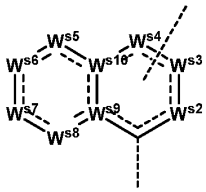
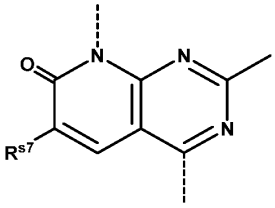
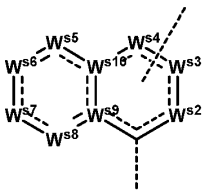
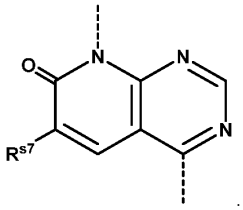


or . In some embodiments,  is


. In some embodiments,  is  , such as


. In some embodiments,  is selected from


,  , and  . In some embodiments,


is  . In some embodiments,  is


. In some embodiments,  is  .

[536] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-C), (SI-D), or (SI-E), R^{s2}, R^{s2a}, R^{s3a}, R^{s4a}, R^{s5a}, R^{s6a}, R^{s7a}, R^{s8}, and R^{s8a} are each independently selected from hydrogen, halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, -OH, $-NH_2$, $-NHCH_3$, and $-N(CH_3)_2$. In some embodiments, R^{s2}, R^{s2a}, R^{s3a}, R^{s4a}, R^{s5a}, R^{s6a}, R^{s7a}, R^{s8}, and R^{s8a} are each independently selected from hydrogen and $-CH_3$, such as hydrogen.

[537] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-C), (SI-D), or (SI-E), R^{s3}, R^{s4}, R^{s5}, and R^{s6} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{3-6} carbocycle, 3- to 6-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, and $-S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{3-6} carbocycle, and

3- to 6-membered heterocycle is independently optionally substituted with one, two, or three R^{s20}; and R^{s7} is selected from a bond to L^{s2}, C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s3}, R^{s4}, R^{s5}, and R^{s6} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$; and R^{s7} is selected from a bond to L^{s2}, C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s3}, R^{s4}, R^{s5}, and R^{s6} are each independently selected from a bond to L^{s2}, hydrogen, $-CH_3$, and $-OCH_3$; and R^{s7} is selected from a bond to L^{s2}, C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}.

[538] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-C), (SI-D), or (SI-E), R^{s2b} and R^{s8b} are each independently selected from hydrogen and C_{1-3} alkyl, such as hydrogen and $-CH_3$. In some embodiments, R^{s3b}, R^{s4b}, R^{s5b}, R^{s6b}, and R^{s7b} are each independently selected from a bond to L^{s2}, hydrogen, and C_{1-3} alkyl, such as a bond to L^{s2}, hydrogen, and $-CH_3$. In some embodiments, R^{s3b}, R^{s4b}, R^{s5b}, R^{s6b}, and R^{s7b} are each independently selected from a bond to L^{s2} and $-CH_3$. In some embodiments, R^{s3b}, R^{s4b}, R^{s5b}, R^{s6b}, and R^{s7b} are each independently selected from a bond to L^{s2}. In some embodiments, R^{s9} and R^{s10} are each hydrogen.

[539] For a compound of Formula (SI) wherein L^{s2} is $-L^{s3}$-D-L^{s4}-, it is understood that the selection of "a bond to L^{s2}" for one of R^{s3}, R^{s4}, R^{s5}, R^{s6}, R^{s7}, R^{s3b}, R^{s4b}, R^{s5b}, R^{s6b}, or R^{s7b} inherently includes a bond to $-L^{s3}$-D-L^{s4}-, specifically to L^{s4}. For the avoidance of doubt, any recitation of R^{s3}, R^{s4}, R^{s5}, R^{s6}, R^{s7}, R^{s3b}, R^{s4b}, R^{s5b}, R^{s6b}, and/or R^{s7b} that includes "a bond to L^{s2}" also may be considered to include "a bond to L^{s4}".

[540] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1), R^{s1} is selected from C_{1-3} alkyl and C_{1-3} haloalkyl, such as $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, CH_2CH_2F, $-CH_2CHF_2$, and $-CH_2CF_3$. In some embodiments, R^{s1} is selected from C_{1-3} alkyl, such as $-CH_3$ and $-CH_2CH_3$. In some embodiments, R^{s1} is $-CH_3$. In some embodiments, R^{s1} is (*R*)-CH_3. In some embodiments, R^{s1} is (*S*)-CH_3.

[541] In some embodiments, for a compound of Formula (SI), (SI-B), (SI-C), (SI-C1), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1), R^{s3} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{3-6} carbocycle, 3- to 6-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, and $-S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{3-6} carbocycle, and 3- to 6-membered heterocycle is independently optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s3} is selected from hydrogen, halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$. In some embodiments, R^{s3} is selected from hydrogen, halogen, -CN, $-OR^{s12}$, and C_{1-6} alkyl optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s3} is C_{1-6} alkyl optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s3} is hydrogen or $-CH_3$. In some embodiments, R^{s3} is hydrogen. In some embodiments, R^{s3} is $-CH_3$.

[542] In some embodiments, for a compound of Formula (SI), (SI-B), (SI-C), (SI-C2), (SI-D), or (SI-E), R^{s3b} is selected from hydrogen and C_{1-3} alkyl, such as hydrogen and $-CH_3$. In some embodiments, R^{s3b} is $-CH_3$. In some embodiments, R^{s3b} is hydrogen.

[543] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B2), (SI-D), (SI-D2), (SI-E), or (SI-E1), R^{s5} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{3-6} carbocycle, 3- to 6-membered heterocycle, $-OR^{s12}$,

$-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, and $-S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{3-6} carbocycle, and 3- to 6-membered heterocycle is independently optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s5} is selected from hydrogen, halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$. In some embodiments, R^{s5} is selected from hydrogen, $-OR^{s12}$, and C_{1-6} alkyl optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s5} is hydrogen or $-CH_3$. In some embodiments, R^{s5} is hydrogen. In some embodiments, R^{s5} is $-CH_3$.

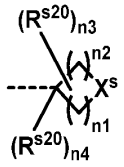
[544] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-D), or (SI-E), R^{s5b} is selected from hydrogen and C_{1-3} alkyl, such as hydrogen and $-CH_3$. In some embodiments, R^{s5b} is selected from hydrogen and C_{1-6} alkyl optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s5b} is $-CH_3$. In some embodiments, R^{s5b} is hydrogen. In some embodiments, R^{s5b} is a bond to L^{s2}.

[545] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B2), (SI-C), (SI-C3), (SI-E), or (SI-E1), R^{s6} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{3-6} carbocycle, 3- to 6-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, and $-S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{3-6} carbocycle, and 3- to 6-membered heterocycle is independently optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s6} is selected from hydrogen, halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, and $-N(CH_3)_2$. In some embodiments, R^{s6} is selected from hydrogen, $-OR^{s12}$, and C_{1-6} alkyl optionally substituted with one, two, or three R^{s20}, and wherein R^{s12} is selected from C_{1-6} alkyl. In some embodiments, R^{s6} is selected from hydrogen and $-OCH_3$. In some embodiments, R^{s6} is hydrogen. In some embodiments, R^{s6} is $-OCH_3$.

[546] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), or (SI-D2), R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s7} is selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $-N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl are optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s7} is 3- to 10-membered heterocycloalkyl optionally substituted with one, two, or three R^{s20}, such as R^{s7} is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s7} is 3- to 10-membered heterocycloalkyl optionally substituted with one, two, or three R^{s20}, wherein the heterocycloalkyl comprises at least one O, N, or S, such as one O atom, one or two N atoms, or one S atom. In some embodiments, R^{s7} is 3- to 6-membered heterocycloalkyl optionally substituted with one, two, or three R^{s20}, wherein the heterocycloalkyl comprises $S(O)_2$. In some embodiments, R^{s7} is C_{3-10} cycloalkyl optionally substituted with one, two, or three R^{s20}, such as R^{s7} is C_{3-6} cycloalkyl optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s7} is C_{3-4} cycloalkyl optionally substituted with one R^{s20}, optionally wherein R^{s20} is -CN. In some embodiments, R^{s7} is C_{1-6} alkyl optionally substituted with one, two, or three R^{s20}, such as R^{s7} is C_{1-6} alkyl substituted with one or two R^{s20}. In some embodiments, R^{s7} is $-N(R^{s12})(R^{s13})$. In some embodiments, R^{s7} is $-OR^{s12}$, such as -O(3- to 6-membered heterocycloalkyl). In some embodiments, R^{s7} is substituted with at least one -CN. In some embodiments, R^{s7} is unsubstituted. In some embodiments, R^{s7} is selected from C_{3-10} carbocycle and 3- to 10-membered

heterocycle, each of which is optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s7} is selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one, two, or three substituents selected from oxo, -CN, and C_{1-6} alkyl. In some embodiments, R^{s7} is 4- to 6-membered heterocycloalkyl substituted with one, two, or three substituents selected from oxo, -CN, and C_{1-3} alkyl. In some embodiments, R^{s7} is C_{3-4} cycloalkyl substituted with one, two, or three substituents selected from oxo, -CN, and C_{1-3} alkyl.

[547] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), or (SI-D2), R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)(NR^{s12})R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)(NR^{s12})R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)(NR^{s12})R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s7} is 3- to 6-membered heterocycloalkyl optionally substituted with one, two, or three R^{s20}, wherein the heterocycloalkyl comprises $S(O)(NR^{s12})$.

[548] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), or (SI-D2), R^{s7} is  , wherein:

n1 is an integer from 1 to 3;

n2 is an integer from 0 to 2;

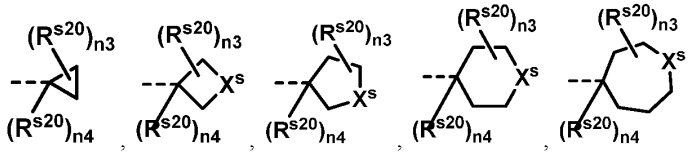
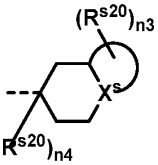
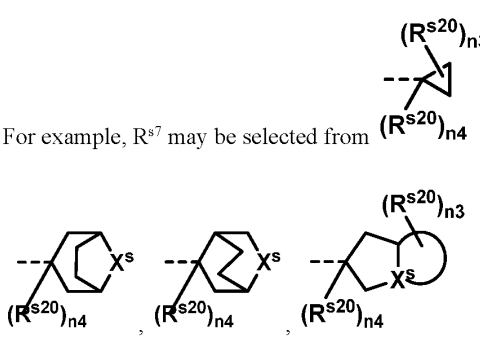
n3 is an integer from 0 to 2;

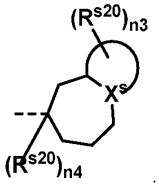
n4 is 0 or 1; and

X^s is selected from -O-, $-S(O_2)-$, -P(O)-, $-CH_2-$, -CH(OH)-, $-CH(OR^{s12})-$, $-CH(R^{s20})-$, $-C(R^{s20})_2-$, $-NR^{s12}-$, $-CH(N(R^{s12})(R^{s13}))-$, $-CH(C(O)N(R^{s12})(R^{s13}))-$, and $-CH(S(O)_2N(R^{s12})(R^{s13}))-$,

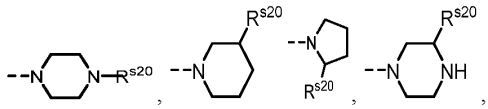
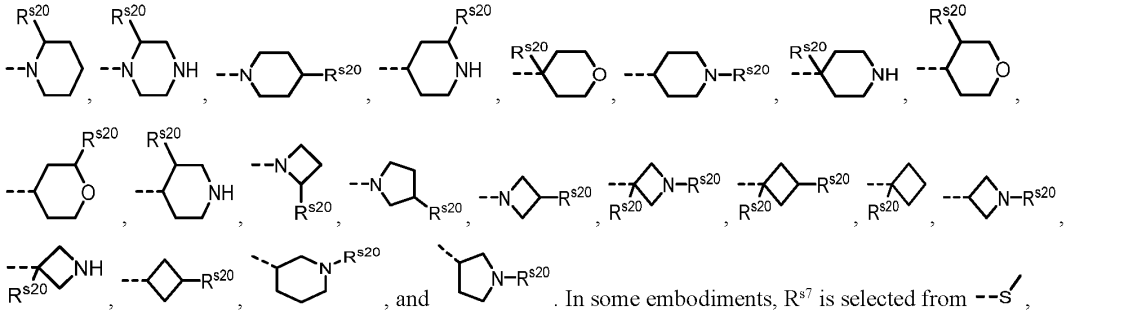
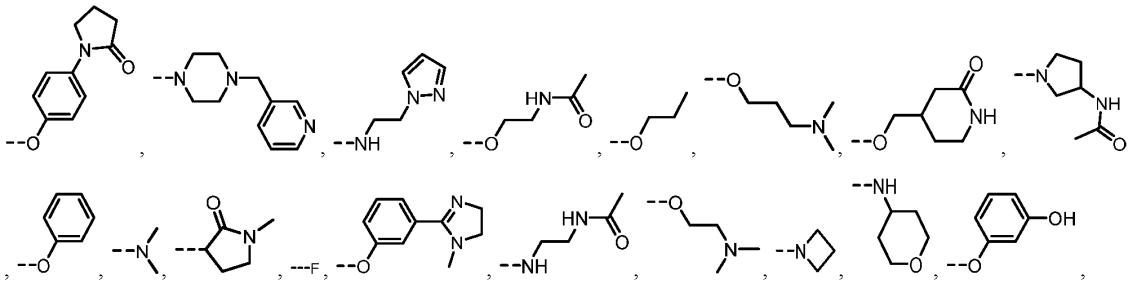
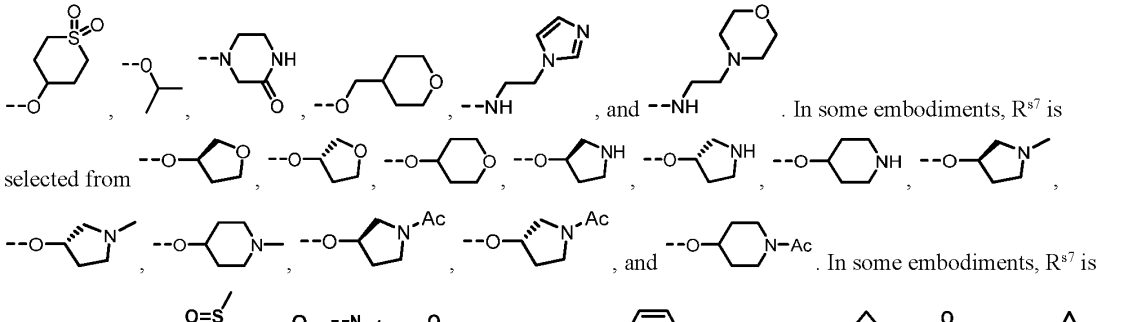
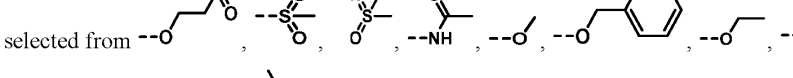
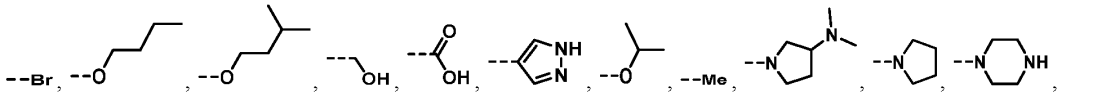
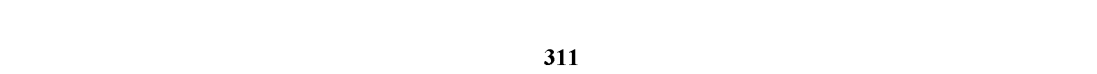
wherein R^{s12}, R^{s13}, and R^{s20} are as defined elsewhere herein, and

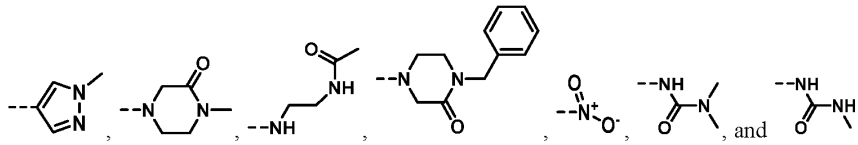
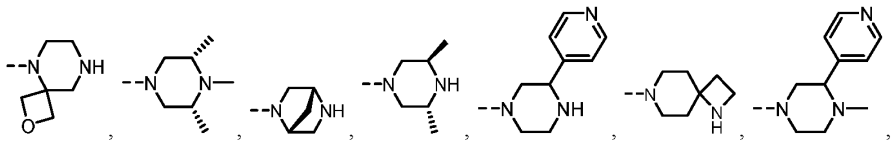
optionally wherein two R^{s20} groups, or R^{s20} and R^{s12}, join together with the atom(s) to which they are attached to form a ring.

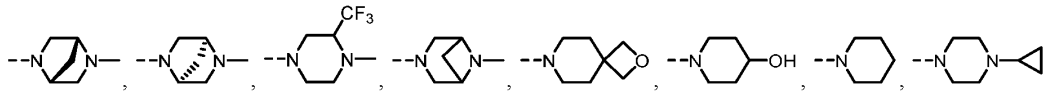
For example, R^{s7} may be selected from  , ,  , and  .

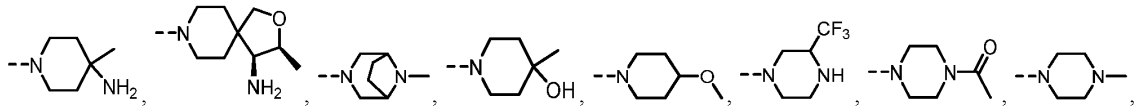


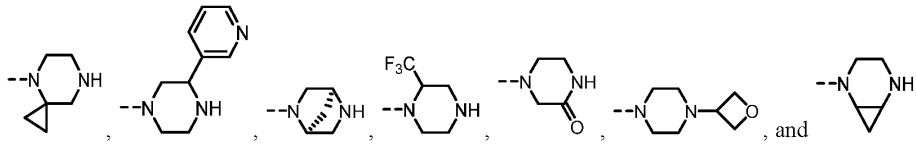
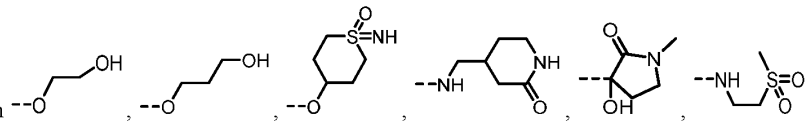
. In some embodiments, X^s is selected from -O-, -$S(O)_2$-, -S(O)(NR^{s12})-, -P(O)-, -CH_2-, -CH(OH)-, -CH(OR^{s12})-, -CH(R^{s20})-, -$C(R^{s20})_2$-, -NR^{s12}-, -CH(N(R^{s12})(R^{s13}))-, -CH(C(O)N(R^{s12})(R^{s13}))-, and -$CH(S(O)_2N(R^{s12})(R^{s13}))$-.

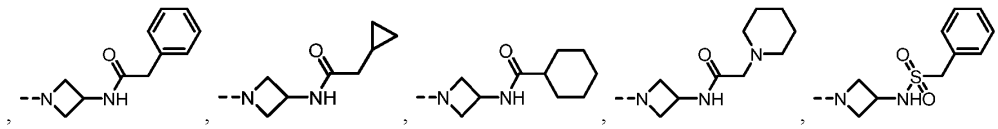
[549] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), or (SI-D2), R^{s7} is selected from  ,  , and . In some embodiments, R^{s7} is selected from  ,  , and  . In some embodiments, R^{s7} is selected from  . In some embodiments, R^{s7} is selected from ,  , and . In some embodiments, R^{s7} is selected from , .

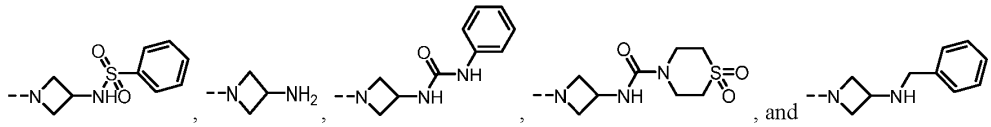
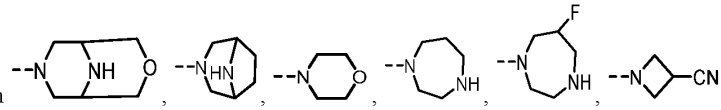
 , and . In some embodiments, R^{s7} is selected from  ,

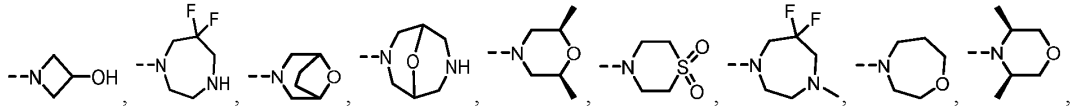
 ,

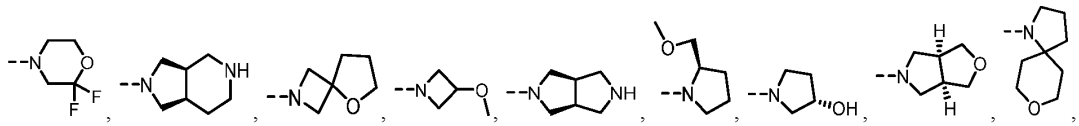
 ,

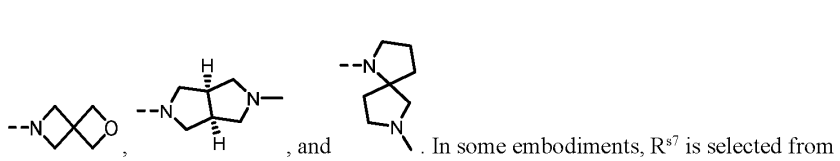
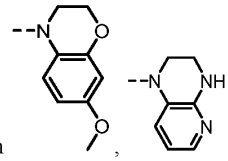
 , and . In some embodiments, R^{s7} is selected from  ,

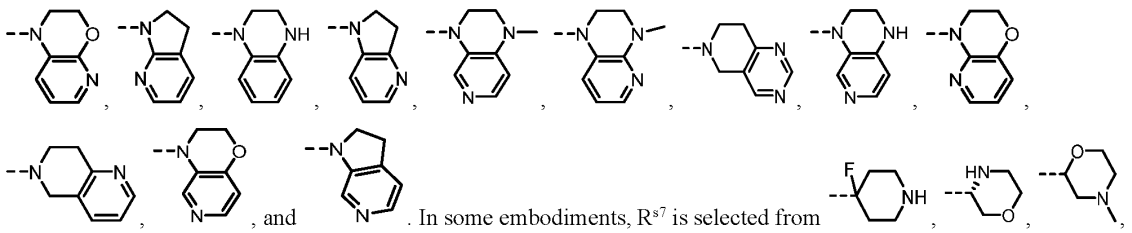
 ,

 , and . In some embodiments, R^{s7} is selected from  ,

 ,

 ,

 , and . In some embodiments, R^{s7} is selected from  ,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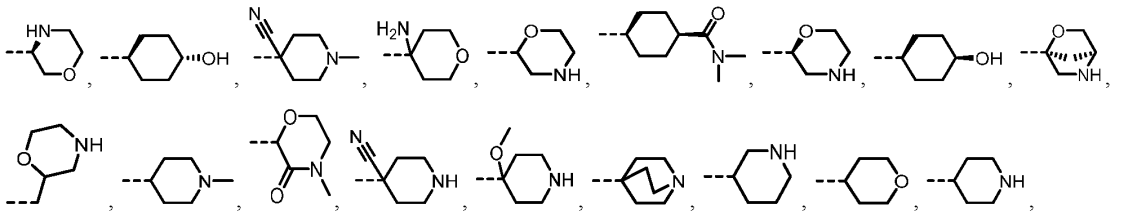

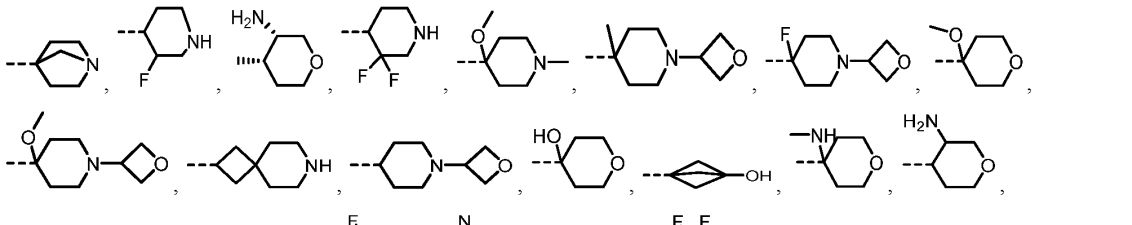

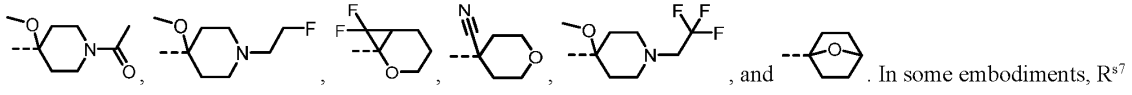
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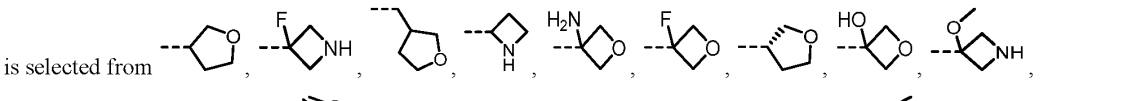

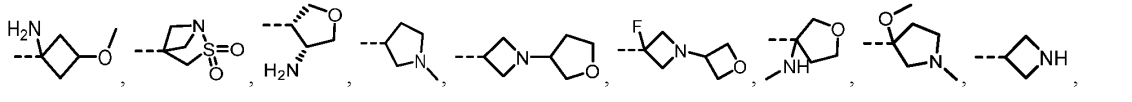

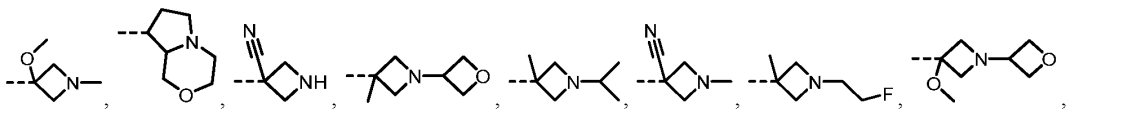

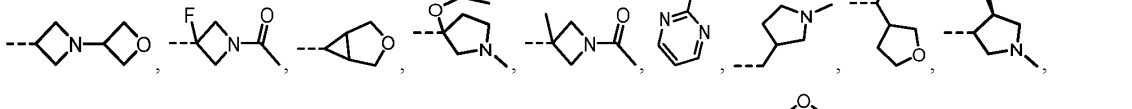

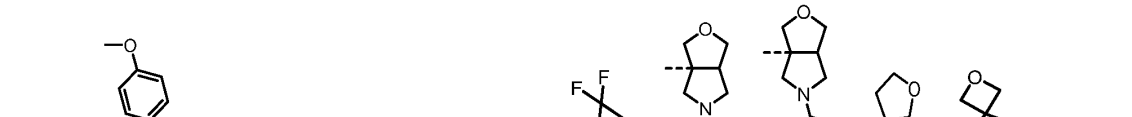
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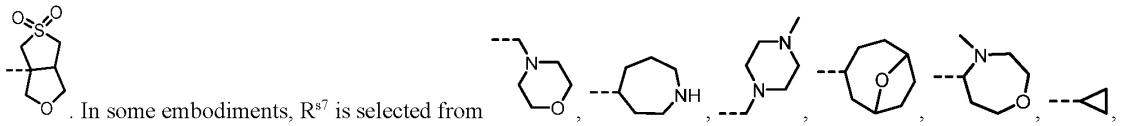
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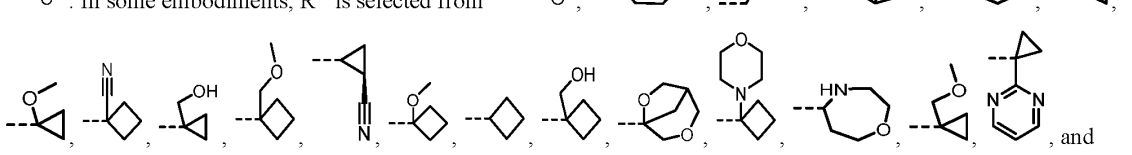
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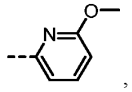
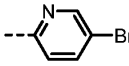
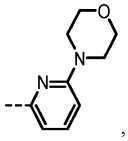
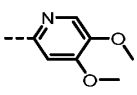
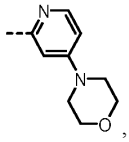
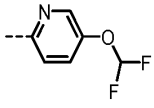
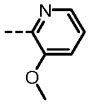
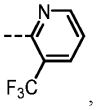
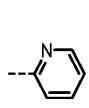
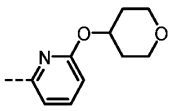
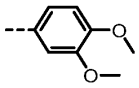
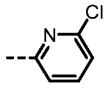
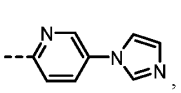
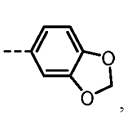
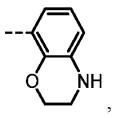
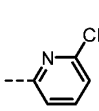
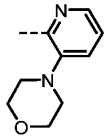
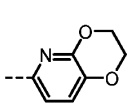
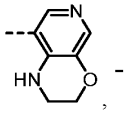
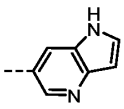
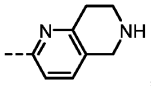
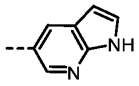
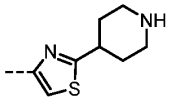
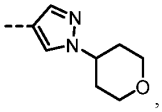
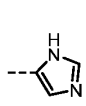
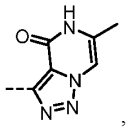
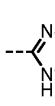
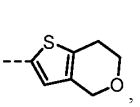
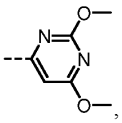
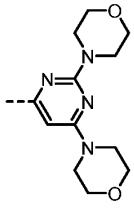
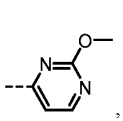
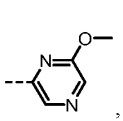
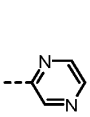
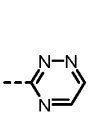
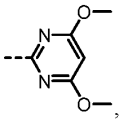
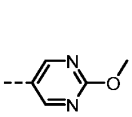
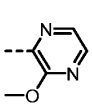
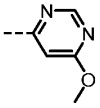
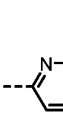
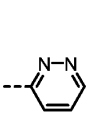
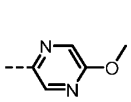
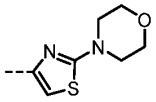
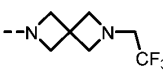
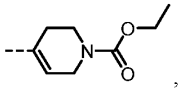
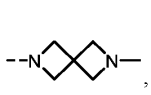
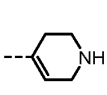
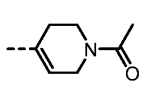
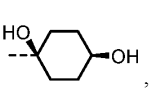
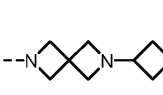
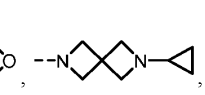
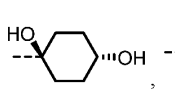
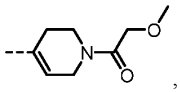
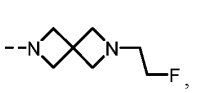
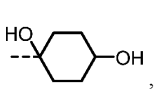
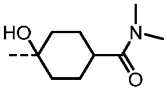
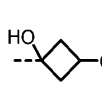
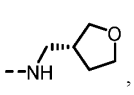
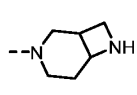
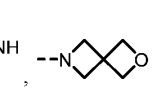
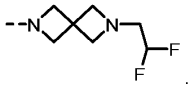
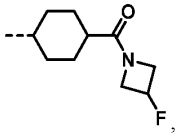
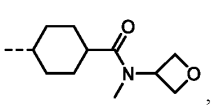
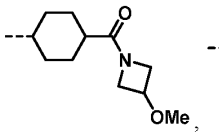
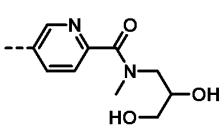
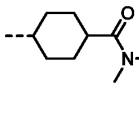
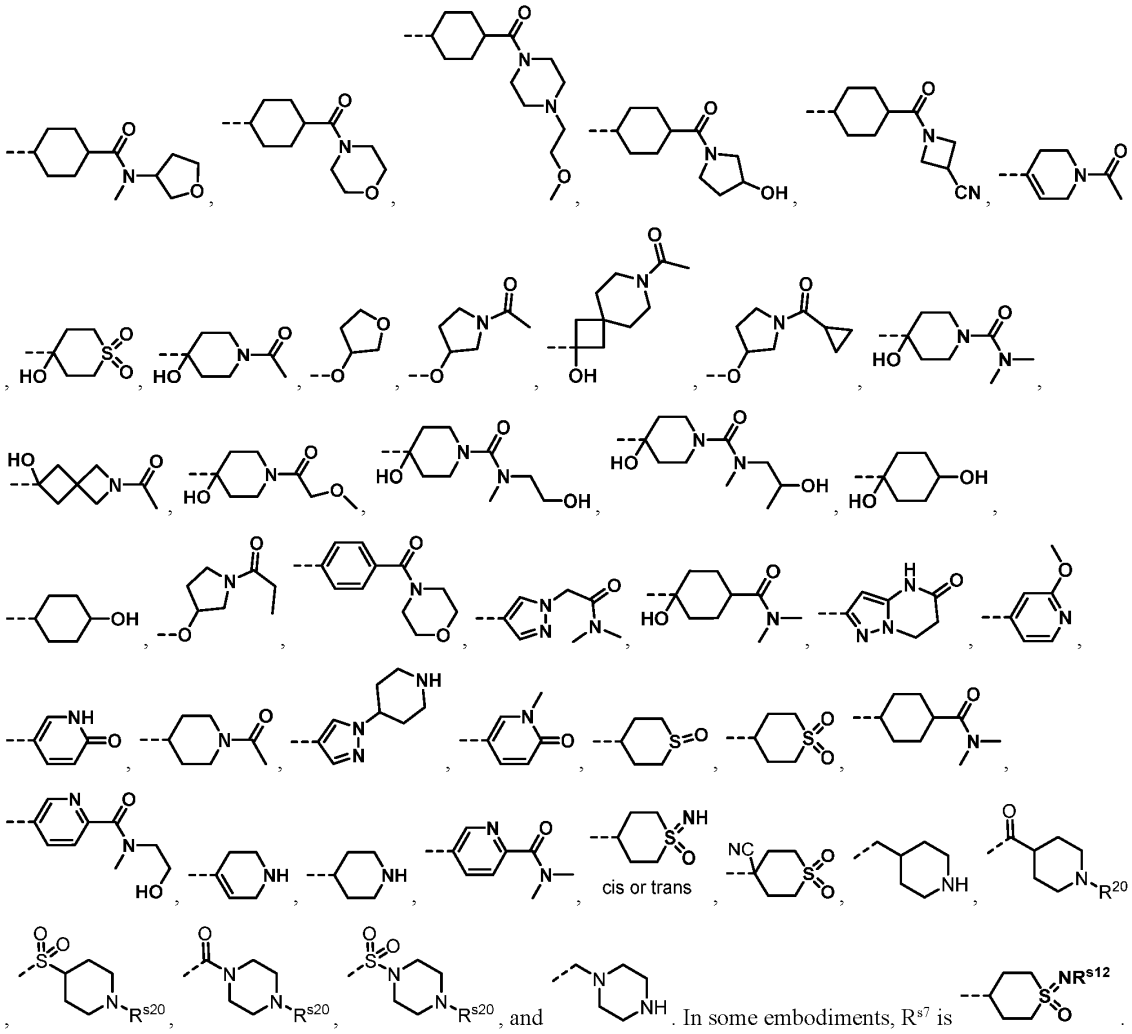
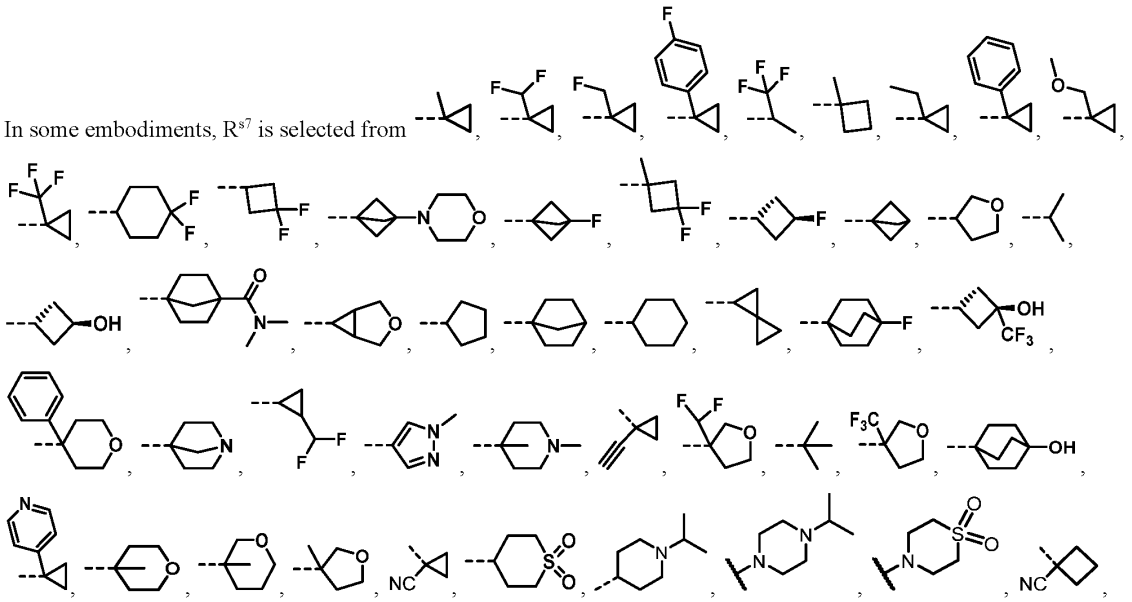
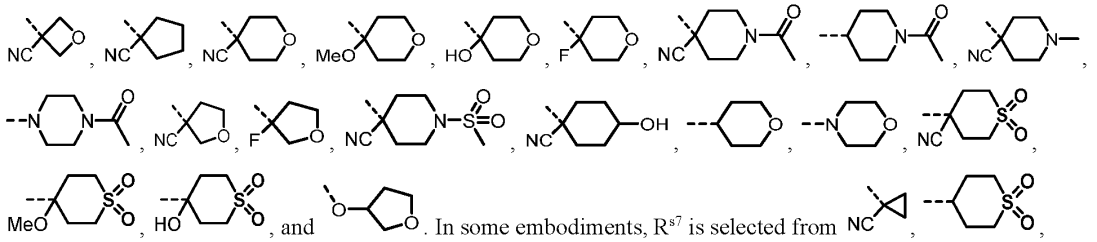
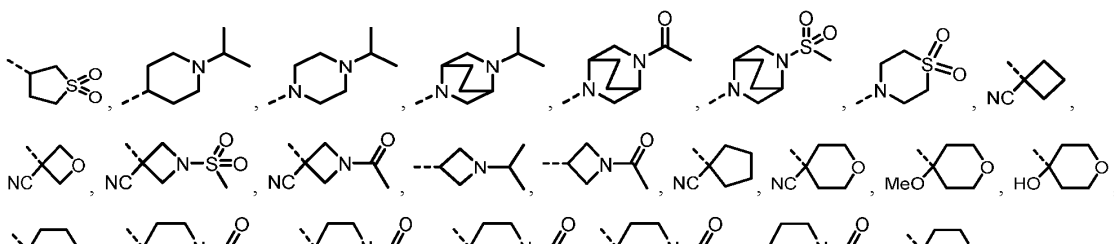
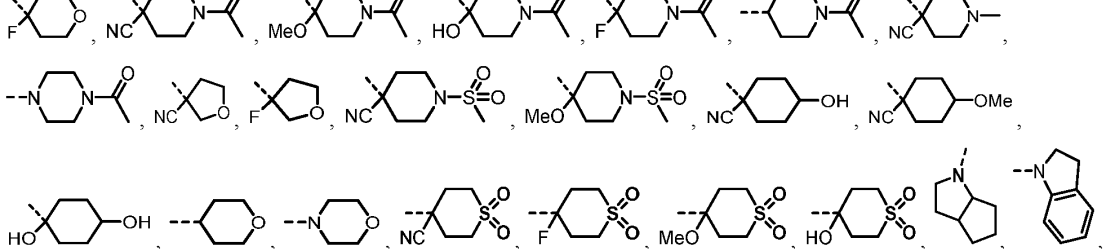
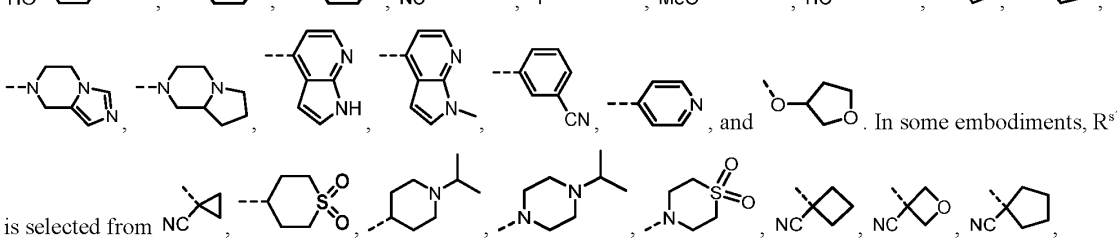
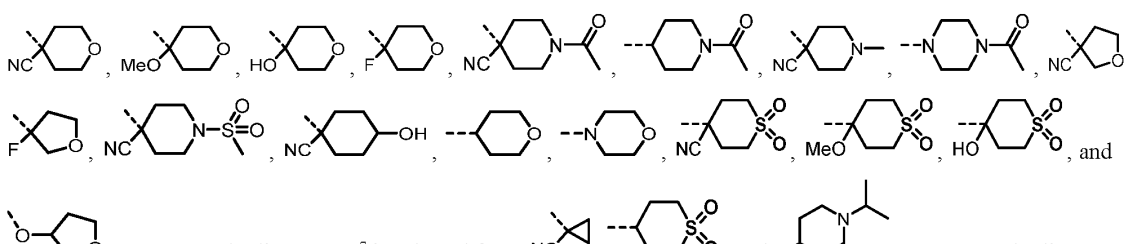
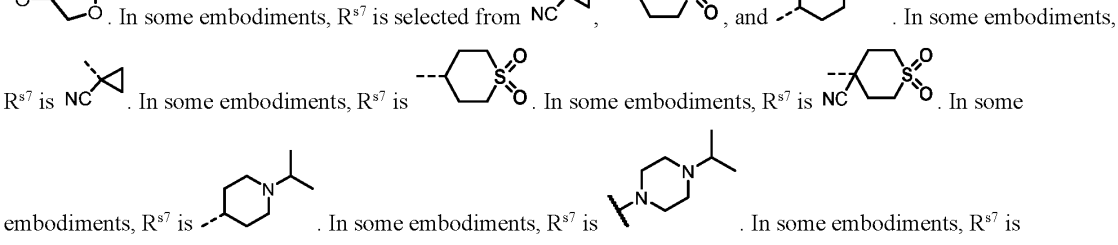
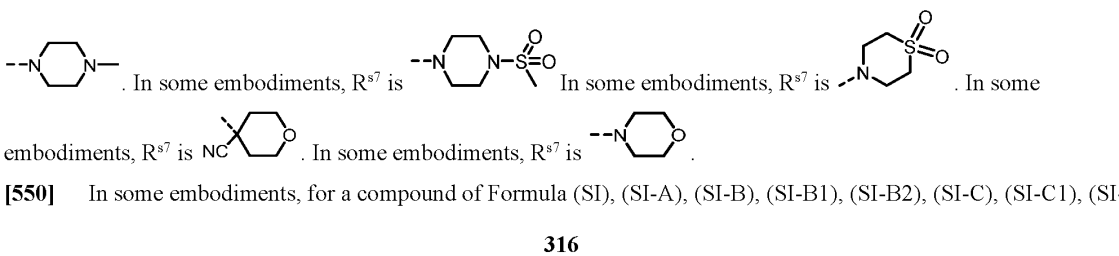
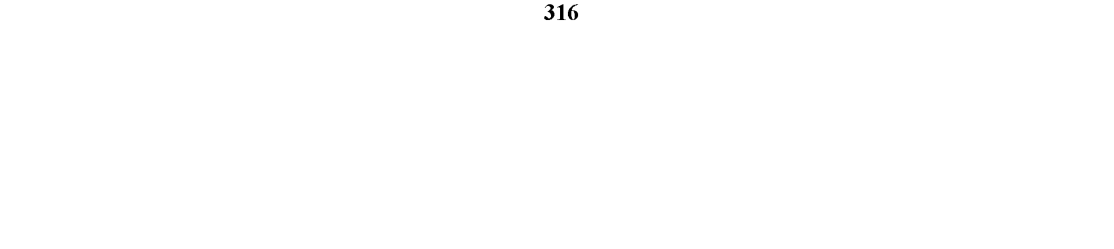
In some embodiments, R^{s7} is selected from  , ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^{s7} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and . In some embodiments, R^{s7} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^{s7} is selected from  ,  ,  ,  ,  .



In some embodiments, R^{s7} is selected from




, and . In some embodiments, R^{s7} is selected from , ,  , and  . In some embodiments, R^{s7} is selected from  , and  . In some embodiments, R^{s7} is  . In some embodiments, R^{s7} is  . In some embodiments, R^{s7} is  . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is . In some embodiments, R^{s7} is .

[550] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-

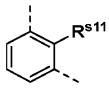
C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1), R^{s8} is selected from hydrogen, halogen, and C_{1-6} alkyl optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s8} is hydrogen.

[551] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1),

is selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, such as C_{5-7} carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R^{s11}. In some embodiments,

is selected from C_{5-7} cycloalkyl, 5- to 7-membered heterocycloalkyl, 5- to 7-membered heteroaryl, and phenyl, each of which is optionally substituted with one or more R^{s11}. In some embodiments,

is selected from phenyl, pyridyl, and thiophenyl, each of which is optionally substituted with one or more R^{s11}. In some embodiments,

is selected from 

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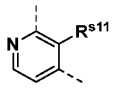
, 

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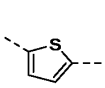
, and 

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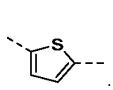
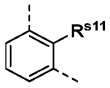
, and 

. In some embodiments, R^{s11}, when present, is independently selected at each occurrence from fluorine and $-CH_3$. In some embodiments,

is selected from 

and
, such as

and
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is

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is
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is

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[552] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1), L^{sl} is selected from C_{1-6} alkylene and C_{1-6} haloalkylene, such as C_{1-3} alkylene and C_{1-3} haloalkylene. In some embodiments, L^{sl} is selected from a bond and C_{1-3} haloalkylene. In some embodiments, L^{sl} is C_{1-3} haloalkylene, such as $-CF_2-$, $-CF_2CH_2-$, or $-CF_2CH_2CH_2-$. In some embodiments, L^{sl} is C_{1-2} haloalkylene, such as $-CF_2-$ or $-CF_2CH_2-$. In some embodiments, L^{sl} is $-CF_2-$. In some embodiments, L^{sl} is $-CF_2CH_2-$. In some embodiments, L^{sl} is $-CF_2CH_2CH_2-$. In some embodiments, L^{sl} is a bond. In some embodiments, L^{sl} is selected from a bond, -O-, $-NR^{s12}-$, -S-, C_{1-6} alkylene, C_{1-6} haloalkylene, and 2- to 6-membered heteroalkylene, wherein C_{1-6} alkylene, C_{1-6} haloalkylene, and 2- to 6-membered heteroalkylene are optionally substituted with one or more R^{s11b}. In some embodiments, L^{sl} is selected from -O-, $-NR^{s12}-$, -S-, and 2- to 6-membered heteroalkylene, wherein 2- to 6-membered heteroalkylene is optionally substituted with one or more R^{s11b}. In some embodiments, L^{sl} is C_{1-6} alkylene optionally substituted with one or more R^{s11b}, such as one, two, or three R^{s11b}. In some embodiments, L^{sl} is selected from a bond, -O-, $-NR^{s12}-$, -S-, C_{1-3} alkylene, C_{1-3} haloalkylene, and 2- to 3-membered heteroalkylene, wherein C_{1-3} alkylene, C_{1-3} haloalkylene, and 2- to 3-membered heteroalkylene are optionally substituted with one or more R^{s11b}. In some embodiments, L^{sl} is selected from -O-, $-NR^{s12}-$, -S-, and 2- to 3-membered heteroalkylene, wherein 2- to 3-membered heteroalkylene is optionally substituted with one or more R^{s11b}. In some embodiments, L^{sl} is C_{1-3} alkylene substituted with one or more R^{s11b}, such as one, two, or three R^{s11b}.

[553] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1),

is absent or selected from C_{4-8} carbocycle and 4- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{sl1a}. In some embodiments,

is absent or selected from phenyl and 4- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{sl1a}. In some embodiments,

is selected from phenyl and 4- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{sl1a}. In some embodiments,

is absent or selected from phenyl, azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more R^{sl1a}. In some embodiments,

is selected from phenyl, azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more R^{sl1a}. In some embodiments,

is selected from azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more $-CH_3$. In some embodiments,

is phenyl, optionally substituted with one or more R^{sl1a}. In some embodiments,

is , optionally substituted with one or more R^{sl1a}. In some embodiments,

is . In some embodiments,

is azetidine, optionally substituted with one or more R^{sl1a}. In some embodiments,

is

, optionally substituted with one or more R^{sl1a}. In some embodiments,

is

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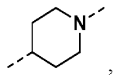
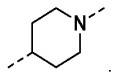
is pyrrolidine, optionally substituted with one or more R^{sl1a}. In some embodiments,

is piperidine, optionally substituted with one or more R^{sl1a}. In some embodiments,

is 

, optionally substituted with one or more R^{sl1a}. In some embodiments,

is 

. In some embodiments,

is unsubstituted. In some embodiments,

is substituted with one or more R^{sl1a}, such as one, two or three R^{sl1a}. In some embodiments, R^{sl1a} is independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{3-6} carbocycle, 3- to 6-membered heterocycle, $-OR^{sl2}$, $-N(R^{sl2})(R^{sl3})$, $-N(R^{sl4})S(O)_2R^{sl5}$, $-C(O)N(R^{sl2})(R^{sl3})$, $-N(R^{sl4})C(O)R^{sl5}$, $-S(O)_2R^{sl5}$, and $-S(O)_2N(R^{sl2})(R^{sl3})$, wherein C_{1-6} alkyl, C_{3-6}

carbocycle, and 3- to 6-membered heterocycle are optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s11a} is independently selected at each occurrence from halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments, R^{s11a} is independently selected at each occurrence from C_{1-6} alkyl. In some embodiments, R^{s11a} is $-CH_3$.

[554] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1), L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2}, together with the atoms to which it is attached, forms a 16- to 36-membered macrocyclic ring, such as a 16- to 24-membered macrocyclic ring. In some embodiments, L^{s2} is selected from C_{6-15} alkylene, C_{6-15} alkenylene, C_{6-15} alkynylene, 6- to 15-membered heteroalkylene, and 6- to 15-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, an alkenylene or heteroalkenylene of L^{s2} comprises one carbon-carbon double bond. In some embodiments, a heteroalkylene or heteroalkenylene of L^{s2} comprises at least one oxygen or nitrogen atom. In some embodiments, a heteroalkylene or heteroalkenylene of L^{s2} comprises at least one basic nitrogen. In some embodiments, L^{s2} is selected from C_{5-9} alkylene, C_{5-9} alkenylene, and 5- to 9-membered heteroalkylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_{6-9} alkylene, C_{6-9} alkenylene, and 6- to 9-membered heteroalkylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_{5-8} alkylene, C_{5-8} alkenylene, and 5- to 8-membered heteroalkylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_{6-8} alkylene, C_{6-8} alkenylene, and 6- to 8-membered heteroalkylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_{6-8} alkylene and C_{6-8} alkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_6 alkylene and C_6 alkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_7 alkylene and C_7 alkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_8 alkylene and C_8 alkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is $-CH_2CHCH(CH_2)_4-$. In some embodiments, L^{s2} is 6- to 8-membered heteroalkylene, optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is 6-membered heteroalkylene, optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is 7-membered heteroalkylene, optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is 8-membered heteroalkylene, optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is 8-membered heteroalkylene, wherein the heteroalkylene comprises one oxygen atom. In some embodiments, L^{s2} is $-(CH_2)_{2-5}O(CH_2)_{0-5}-$, such as L^{s2} is $-(CH_2)_{2-5}O(CH_2)_{2-5}-$. In some embodiments, L^{s2} is $-(CH_2)_4O(CH_2)_3-$. In some embodiments, R^{s11b} is independently selected at each occurrence from halogen, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} alkyl)-OH, and -OH. In some embodiments, R^{s11b} is independently selected at each occurrence from -F, =O, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2OH$, and -OH. In some embodiments, R^{s11b} is independently selected at each occurrence from $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, and $-CF_3$, or two R^{s11b} join to form =O or C_{3-6} cycloalkyl, such as cyclopropyl. In some embodiments, R^{s11b} is independently selected at each occurrence from $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, and $-CF_3$, or two R^{s11b} join to form C_{3-6} cycloalkyl, such as cyclopropyl. In some embodiments, R^{s11b} is independently selected at each occurrence from $-CH_3$, -F, -CN, and -OH. In some embodiments, L^{s2} comprises $-C(O)N(R^{s14})-$ or $-N(R^{s14})C(O)-$. In some embodiments, L^{s2} comprises -O-. In some

embodiments, L^{s2} is substituted with at least one $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, or $-CF_3$, or two substituents join to form cyclopropyl. In some embodiments, L^{s2} is substituted with at least one $-CH_3$, -F, -CN, or -OH. In some embodiments, L^{s2} is unsubstituted.

[555] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1), L^{s2} is -(C_{1-5} alkylene)-C(O)N(R^{s14})-(C_{1-5} alkylene)-, such as -(C_{1-5} alkylene)-C(O)N(CH_3)-(C_{1-5} alkylene)- or -(C_{1-5} alkylene)-C(O)NH-(C_{1-5} alkylene)-, wherein C_{1-5} alkylene is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is -(C_{1-2} alkylene)-C(O)N(R^{s14})-(C_{3-4} alkylene)-, such as -(C_{1-2} alkylene)-C(O)N(CH_3)-(C_{3-4} alkylene)- or -(C_{1-2} alkylene)-C(O)NH-(C_{3-4} alkylene)-, wherein C_{1-2} alkylene and C_{3-4} alkylene are each independently optionally substituted with one or more R^{s11b}. In some embodiments, R^{s11b} is independently selected at each occurrence from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} alkyl)-OH, and -OH. In some embodiments, R^{s11b} is independently selected at each occurrence from -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2OH$, and -OH. In some embodiments, R^{s11b} is independently selected at each occurrence from $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, and $-CF_3$, or two R^{s11b} join to form C_{3-6} cycloalkyl, such as cyclopropyl. In some embodiments, R^{s11b} is independently selected at each occurrence from $-CH_3$, -F, -CN, and -OH. In some embodiments, L^{s2} is substituted with at least one $-CH_3$, -F, -CN, or -OH.

[556] In some embodiments, L^{s2} is selected from -C(R^{s11b})(R^{s11b})-(C_{3-10} alkylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(C_{3-10} alkylene)-C(R^{s11b})(R^{s11b})-, $-CH_2$-(C_{3-10} alkylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(C_{3-10} alkylene)-CH(R^{s11b})-, $-CH_2$-(C_{3-10} alkylene)-CH(R^{s11b})-, -C(R^{s11b})(R^{s11b})-(C_{3-10} alkenylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(C_{3-10} alkenylene)-C(R^{s11b})(R^{s11b})-, $-CH_2$-(C_{3-10} alkenylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(C_{3-10} alkenylene)-CH(R^{s11b})-, $-CH_2$-(C_{3-10} alkenylene)-CH(R^{s11b})-, -C(R^{s11b})(R^{s11b})-(3- to 10-membered heteroalkylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(3- to 10-membered heteroalkylene)-C(R^{s11b})(R^{s11b})-, $-CH_2$-(3- to 10-membered heteroalkylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(3- to 10-membered heteroalkylene)-CH(R^{s11b})-, $-CH_2$-(3- to 10-membered heteroalkylene)-CH(R^{s11b})-, -C(R^{s11b})(R^{s11b})-(3- to 10-membered heteroalkenylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(3- to 10-membered heteroalkenylene)-C(R^{s11b})(R^{s11b})-, $-CH_2$-(3- to 10-membered heteroalkenylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(3- to 10-membered heteroalkenylene)-CH(R^{s11b})-, and $-CH_2$-(3- to 10-membered heteroalkenylene)-CH(R^{s11b})-. In some embodiments, L^{s2} is selected from -C(R^{s11b})(R^{s11b})-(C_{3-10} alkylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(C_{3-10} alkylene)-C(R^{s11b})(R^{s11b})-, $-CH_2$-(C_{3-10} alkylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(C_{3-10} alkylene)-CH(R^{s11b})-, and $-CH_2$-(C_{3-10} alkylene)-CH(R^{s11b})-. In some embodiments, L^{s2} is selected from -C(R^{s11b})(R^{s11b})-(C_{3-10} alkenylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(C_{3-10} alkenylene)-C(R^{s11b})(R^{s11b})-, $-CH_2$-(C_{3-10} alkenylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(C_{3-10} alkenylene)-CH(R^{s11b})-, and $-CH_2$-(C_{3-10} alkenylene)-CH(R^{s11b})-. In some embodiments, L^{s2} is selected from -C(R^{s11b})(R^{s11b})-(3- to 10-membered heteroalkylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(3- to 10-membered heteroalkylene)-C(R^{s11b})(R^{s11b})-, $-CH_2$-(3- to 10-membered heteroalkylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(3- to 10-membered heteroalkylene)-CH(R^{s11b})-, and $-CH_2$-(3- to 10-membered heteroalkylene)-CH(R^{s11b})-. In some embodiments, L^{s2} is selected from -C(R^{s11b})(R^{s11b})-(3- to 10-membered heteroalkenylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(3- to 10-membered heteroalkenylene)-C(R^{s11b})(R^{s11b})-, $-CH_2$-(3- to 10-membered heteroalkenylene)-C(R^{s11b})(R^{s11b})-, -CH(R^{s11b})-(3- to 10-membered heteroalkenylene)-CH(R^{s11b})-, and $-CH_2$-(3- to 10-membered heteroalkenylene)-CH(R^{s11b})-. Any C_{3-10} alkylene, C_{3-10} alkenylene, 3- to 10-membered heteroalkylene, or 3- to 10-membered heteroalkenylene in this paragraph may optionally be substituted with one or more R^{s11b}. In some embodiments, R^{s11b} is independently selected at each occurrence from halogen, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} alkyl)-OH, and -OH. In some embodiments, R^{s11b} is independently selected at each occurrence from -F, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2OH$, and -OH. In some embodiments, R^{s11b} is independently selected at each occurrence from $-CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, and $-CF_3$, or two R^{s11b} join to form =O or C_{3-6} cycloalkyl, such as

cyclopropyl.

[557] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1), L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s3} is selected from C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}; D is absent or selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{s11d}; and L^{s4} is selected from C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. As noted above, alkenylene and alkynylene groups comprise one or more carbon-carbon double or triple bonds, respectively (i.e., comprising two or more carbon atoms, for example as in C_{2-10} alkenylene, C_{2-10} alkynylene, C_{2-8} alkenylene, C_{2-8} alkynylene, C_{5-25} alkenylene, C_{5-25} alkynylene, C_{6-15} alkenylene, C_{6-15} alkynylene, C_{5-10} alkenylene, and C_{5-10} alkynylene). Similarly, a heteroalkenylene group comprises one or more carbon-carbon double bond (i.e., comprising two or more carbon atoms and one or more heteroatom, for example as in 3- to 10-membered heteroalkenylene, 3- to 8-membered heteroalkenylene, 5- to 25-membered heteroalkenylene, 6- to 15-membered heteroalkenylene, and 5- to 10-membered heteroalkenylene. In some embodiments, L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s3} is selected from C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}; D is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{s11d}; and L^{s4} is absent. In some embodiments, L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s3} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}; D is absent or selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{s11d}; and L^{s4} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s3} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}; D is selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{s11d}; and L^{s4} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, R^{s11b} is independently selected at each occurrence from halogen, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} alkyl)-OH, and -OH. In some embodiments, R^{s11b} is independently selected at each occurrence from -F, -CH_3, -CH_2F, -CHF_2, -CF_3, -CH_2CH_2F, -CH_2CHF_2, -CH_2OH, and -OH. In some embodiments, R^{s11b} is independently selected at each occurrence from -CH_3, -CH_2OH, -CH_2F, -CHF_2, and -CF_3, or two R^{s11b} join to form =O or C_{3-6} cycloalkyl, such as cyclopropyl. In some embodiments, D is selected from phenyl and 5- to 8-membered heteroaryl, such as triazole and imidazole. In some embodiments, D is unsubstituted. In some embodiments, D is substituted with one or more R^{s11d}, such as one, two, or three R^{s11d}.

[558] In some embodiments, for a compound of Formula (SI), L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7}; or L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s4} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7}. For example, L^{s2} may be covalently bound to W^{s3}—wherein R^{s3b} or R^{s3} is a bond to L^{s2}—as depicted in Formula (SI-A). In some embodiments, L^{s2} is covalently bound to W^{s4}—wherein R^{s4b} or R^{s4} is a bond to L^{s2}—as depicted in Formula (SI-B). In some embodiments, L^{s2} is covalently bound to W^{s5}—wherein R^{s5b} or R^{s5} is a bond to L^{s2}—as depicted in Formula (SI-C). In some embodiments, L^{s2} is covalently bound to W^{s6}—wherein R^{s6b} or R^{s6} is a bond to L^{s2}—as depicted in Formula

(SI-D). In some embodiments, L^{s2} is covalently bound to W^{s7}—wherein R^{s7b} or R^{s7} is a bond to L^{s2}—as depicted in Formula (SI-E).

[559] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1):

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, -CH_2-(3- to 10-membered heterocycle), -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, -$OCH_2C(O)OR^{s22}$, and -$OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{s21}, -SR^{s21}, and -$N(R^{s22})(R^{s23})$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl; and

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

[560] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1), R^{s20} is independently selected at each occurrence from halogen, oxo, =NR^{s22}, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, -CH_2-(3- to 10-membered heterocycle), -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)(NR^{s22})R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, -$OCH_2C(O)OR^{s22}$, and -$OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NR^{s22}, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{s21}, -SR^{s21}, and -$N(R^{s22})(R^{s23})$.

[561] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1), R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, -NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, -CH_2-(3- to 10-membered heterocycle), -OH, -OCH_3, -OCH_2CH_3, -NH_2, -$NHCH_3$, and -$NHCH_2CH_3$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, -NO_2, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -OH, -

OCH_3, $-OCH_2CH_3$, $-NH_2$, $-NHCH_3$, and $-NHCH_2CH_3$.

[562] In some embodiments, for a compound of Formula (SI-B1), R^{s5b} is $-CH_3$; R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}; and R^{s8} is hydrogen. In some embodiments, for a compound of Formula (SI-B2), R^{s5} is hydrogen; R^{s6} is selected from hydrogen and $-OCH_3$; R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}; and R^{s8} is hydrogen.

[563] In some embodiments, for a compound of Formula (SI-C1), R^{s3} is hydrogen or $-CH_3$; R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}; and R^{s8} is hydrogen. In some embodiments, for a compound of Formula (SI-C2), R^{s3b} is $-CH_3$; R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}; and R^{s8} is hydrogen. In some embodiments, for a compound of Formula (SI-C3), R^{s3} is hydrogen or $-CH_3$; R^{s6} is selected from hydrogen and $-OCH_3$; R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}; and R^{s8} is hydrogen.

[564] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1): R^{s1} is $-CH_3$;

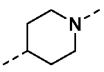
is selected from phenyl and 5- to 7-membered heteroaryl, each of which is optionally substituted with one or more R^{s11}; L^{s1} is selected from a bond and C_{1-3} haloalkylene;

is selected from absent, phenyl, and 4- to 8-membered heterocycle, wherein the phenyl and 4- to 8-membered heterocycle are optionally substituted with one or more R^{s11a}; and L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, R^{s11}, when present, is fluorine; R^{s11a}, when present, is $-CH_3$; and R^{s11b}, when present, is selected from halogen, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} alkyl)-OH, and -OH.

[565] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1): R^{s1} is $-CH_3$;

is selected from

and ; L^{s1} is C_{1-2} haloalkylene;

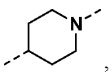
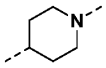
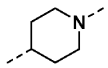
is 

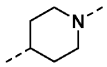
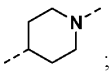
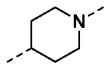
, optionally substituted with one or more R^{s11a}; and L^{s2} is selected from C_{6-8} alkylene, C_{6-8} alkenylene, and 6- to 8-membered heteroalkylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, R^{s1} is $-CH_3$;

is ; L^{s1} is C_{1-2} haloalkylene;

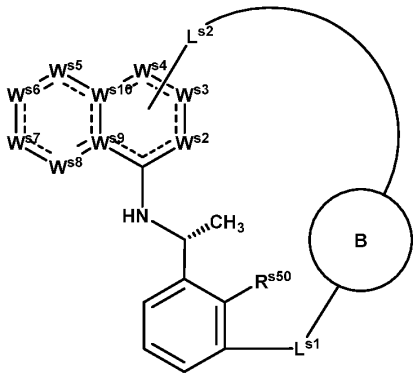
is

; and L^{s2} is 6- to 8-membered heteroalkylene, optionally substituted with one or more R^{s11b}. In some embodiments, R^{s1} is -

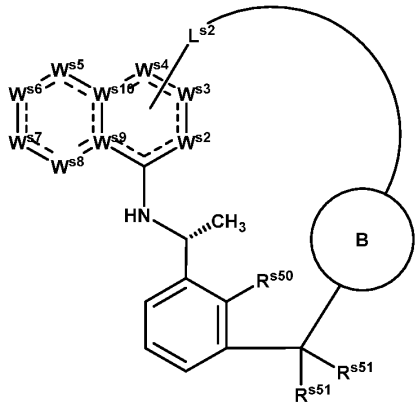
CH_3; is selected from and ; L^{s1} is C_{1-2} haloalkylene; is  , optionally substituted with one or more R^{s11a}; and L^{s2} is selected from C_{6-8} alkylene and C_{6-8} alkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, R^{s1} is $-CH_3$; is ; L^{s1} is C_{1-2} haloalkylene; is  ; and L^{s2} is C_{6-8} alkenylene, optionally substituted with one or more R^{s11b}. In some embodiments, R^{s1} is $-CH_3$; is selected from and ; L^{s1} is C_{1-2} haloalkylene; is  , optionally substituted with one or more R^{s11a}; and L^{s2} is $-(C_{1-2}$ alkylene$)-C(O)N(CH_3)-(C_{3-4}$ alkylene$)-$ or $-(C_{1-2}$ alkylene$)-C(O)NH-(C_{3-4}$ alkylene$)-$, wherein C_{1-2} alkylene and C_{3-4} alkylene are each independently optionally substituted with one or more R^{s11b}. In some embodiments, R^{s11a}, when present, is $-CH_3$; and R^{s11b}, when present, is selected from halogen, -CN, oxo, C_{1-3} alkyl, C_{1-3} haloalkyl, (C_{1-3} alkyl)-OH, and -OH.

[566] In some embodiments, for a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), or (SI-E1): R^{s1} is $-CH_3$; is selected from and ; L^{s1} is C_{1-2} haloalkylene; is  ; and L^{s2} is selected from C_{6-8} alkylene, C_{6-8} alkenylene, and 6- to 8-membered heteroalkylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, R^{s1} is $-CH_3$; is selected from and ; L^{s1} is C_{1-2} haloalkylene; is  ; and L^{s2} is selected from C_{6-8} alkylene and C_{6-8} alkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, R^{s1} is $-CH_3$; is selected from and ; L^{s1} is C_{1-2} haloalkylene; is  ; and L^{s2} is $-(C_{1-2}$ alkylene$)-C(O)N(CH_3)-(C_{3-4}$ alkylene$)-$ or $-(C_{1-2}$ alkylene$)-C(O)NH-(C_{3-4}$ alkylene$)-$, wherein C_{1-2} alkylene and C_{3-4} alkylene are each independently optionally substituted with one or more R^{s11b}. In some embodiments, R^{s11b}, when present, is selected from halogen, -CN, oxo, C_{1-3} alkyl, C_{1-3} haloalkyl, (C_{1-3} alkyl)-OH, and -OH.

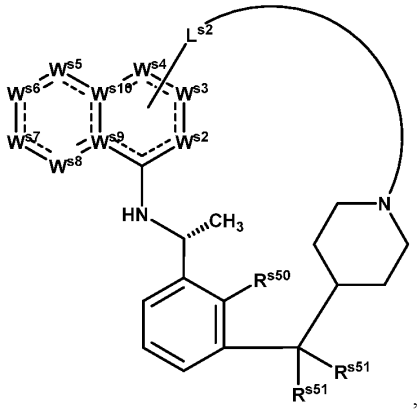
[567] In some embodiments, a compound of Formula (SI) is a compound of the formula:



, such as

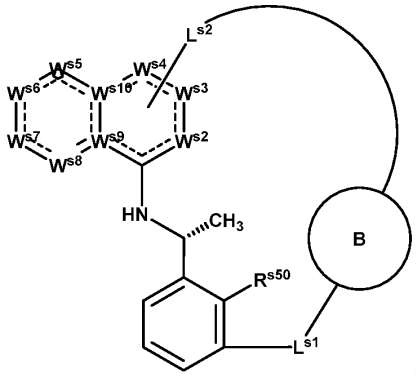


or

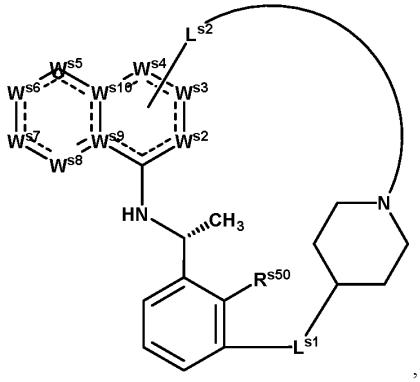


, wherein R^{s50} is hydrogen or R^{s11} and R^{s51} is hydrogen or halogen.

[568] In some embodiments, a compound of Formula (SI) is a compound of the formula:



, such as



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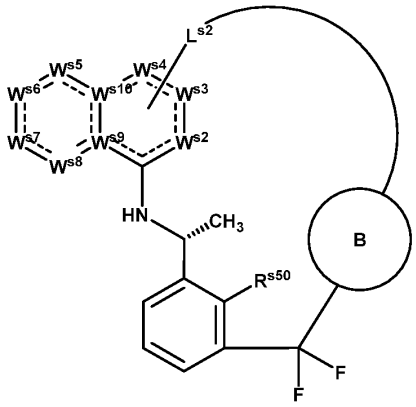
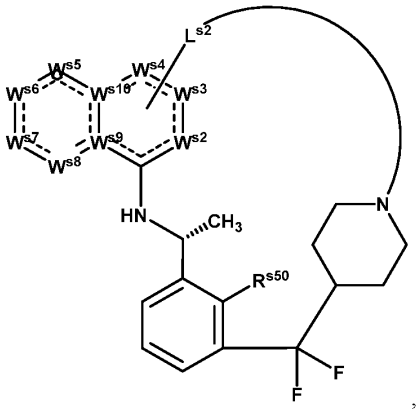
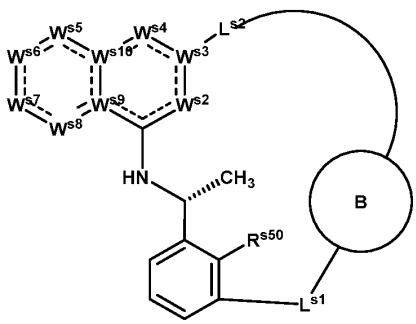


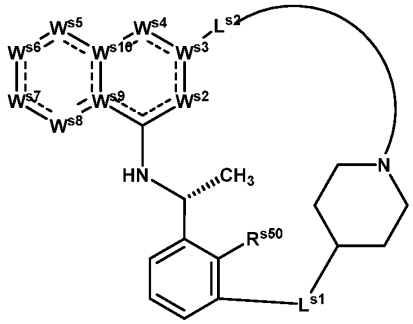
or



, wherein R^{s50} is hydrogen or fluoro. In some embodiments, a compound of Formula (SI-A) is a compound of the formula:



, such as



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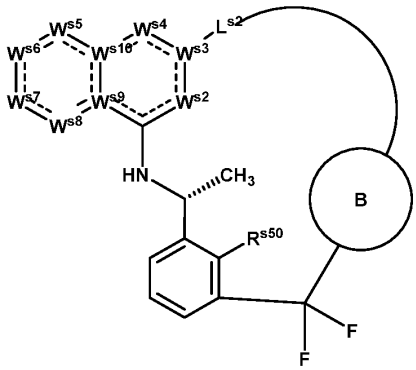
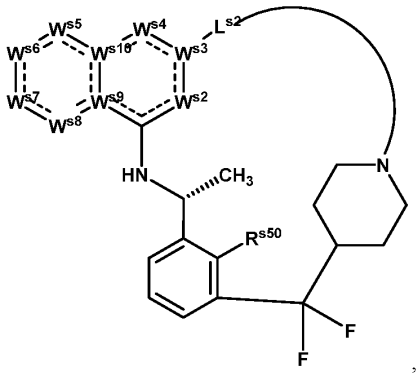
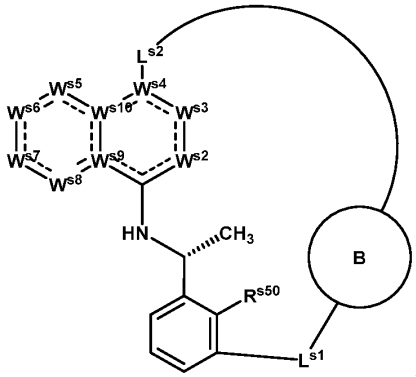


or



, wherein R^{s50} is hydrogen or fluoro. In some embodiments, a compound of Formula (SI-B) is a compound of the formula:



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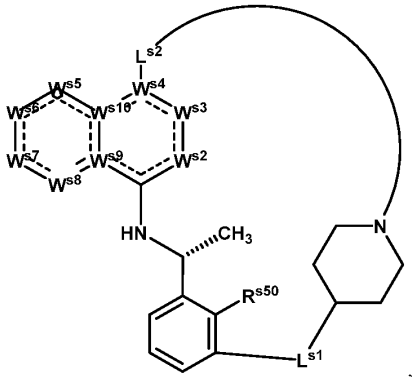

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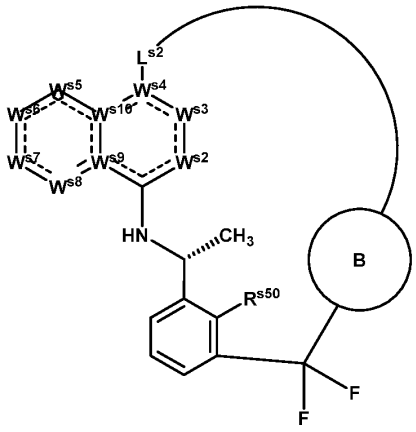
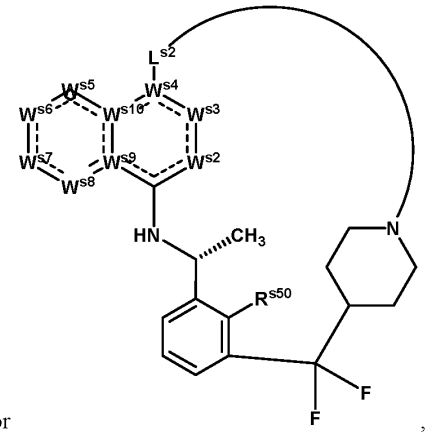
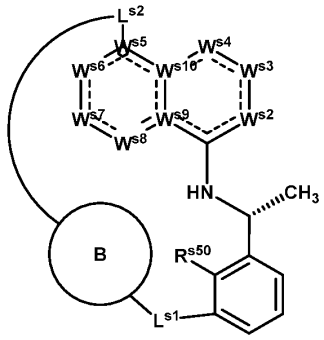
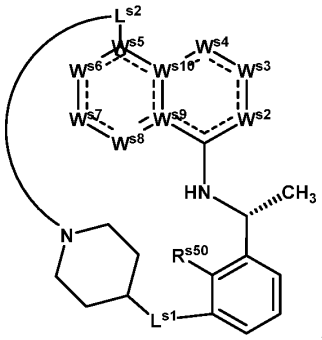
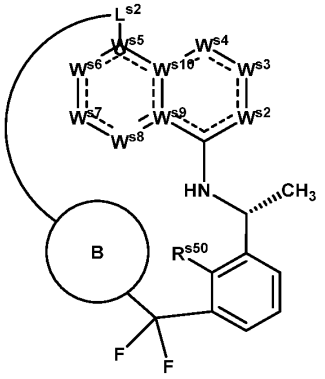
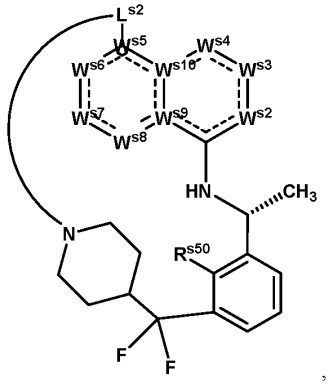



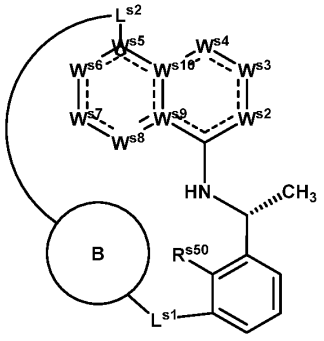
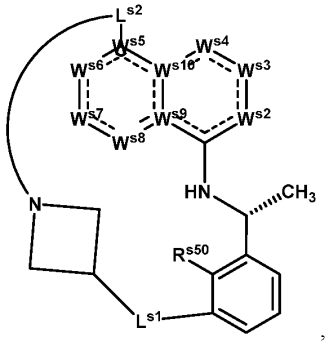
or , wherein R^{s50} is hydrogen or fluoro. In some embodiments, a compound of Formula (SI-C) is a compound of the formula:

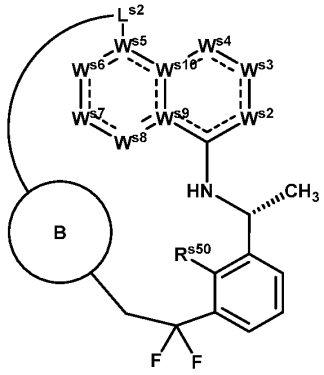
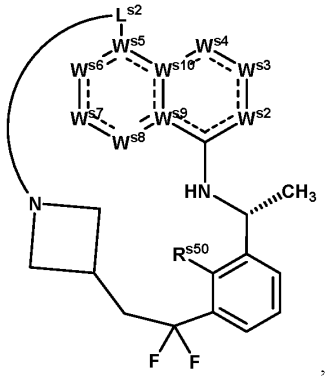
, such as , or



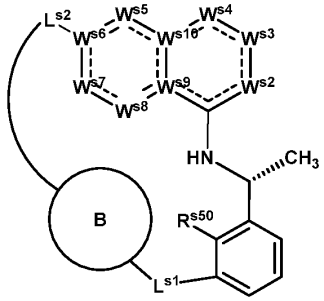
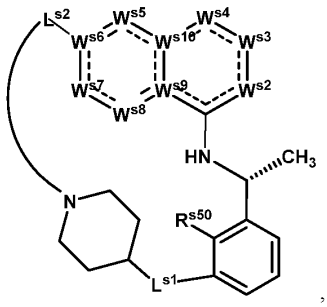
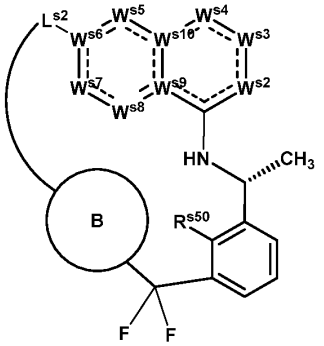
, wherein R^{s50} is hydrogen or fluoro. In some embodiments, a compound of Formula (SI-C) is a compound of the formula,

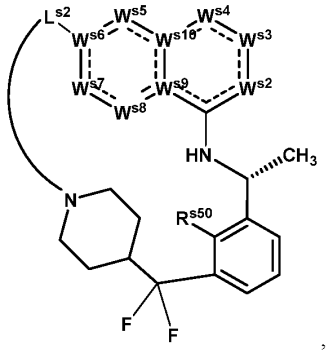
such as ,

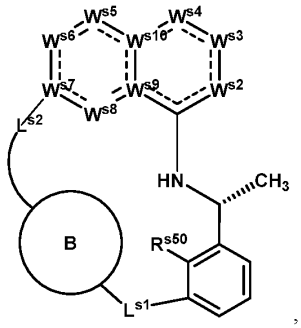
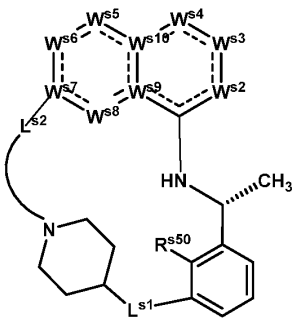
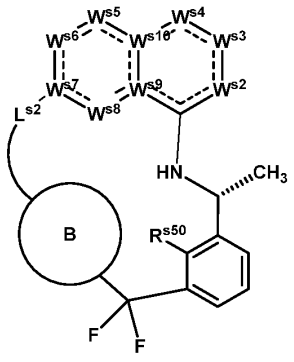
or , wherein R^{s50} is hydrogen or fluoro. In some embodiments, a compound of Formula (SI-D) is a compound of the formula:

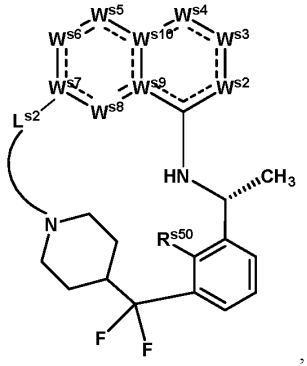
, such as , or



, wherein R^{s50} is hydrogen or fluoro. In some embodiments, a compound of Formula (SI-E) is a compound of the formula:

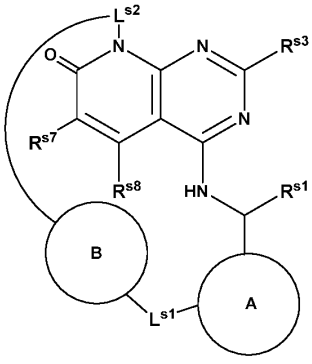




, such as , or



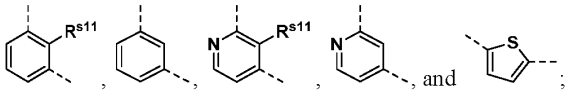
, wherein R^{s50} is hydrogen or fluoro. In some embodiments, L^{s1} is C_{1-3} haloalkylene, such as C_{1-2} haloalkylene or C_{1-2} fluoroalkylene. In some embodiments, L^{s2} is selected from C_{6-8} alkylene, C_{6-8} alkenylene, and 6- to 8-membered heteroalkylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_{6-8} alkylene and C_{6-8} alkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is -(C_{1-2} alkylene)-C(O)N(CH_3)-(C_{3-4} alkylene)- or -(C_{1-2} alkylene)-C(O)NH-(C_{3-4} alkylene)-, wherein C_{1-2} alkylene and C_{3-4} alkylene are each independently optionally substituted with one or more R^{s11b}. In some embodiments, R^{s11b}, when present, is selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, (C_{1-3} alkyl)-OH, and -OH. In some embodiments, R^{s50} is hydrogen. In some embodiments, R^{s50} is fluoro.

[569] In certain aspects, the present disclosure provides a compound of Formula (SI-C1):



(SI-C1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from  ;

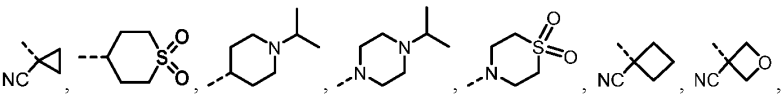
is selected from azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more -CH_3;

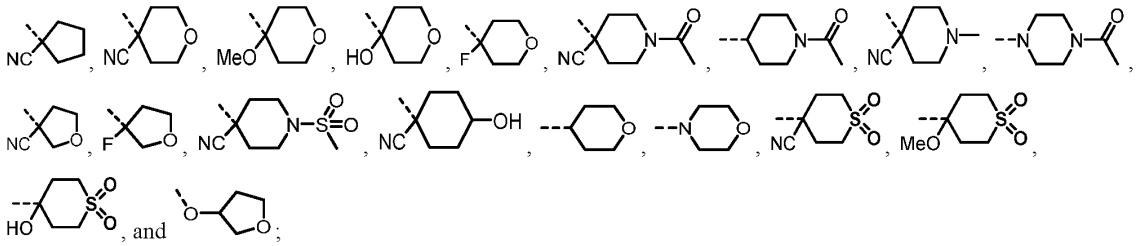
L^{s1} is C_{1-3} haloalkylene;

L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

R^{s1} is -CH_3;

R^{s3} is hydrogen or -CH_3;

R^{s7} is selected from  ,

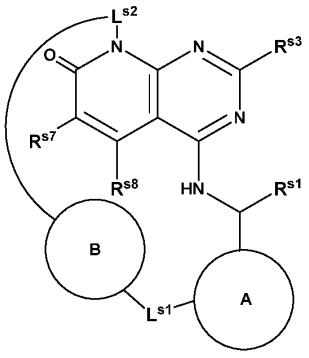


R^{s8} is hydrogen;

R^{s11} is selected from fluorine and $-CH_3$; and

R^{s11b} is selected from halogen, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} alkyl)-OH, and -OH.

[570] In certain aspects, the present disclosure provides a compound of Formula (SI-C1):



(SI-C1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from and ;

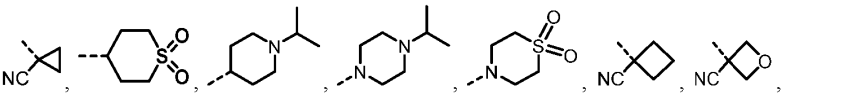
is selected from azetidine, pyrrolidine, and piperidine;

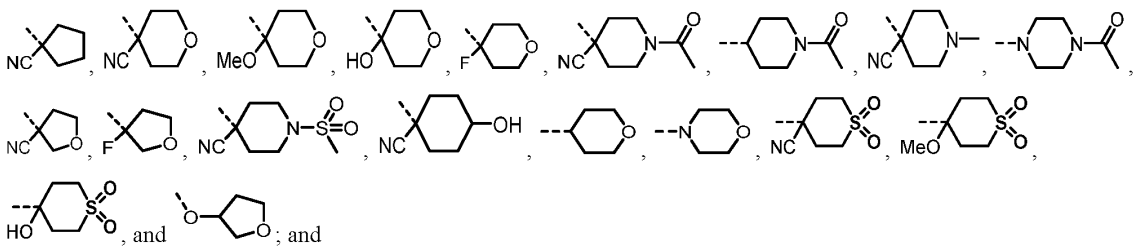
L^{s1} is selected from $-CF_2-$, $-CF_2CH_2-$, and $-CF_2CH_2CH_2-$;

L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene;

R^{s1} is $-CH_3$;

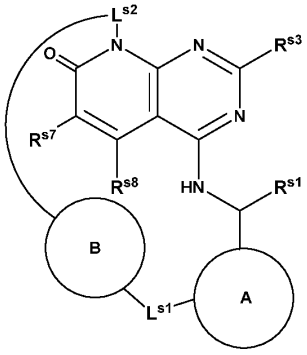
R^{s3} is hydrogen or $-CH_3$;

R^{s7} is selected from 



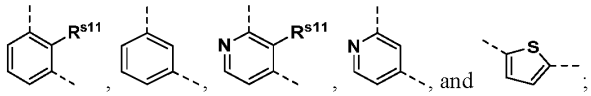
R^{s8} is hydrogen.

[571] In certain aspects, the present disclosure provides a compound of Formula (SI-C1):



(SI-C1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from  ;

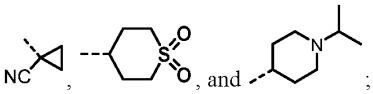
is selected from azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more -CH_3;

L^{s1} is C_{1-3} haloalkylene;

L^{s2} is C_{5-10} alkenylene optionally substituted with one or more R^{s11b};

R^{s1} is -CH_3;

R^{s3} is -CH_3;

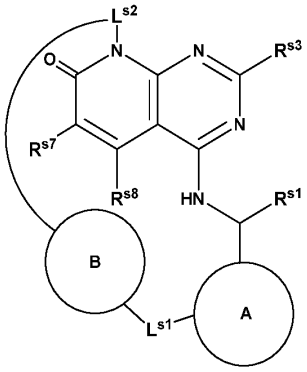
R^{s7} is selected from  ;

R^{s8} is hydrogen;

R^{s11} is selected from fluorine and -CH_3; and

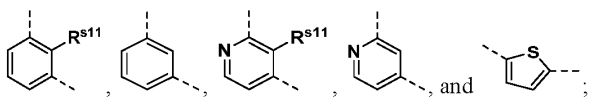
R^{s11b} is selected from halogen, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} alkyl)-OH, and -OH.

[572] In certain aspects, the present disclosure provides a compound of Formula (SI-C1):



(SI-C1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from  ;

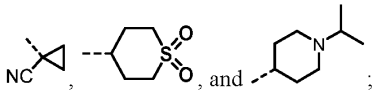
is selected from azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more -CH_3;

L^{s1} is C_{1-3} haloalkylene;

L^{s2} is selected from 5- to 10-membered heteroalkylene optionally substituted with one or more R^{s11b};

R^{s1} is -CH_3;

R^{s3} is hydrogen or -CH_3;

R^{s7} is selected from 

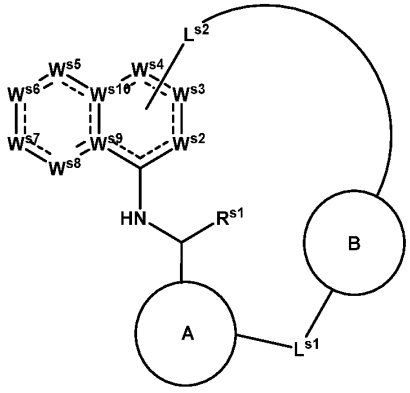
;

R^{s8} is hydrogen;

R^{s11} is selected from fluorine and -CH_3; and

R^{s11b} is selected from halogen, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, (C_{1-6} alkyl)-OH, and -OH.

[573] In certain aspects, the present disclosure provides a compound of Formula (SI):



(SI),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from phenyl and 5- to 7-membered heteroaryl, each of which is optionally substituted with one or more R^{s11};

is absent or selected from phenyl and 4- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond and C_{1-3} haloalkylene;

L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7}; or L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s4} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

L^{s3} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

D is selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{s11d};

L^{s4} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}

W^{s2} is N;

W^{s3} is selected from $N(R^{s3b})$, N, $C(R^{s3})$, and C(O);

W^{s4} is selected from $N(R^{s4b})$, N, $C(R^{s4})$, and C(O);

W^{s5} is selected from $N(R^{s5b})$, N, and $C(R^{s5})$;

W^{s6} is selected from $C(R^{s6})$ and C(O);

W^{s7} is $C(R^{s7})$;

W^{s8} is $C(R^{s8})$;

W^{s9} and W^{s10} are each C;

R^{s1} is $-CH_3$;

R^{s2}, R^{s2a}, R^{s3a}, R^{s4a}, R^{s5a}, R^{s6a}, R^{s7a}, R^{s8}, and R^{s8a} are each independently selected from hydrogen and $-CH_3$;

R^{s3}, R^{s4}, R^{s5}, and R^{s6} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$;

R^{s7} is selected from a bond to L^{s2}, C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, and R^{s5b} are each independently selected from a bond to L^{s2}, hydrogen, and C_{1-3} alkyl;

R^{s11}, R^{s11a}, and R^{s11d} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-

membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

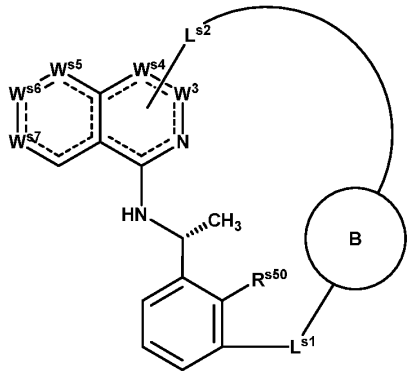
R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[574] In certain aspects, the present disclosure provides a compound of Formula (SIII):



(SIII),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from 3- to 8-membered heterocycle, optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7}; or L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s4} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

L^{s3} is selected from C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

D is absent or selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{s11d};

L^{s4} is selected from C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

W^{s3} is selected from N(R^{s3b}) and N and W^{s4} is selected from C(R^{s4}) and C(O); or W^{s3} is selected from C(R^{s3}) and C(O), and W^{s4} is selected from N(R^{s4b}) and N;

W^{s5} is selected from N(R^{s5b}), N, and C(R^{s5});

W^{s6} is selected from N, C(R^{s6}), and C(O);

W^{s7} is selected from N, C(R^{s7}), and C(O);

R^{s50} is hydrogen or halogen;

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, -OR^{s12}, -SR^{s12}, -N(R^{s12})(R^{s13}), -C(O)OR^{s12}, -OC(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)OR^{s15}, -N(R^{s14})S(O)$_2R^{s15}$, -C(O)R^{s15}, -S(O)R^{s15}, -OC(O)R^{s15}, -C(O)N(R^{s12})(R^{s13}), -C(O)C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)R^{s15}, -S(O)$_2R^{s15}$, -S(O)$_2$N(R^{s12})(R^{s13}), -S(=O)(=NH)N(R^{s12})(R^{s13}), -CH_2C(O)N(R^{s12})(R^{s13}), -CH_2N(R^{s14})C(O)R^{s15}, -CH_2S(O)$_2R^{s15}$, and -CH_2S(O)$_2$N(R^{s12})(R^{s13}), wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, and R^{s5b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, -OR^{s12}, -SR^{s12}, -C(O)OR^{s12}, -OC(O)N(R^{s12})(R^{s13}), -C(O)R^{s15}, -S(O)R^{s15}, -OC(O)R^{s15}, -C(O)N(R^{s12})(R^{s13}), -C(O)C(O)N(R^{s12})(R^{s13}), -S(O)$_2R^{s15}$, -S(O)$_2$N(R^{s12})(R^{s13}), -S(=O)(=NH)N(R^{s12})(R^{s13}), -CH_2C(O)N(R^{s12})(R^{s13}), -CH_2N(R^{s14})C(O)R^{s15}, -CH_2S(O)$_2R^{s15}$, and -CH_2S(O)$_2$N(R^{s12})(R^{s13}), wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s11a} and R^{s11d} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, -OR^{s12}, -SR^{s12}, -N(R^{s12})(R^{s13}), -C(O)OR^{s12}, -OC(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)OR^{s15}, -N(R^{s14})S(O)$_2R^{s15}$, -C(O)R^{s15}, -S(O)R^{s15}, -OC(O)R^{s15}, -C(O)N(R^{s12})(R^{s13}), -C(O)C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)R^{s15}, -S(O)$_2R^{s15}$, -S(O)$_2$N(R^{s12})(R^{s13}), -S(=O)(=NH)N(R^{s12})(R^{s13}), -CH_2C(O)N(R^{s12})(R^{s13}), -CH_2N(R^{s14})C(O)R^{s15}, -CH_2S(O)$_2R^{s15}$, -CH_2S(O)$_2$N(R^{s12})(R^{s13}), -CH_2N(R^{s12})S(O)$_2$(R^{s13}), and -P(O)(R^{s17})(R^{s17a}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, -OR^{s12}, -SR^{s12}, -N(R^{s12})(R^{s13}), -C(O)OR^{s12}, -OC(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)OR^{s15}, -N(R^{s14})S(O)$_2R^{s15}$, -C(O)R^{s15}, -S(O)R^{s15}, -OC(O)R^{s15}, -C(O)N(R^{s12})(R^{s13}), -C(O)C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)R^{s15}, -S(O)$_2R^{s15}$, -S(O)$_2$N(R^{s12})(R^{s13}), -

$S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

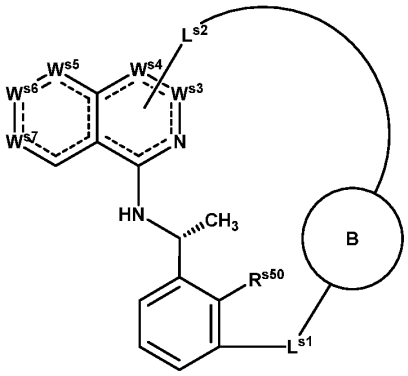
R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[575] In certain aspects, the present disclosure provides a compound of Formula (SIII):



(SIII),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from 3- to 8-membered heterocycle, optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

W^{s3} is selected from $N(R^{s3b})$ and N and W^{s4} is selected from $C(R^{s4})$ and C(O); or W^{s3} is selected from $C(R^{s3})$ and C(O), and W^{s4} is selected from $N(R^{s4b})$ and N;

W^{s5} is selected from $N(R^{s5b})$, N, and $C(R^{s5})$;

W^{s6} is selected from N, $C(R^{s6})$, and C(O);

W^{s7} is selected from N, $C(R^{s7})$, and C(O);

R^{s50} is hydrogen or halogen;

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, and R^{s5b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s11a} is independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, -

$CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

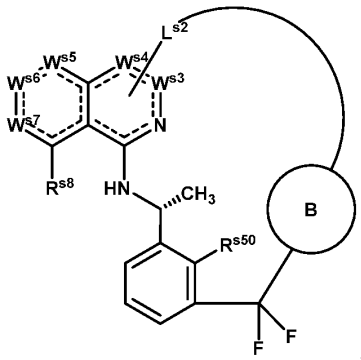
R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle,

and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[576] In some embodiments, a compound of Formula (SIII) is a compound of the formula: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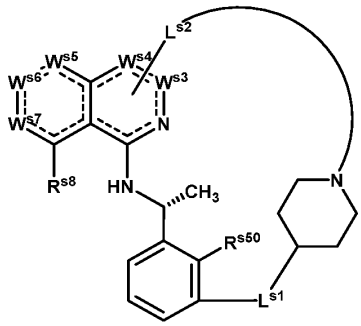
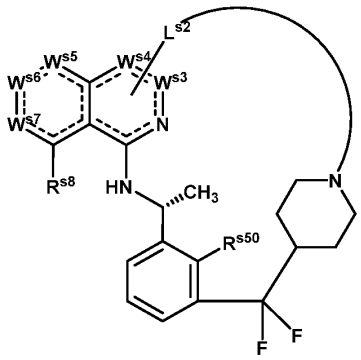
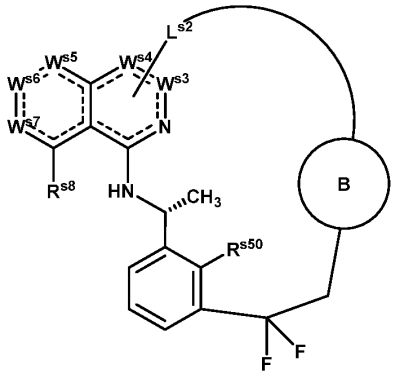

, or

.

[577] In some embodiments, a compound of Formula (SIII) is a compound of the formula: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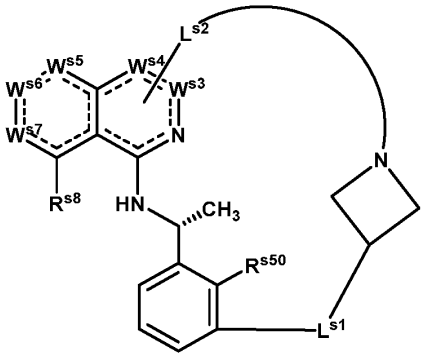
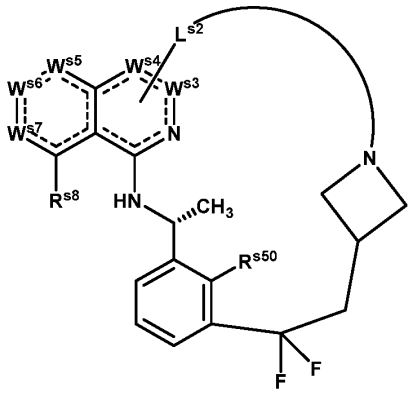
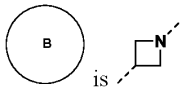
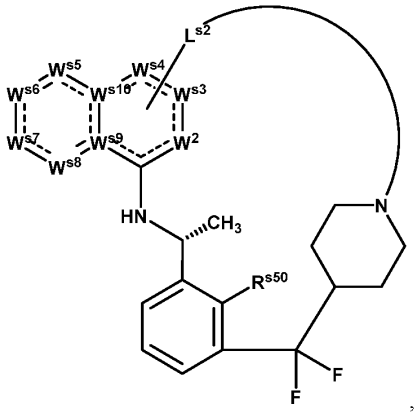

, or

.

[578] In some embodiments, for a compound of Formula (SIII), is selected from azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more R^{s11a}. In some embodiments, is

, each of which is optionally substituted with one or more R^{s11a}. In some embodiments,  is optionally substituted with one or more R^{s11a}. In some embodiments, L^{s1} is C_{1-3} haloalkylene. In some embodiments, L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7}; or L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s4} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7}; L^{s3} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}; D is selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{s11d}; and L^{s4} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}.

[579] In certain aspects, the present disclosure provides a compound of the formula:



,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7}; or L^{s2} is -L^{s3}-D-L^{s4}-, wherein L^{s4} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

L^{s3} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

D is selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{s11d};

L^{s4} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

W^{s2} is selected from N(R^{s2b}), N, C(R^{s2}), C(R^{s2})(R^{s2a}), and C(O);

W^{s3} is selected from N(R^{s3b}), N, C(R^{s3}), C(R^{s3})(R^{s3a}), and C(O);

W^{s4} is selected from N(R^{s4b}), N, C(R^{s4}), C(R^{s4})(R^{s4a}), and C(O);

W^{s5} is selected from N(R^{s5b}), N, C(R^{s5}), C(R^{s5})(R^{s5a}), and C(O);

W^{s6} is selected from N(R^{s6b}), N, C(R^{s6}), C(R^{s6})(R^{s6a}), and C(O);

W^{s7} is selected from N(R^{s7b}), N, C(R^{s7}), C(R^{s7})(R^{s7a}), and C(O);

W^{s8} is selected from N(R^{s8b}), N, C(R^{s8}), C(R^{s8})(R^{s8a}), and C(O);

W^{s9} is selected from N, $C(R^{s9})$, and C;

W^{s10} is selected from N, $C(R^{s10})$, and C;

R^{s2}, R^{s2a}, R^{s3a}, R^{s4a}, R^{s5a}, R^{s6a}, R^{s7a}, R^{s8}, and R^{s8a} are each independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s2b} and R^{s8b} are each independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, R^{s5b}, R^{s6b}, and R^{s7b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s9} and R^{s10} are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle), wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) is independently optionally substituted with one, two, or three R^{s20};

R^{s11d} is independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

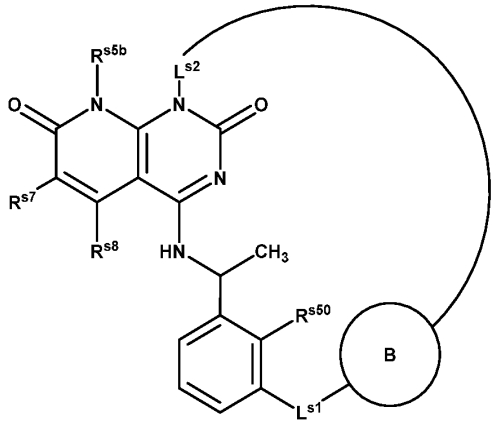
R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

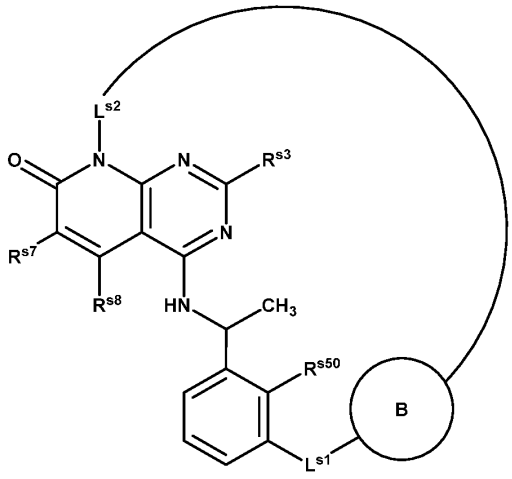
R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[580] In certain aspects, the present disclosure provides a compound of Formula (SII-B) or (SII-C):



(SII-B) or



(SII-C),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is absent or 4- to 8-membered heterocycle optionally substituted with one or more R^{s11a};

L^{s1} is C_{1-3} haloalkylene;

L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}; or L^{s2} is $-L^{s3}$-D-L^{s4}-;

L^{s3} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

D is selected from C_{3-10} carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{s11d};

L^{s4} is selected from C_{1-8} alkylene, C_{2-8} alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

R^{s3} and R^{s8} are each independently selected from hydrogen and $-CH_3$;

R^{s7} is selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one, two, or three R^{s20};

R^{s5b} is selected from hydrogen and C_{1-3} alkyl;

R^{s50} is selected from hydrogen and halogen;

R^{s11a} and R^{s11d} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, -

$OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

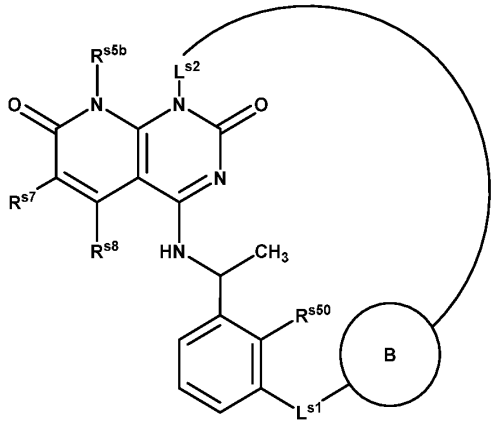
R^{s23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; and

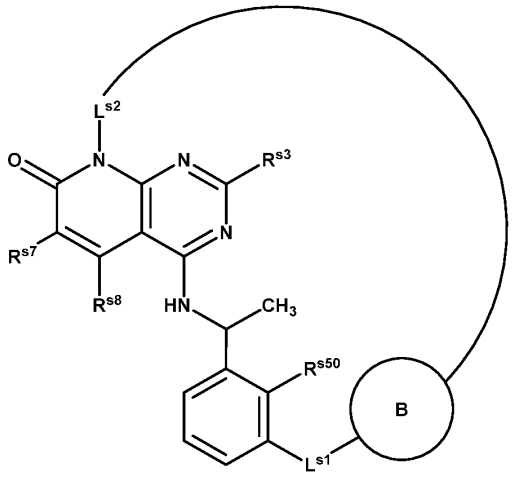
R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-}

$_6$ alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

[581] In some embodiments, the present disclosure provides a compound of Formula (SII-B) or (SII-C):



(SII-B) or



(SII-C),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is absent or 4- to 8-membered heterocycle optionally substituted with one or more R^{s11a};

L^{s1} is C_{1-3} haloalkylene;

L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

R^{s3}, R^{s5b}, and R^{s8} are each independently selected from hydrogen and $-CH_3$;

R^{s7} is selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one, two, or three R^{s20};

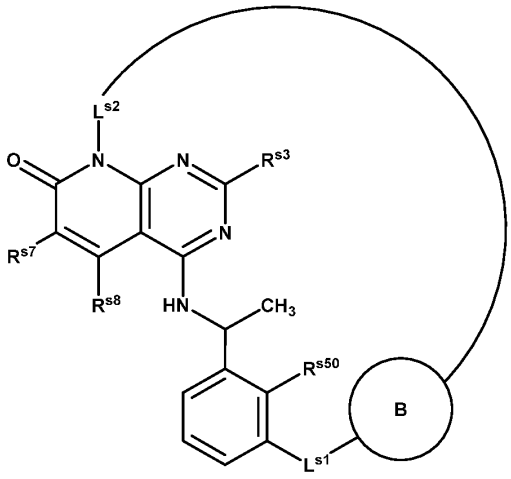
R^{s50} is selected from hydrogen and halogen;

R^{s11a} is independently selected at each occurrence from halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-3} alkyl, and -OH; and

R^{s20} is independently selected at each occurrence from halogen, oxo, -CN, and C_{1-6} alkyl.

[582] In some embodiments, the present disclosure provides a compound of Formula (SII-C):



(SII-C),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

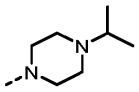
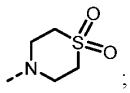
is absent or 4- to 8-membered heterocycle optionally substituted with one or more R^{s11a};

L^{s1} is C_{1-3} haloalkylene;

L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

R^{s3} is hydrogen;

R^{s8} is selected from hydrogen and $-CH_3$;

R^{s7} is selected from  and  ;

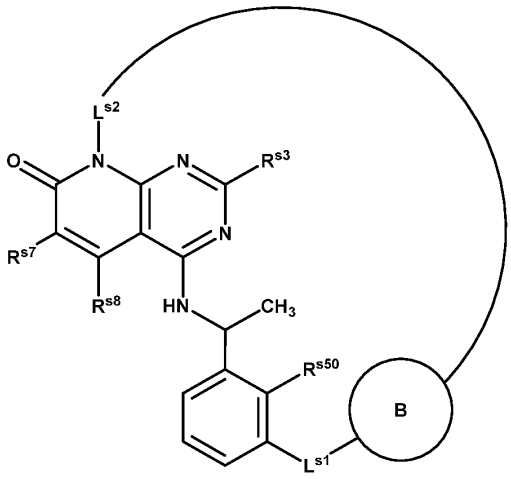
R^{s50} is selected from hydrogen and halogen;

R^{s11a} is independently selected at each occurrence from halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-3} alkyl, and -OH; and

R^{s20} is independently selected at each occurrence from halogen, oxo, -CN, and C_{1-6} alkyl.

[583] In some embodiments, the present disclosure provides a compound of Formula (SII-C):



(SII-C),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

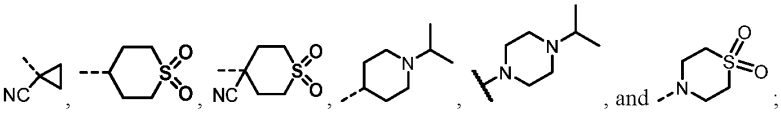
is 4- to 8-membered heterocycle optionally substituted with one or more R^{s11a};

L^{s1} is C_{1-3} haloalkylene;

L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b};

R^{s3} is selected from hydrogen and $-CH_3$;

R^{s8} is selected from hydrogen and $-CH_3$;

R^{s7} is selected from 

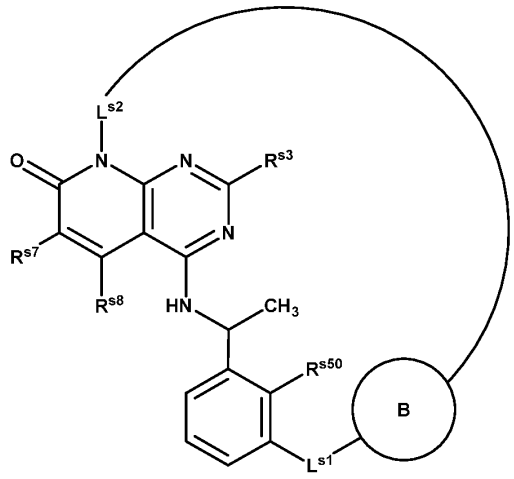
;

R^{s50} is selected from hydrogen and halogen;

R^{s11a} is independently selected at each occurrence from halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-3} alkyl, and -OH.

[584] In some embodiments, the present disclosure provides a compound of Formula (SII-C):



(SII-C),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

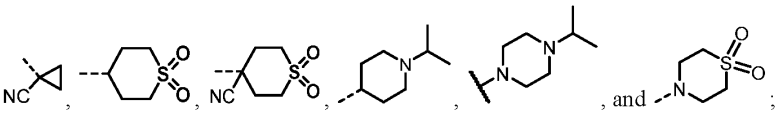
is 4- to 6-membered heterocycle;

L^{s1} is C_{1-3} haloalkylene;

L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, and 5- to 10-membered heteroalkylene;

R^{s3} is selected from hydrogen and $-CH_3$;

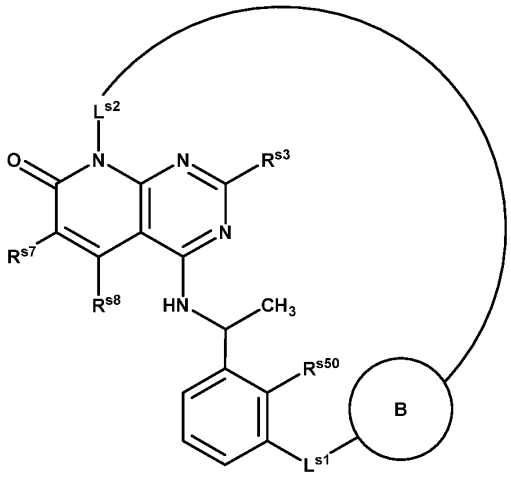
R^{s8} is hydrogen;

R^{s7} is selected from 

; and

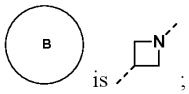
R^{s50} is selected from hydrogen and halogen.

[585] In some embodiments, the present disclosure provides a compound of Formula (SII-C):



(SII-C),

or a pharmaceutically acceptable salt or solvate thereof, wherein:



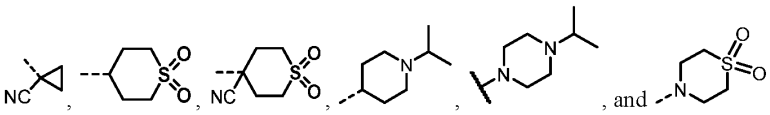
;

L^{s1} is $-CF_2CH_2-$;

L^{s2} is 5- to 10-membered heteroalkylene, wherein the heteroalkylene comprises one oxygen atom;

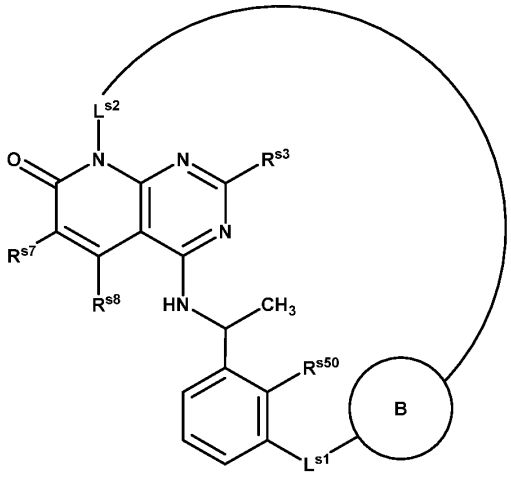
R^{s3} is selected from hydrogen and $-CH_3$;

R^{s8} is hydrogen;

R^{s7} is selected from  ; and

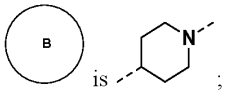
R^{s50} is selected from hydrogen and halogen.

[586] In some embodiments, the present disclosure provides a compound of Formula (SII-C):



(SII-C),

or a pharmaceutically acceptable salt or solvate thereof, wherein:



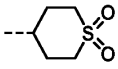
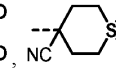
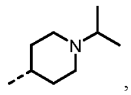
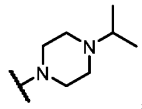
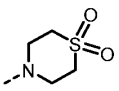
;

L^{s1} is $-CF_2-$;

L^{s2} is selected from C_{5-10} alkenylene;

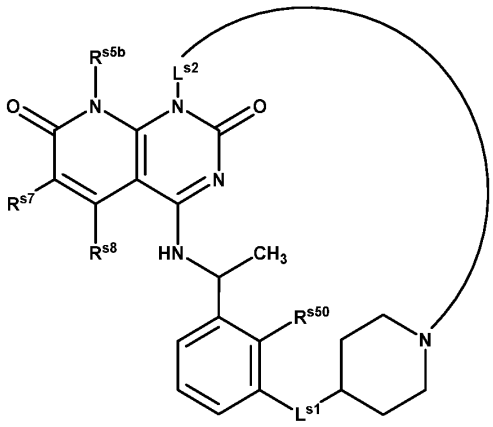
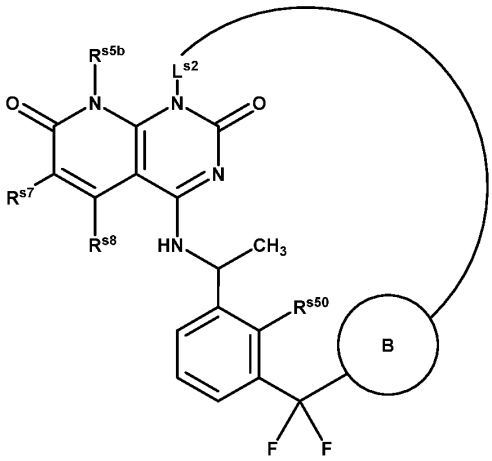
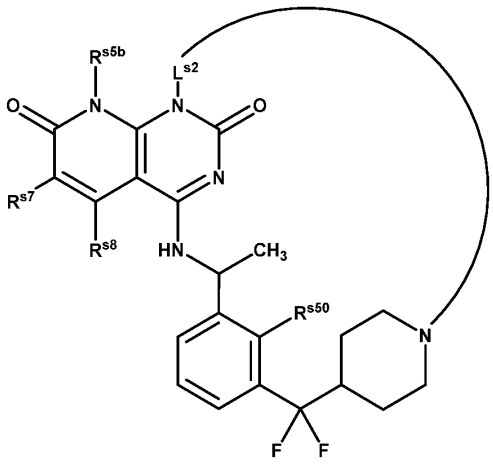
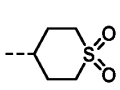
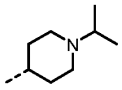
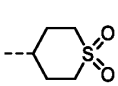
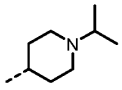
R^{s3} is selected from hydrogen and $-CH_3$;

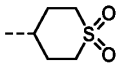
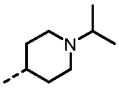
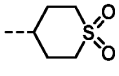
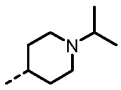
R^{s8} is hydrogen;

R^{s7} is selected from ,  ,  ,  ,  , and  ; and

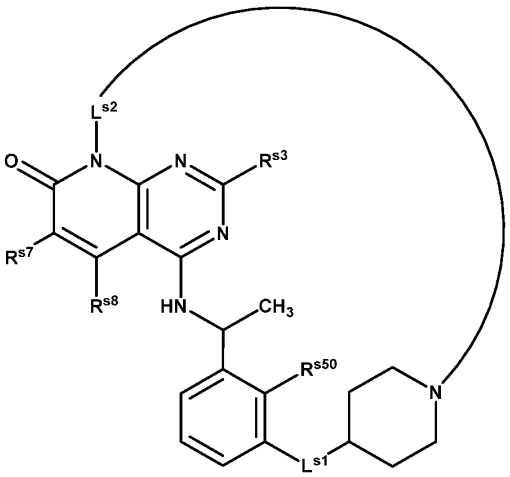
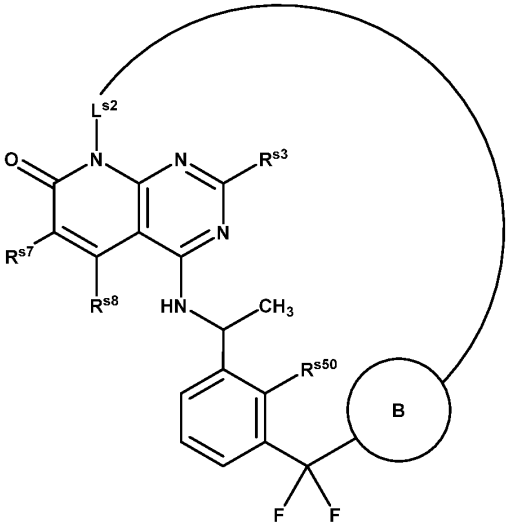
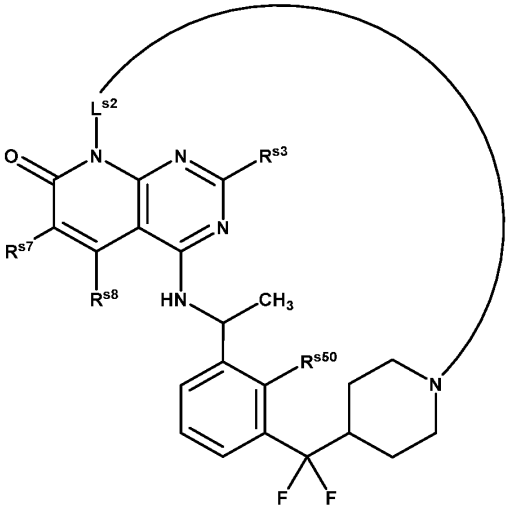
R^{s50} is selected from hydrogen and halogen.

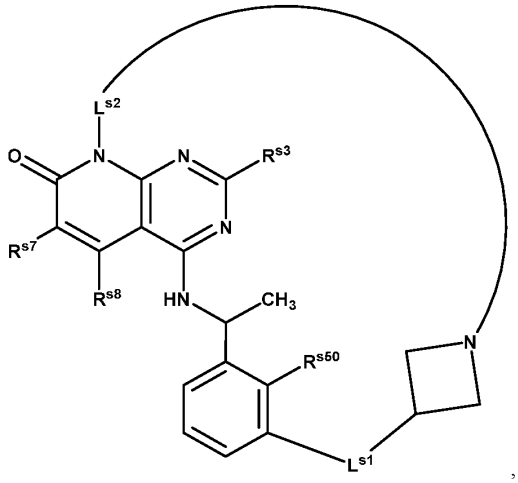
[587] In some embodiments, a compound of Formula (SII-B) is a compound of the formula:

 ,  , or  . In some embodiments, R^{s5b} is $-CH_3$; R^{s8} is hydrogen; and R^{s50} is selected from hydrogen and fluoro. In some embodiments, R^{s5b} is $-CH_3$; R^{s8} is hydrogen; and R^{s50} is hydrogen. In some embodiments, R^{s5b} is $-CH_3$; R^{s8} is hydrogen; and R^{s50} is fluoro. In some embodiments, R^{s7} is selected from ,  , and  . In some embodiments, R^{s5b} is $-CH_3$; R^{s8} is hydrogen; R^{s50} is hydrogen; and R^{s7} is selected from ,  , and  . In some embodiments, R^{s5b} is $-CH_3$; R^{s8} is hydrogen; R^{s50} is

fluoro; and R^{s7} is selected from ,  , and  . In some embodiments, R^{s5b} is $-CH_3$; R^{s8} is hydrogen; R^{s50} is selected from hydrogen and fluoro; and R^{s7} is  . In some embodiments, R^{s5b} is $-CH_3$; R^{s8} is hydrogen; R^{s50} is selected from hydrogen and fluoro; and R^{s7} is . In some embodiments, R^{s5b} is $-CH_3$; R^{s8} is hydrogen; R^{s50} is selected from hydrogen and fluoro; and R^{s7} is  .

[588] In some embodiments, a compound of Formula (SII-C) is a compound of the formula:

 ,  , or  . In some embodiments, a compound of Formula (SII-C) is a compound of the formula:



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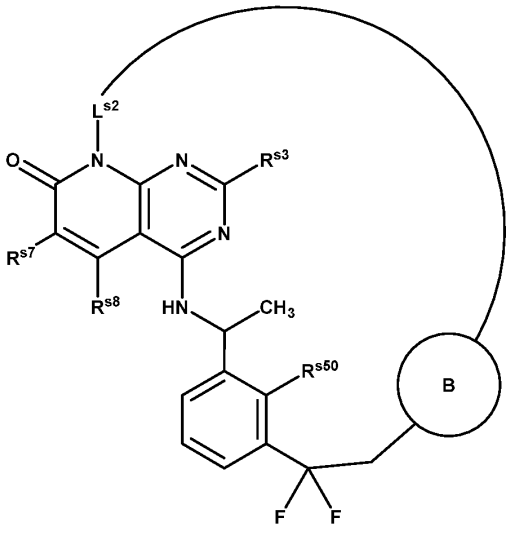
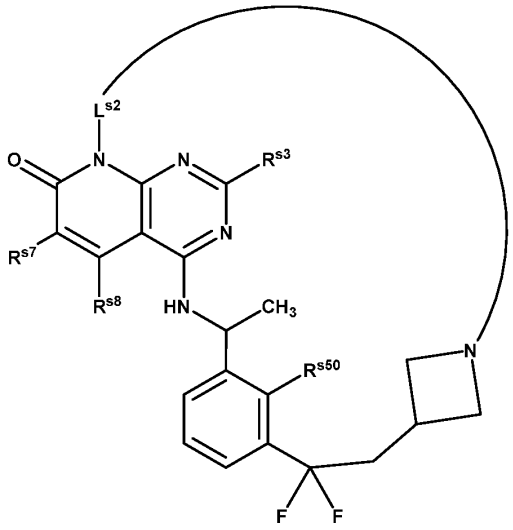
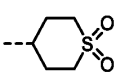
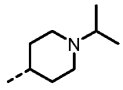


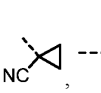
, or

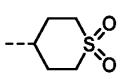


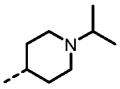
. In some embodiments, R^{s3} is selected from hydrogen and $-CH_3$; R^{s8} is hydrogen; and R^{s50} is selected from hydrogen and fluoro. In some embodiments, R^{s3} is selected from hydrogen and $-CH_3$; R^{s8} is hydrogen; and R^{s50} is hydrogen. In some embodiments, R^{s3} is selected from hydrogen and $-CH_3$; R^{s8} is hydrogen; and R^{s50} is fluoro. In some embodiments, R^{s3} is hydrogen; R^{s8} is hydrogen; and R^{s50} is hydrogen. In some embodiments, R^{s3} is hydrogen; R^{s8} is hydrogen; and R^{s50} is fluoro. In some embodiments, R^{s3} is $-CH_3$; R^{s8} is hydrogen; and R^{s50} is hydrogen. In some embodiments, R^{s3} is $-CH_3$; R^{s8} is hydrogen; and R^{s50} is fluoro. In some embodiments, R^{s7} is selected from

, 

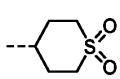
, and 

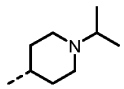
. In some embodiments, R^{s3} is selected from hydrogen and $-CH_3$; R^{s8} is hydrogen; R^{s50} is hydrogen; and R^{s7} is selected from 

, 

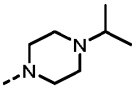
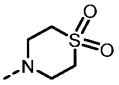
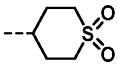
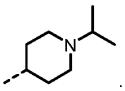
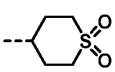
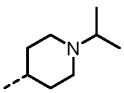
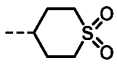
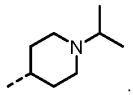
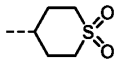
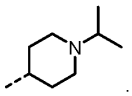
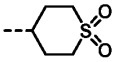
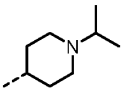
, and 

. In some embodiments, R^{s3} is selected from hydrogen and $-CH_3$; R^{s8} is hydrogen; R^{s50} is fluoro; and R^{s7} is selected from

, 

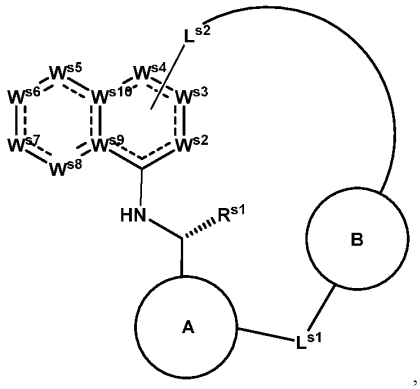
, and 

. In some embodiments, R^{s3} is hydrogen; R^{s8} is hydrogen; R^{s50} is selected from hydrogen

and fluoro; and R^{s7} is selected from  and  . In some embodiments, R^{s3} is hydrogen; R^{s8} is hydrogen; R^{s50} is hydrogen; and R^{s7} is selected from ,  , and  . In some embodiments, R^{s3} is hydrogen; R^{s8} is hydrogen; R^{s50} is fluoro; and R^{s7} is selected from ,  , and  . In some embodiments, R^{s3} is $-CH_3$; R^{s8} is hydrogen; R^{s50} is hydrogen; and R^{s7} is selected from ,  , and  . In some embodiments, R^{s3} is $-CH_3$; R^{s8} is hydrogen; R^{s50} is fluoro; and R^{s7} is selected from ,  , and  . In some embodiments, R^{s3} is selected from hydrogen and $-CH_3$; R^{s8} is hydrogen; R^{s50} is selected from hydrogen and fluoro; and R^{s7} is . In some embodiments, R^{s3} is selected from hydrogen and $-CH_3$; R^{s8} is hydrogen; R^{s50} is selected from hydrogen and fluoro; and R^{s7} is  . In some embodiments, R^{s3} is selected from hydrogen and $-CH_3$; R^{s8} is hydrogen; R^{s50} is selected from hydrogen and fluoro; and R^{s7} is  .

[589] Embodiments disclosed herein that refer to a compound of Formula (SI), (SI-A), (SI-B), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), and/or (SI-E1) are also intended to apply to a compound of Formula (SI-1), (SII-B), (SII-C), and (SIII) unless the context of the embodiment clearly dictates otherwise (e.g., the embodiment refers solely to a variable not present in the compound of Formula (SI-1), (SII-B), (SII-C), or (SIII), such as R^{s1}).

[590] In some embodiments, a compound of Formula (SI) is a compound of the formula:



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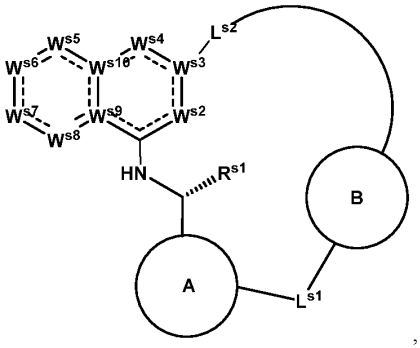

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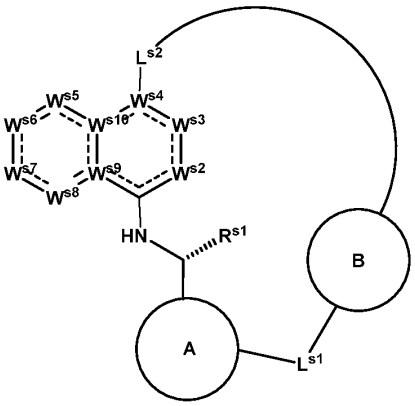
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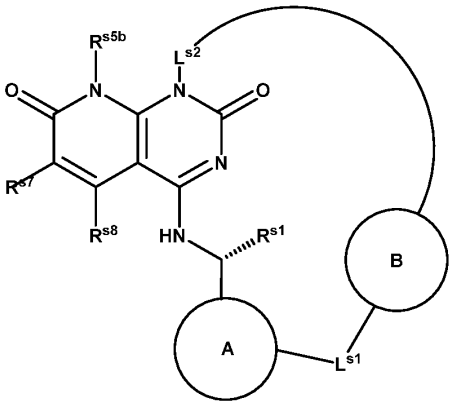
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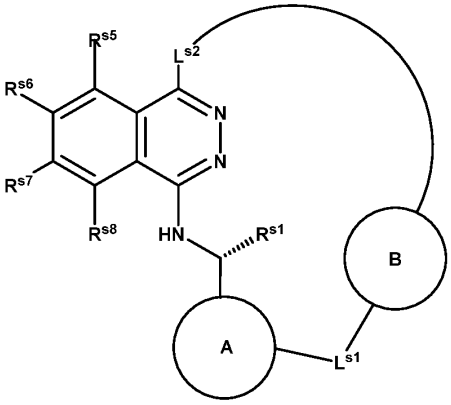
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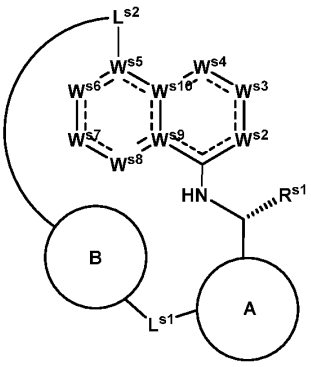
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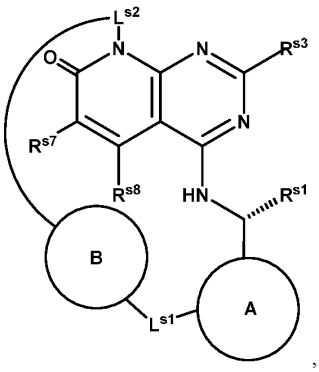
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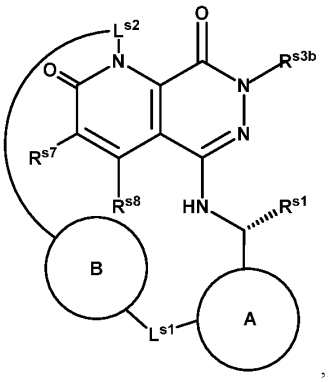
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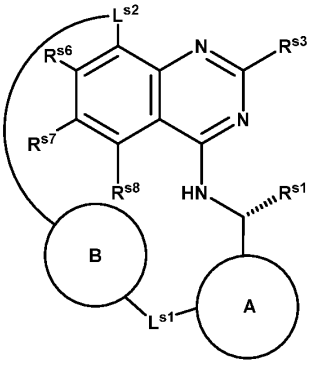
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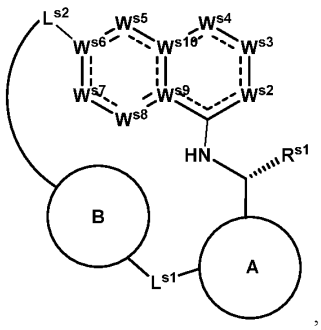
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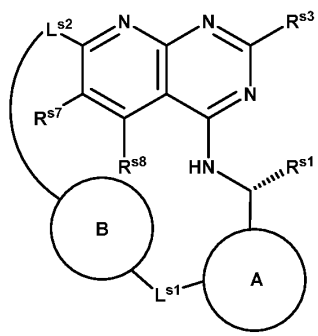
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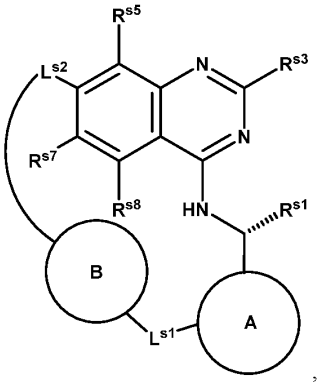
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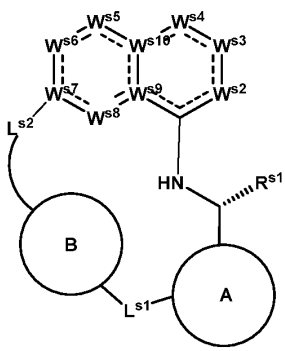
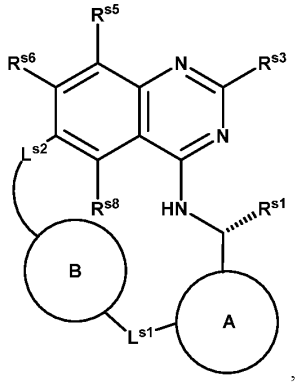
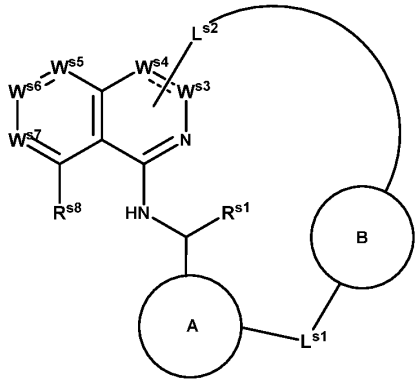

, or



, or a salt or solvate thereof.

[591] In certain aspects, the present disclosure provides a compound of Formula (SI-1):



(SI-1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from C_{5-7} carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R^{s11};

is absent or selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

W^{s3} is selected from $N(R^{s3b})$, N, $C(R^{s3})$, and C(O);

W^{s4} is selected from $N(R^{s4b})$, N, $C(R^{s4})$, and C(O);

W^{s5} is selected from $N(R^{s5b})$, N, and $C(R^{s5})$;

W^{s6} is selected from $C(R^{s6})$ and C(O);

W^{s7} is $C(R^{s7})$;

R^{s1} is C_{1-3} alkyl optionally substituted with one or more R^{s11c};

R^{s8} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, -

$N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, and R^{s5b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s11} and R^{s11a} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11c} is independently selected at each occurrence from halogen, $-OR^{s12}$, and $-N(R^{s12})(R^{s13})$;

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-

membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

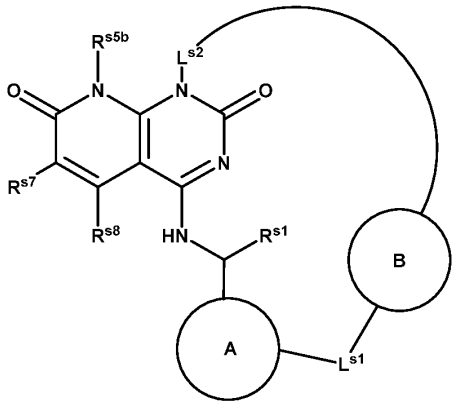
R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

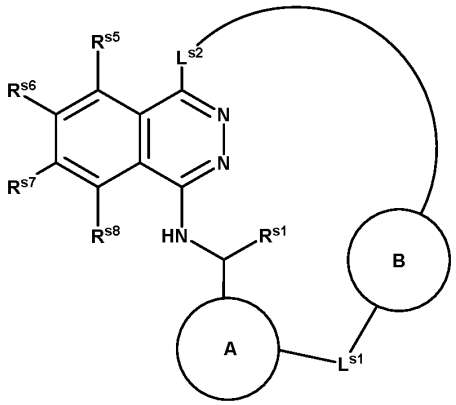
R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[592] In some embodiments, the compound of Formula (SI-1) is a compound of Formula (SI-B1) or (SI-B2):



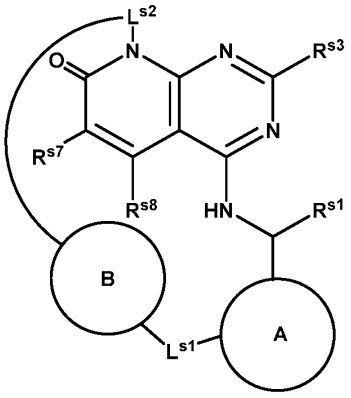
(SI-B1) or



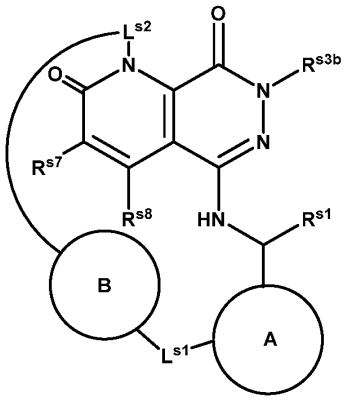
(SI-B2),

or a pharmaceutically acceptable salt or solvate thereof.

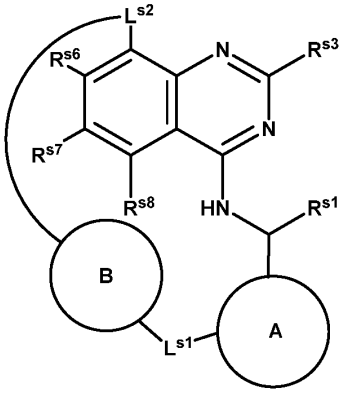
[593] In some embodiments, the compound of Formula (SI-1) is a compound of Formula (SI-C1), (SI-C2), or (SI-C3):



(SI-C1),



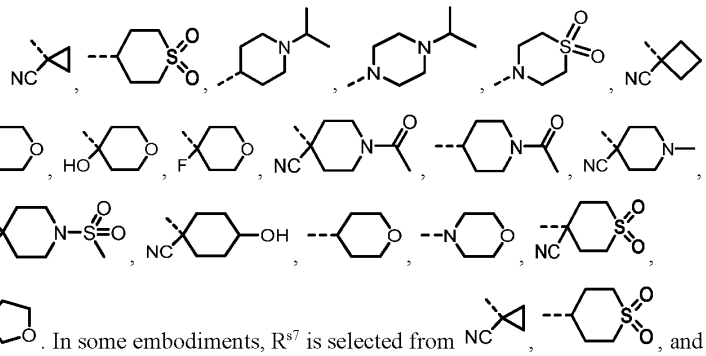
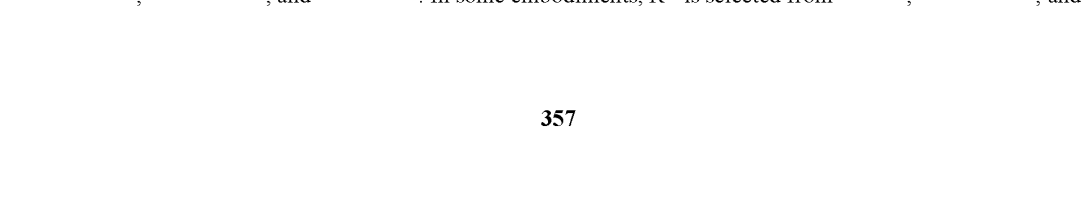
(SI-C2), or

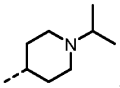


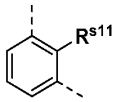
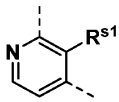
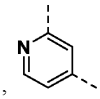
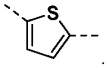
(SI-C3),

or a pharmaceutically acceptable salt or solvate thereof.

[594] In some embodiments, for a compound of Formula (SI-1), (SI-B1), (SI-B2), (SI-C1), (SI-C2), or (SI-C3), R^{s1} is $-CH_3$. In some embodiments, for a compound of Formula (SI-1), (SI-C1), or (SI-C3), R^{s3} is selected from hydrogen, -CN, $-OR^{s12}$, and $-CH_3$. In some embodiments, for a compound of Formula (SI-1), (SI-B2), or (SI-C3), R^{s6} is selected from hydrogen, $-OR^{s12}$, and C_{1-6} alkyl optionally substituted with one, two, or three R^{s20}, and wherein R^{s12} is selected from C_{1-6} alkyl. In some embodiments, for a compound of Formula (SI-1), (SI-B1), (SI-B2), (SI-C1), (SI-C2), or (SI-C3), R^{s8} is hydrogen.

[595] In some embodiments, for a compound of Formula (SI-1), (SI-B1), (SI-B2), (SI-C1), (SI-C2), or (SI-C3), R^{s7} is selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $-N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl are optionally substituted with one, two, or three R^{s20}. In some embodiments, R^{s7} is selected from  . In some embodiments, R^{s7} is selected from  .



[596] In some embodiments, for a compound of Formula (SI-1), (SI-B1), (SI-B2), (SI-C1), (SI-C2), or (SI-C3), is selected from phenyl and 5- to 7-membered heteroaryl, each of which is optionally substituted with one or more R^{s11}. In some embodiments, is selected from  , ,  ,  , and  . In some embodiments, R^{s11} is independently selected from fluorine and $-CH_3$.

[597] In some embodiments, for a compound of Formula (SI-1), (SI-B1), (SI-B2), (SI-C1), (SI-C2), or (SI-C3), L^{s1} is C_{1-3} haloalkylene. In some embodiments, L^{s1} is selected from $-CF_2-$, $-CF_2CH_2-$, and $-CF_2CH_2CH_2-$.

[598] In some embodiments, for a compound of Formula (SI-1), (SI-B1), (SI-B2), (SI-C1), (SI-C2), or (SI-C3), is selected from absent, phenyl, and 4- to 8-membered heterocycle, wherein the phenyl and 4- to 8-membered heterocycle are optionally substituted with one or more R^{s11a}. In some embodiments, is selected from azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more $-CH_3$.

[599] In some embodiments, for a compound of Formula (SI-1), (SI-B1), (SI-B2), (SI-C1), (SI-C2), or (SI-C3), L^{s2} is selected from C_{6-15} alkylene, C_{6-15} alkenylene, C_{6-15} alkynylene, 6- to 15-membered heteroalkylene, and 6- to 15-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}. In some embodiments, the alkenylene and heteroalkenylene contain one carbon-carbon double bond. In some embodiments, the heteroalkylene and heteroalkenylene comprise at least one oxygen or nitrogen atom.

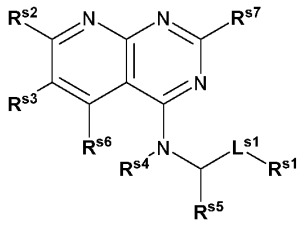
[600] In some embodiments, for a compound of Formula (SI-1), (SI-B1), or (SI-B2), R^{s5} is hydrogen; R^{s5b} is $-CH_3$; R^{s6} is selected from hydrogen and $-OCH_3$; R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}; and R^{s8} is hydrogen.

[601] In some embodiments, for a compound of Formula (SI-1), (SI-C1), (SI-C2), or (SI-C3), R^{s3} is hydrogen or $-CH_3$; R^{s3b} is $-CH_3$; R^{s6} is selected from hydrogen and $-OCH_3$; R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}; and R^{s8} is hydrogen.

[602] The chemical and chemistry-related definitions for compounds of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), and (H), and any sub-formula, embodiments, and specific compounds encompassed by those formulae, may also apply to the compounds of Formula (SIV), (SIV-1), and (SIVa-1). Compounds of Formula (SIV), (SIV-1), and (SIVa-1), and any sub-formula, embodiments, and specific compounds

encompassed by those formulae may be included (e.g., used) in the methods, kits, or pharmaceutical compositions described herein (e.g., as a SOS or SOS1 inhibitor).

[603] In certain aspects, the present disclosure provides a compound of Formula (SIV):



(SIV),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{s1} is a 3-12 membered cycloalkyl ring, 3-12 membered heterocycloalkyl ring, 6-10 membered aryl ring, or 5-10 membered heteroaryl ring, wherein the 3-12 membered cycloalkyl ring, 3-12 membered heterocycloalkyl ring, 6-10 membered aryl ring, and 5-10 membered heteroaryl ring are optionally substituted with one or more R^{s10};

L^{s1} is a bond or C_{1-6}alkyl;

R^{s2} is $-OR^{s2a}$, $-NR^{s2b}R^{s2c}$, $-SR^{s2g}$, $-S(O)R^{s2h}$, $-S(O)_2R^{s2h}$, $-S(O)_2NR^{s2b}R^{s2c}$, $-C(R^{s2d})(R^{s2e})(R^{s2f})$, $C(O)NR^{s2b}R^{s2c}$, -CN, or halogen;

R^{s2a} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-C(O)OR^{s12}$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20a};

R^{s2b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-C(O)OR^{s12}$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-S(O)_2N(R^{s12})(R^{s13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20a};

R^{s2c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20a}; or R^{s2b} and R^{s2c}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{s20a};

R^{s2d} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20a};

R^{s2e} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20a};

R^{s2f} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20a};

R^{s2g} is selected from hydrogen, C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -C(O)OR^{s12}, -C(O)R^{s15}, -C(O)N(R^{s12})(R^{s13}), -S(O)$_2$R^{s15}, -S(O)$_2$N(R^{s12})(R^{s13}), wherein C_{2-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20a};

R^{s2h} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20a};

R^{s3} is selected from halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-14}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -SR^{s12}, -N(R^{s12})(R^{s13}), -C(O)OR^{s12}, -OC(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)OR^{s15}, -N(R^{s14})S(O)$_2$R^{s15}, N(R^{s14})S(O)R^{s15}, -C(O)R^{s15}, -S(O)R^{s15}, -OC(O)R^{s15}, -C(O)N(R^{s12})(R^{s13a}), -C(O)C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)R^{s15}, -S(O)$_2$R^{s15}, -S(O)$_2$N(R^{s12})(R^{s13}), -S(O)N(R^{s12})(R^{s13}), -S(=O)(=NH)N(R^{s12})(R^{s13}), -CH$_2$C(O)N(R^{s12})(R^{s13}), -CH$_2$N(R^{s14})C(O)R^{s15}, -CH$_2$S(O)$_2$R^{s15}, -CH$_2$S(O)$_2$N(R^{s12})(R^{s13}), -CH$_2$N(R^{s12})S(O)$_2$(R^{s13}), CH$_2$S(O) R^{s15}, -CH$_2$S(O)N(R^{s12})(R^{s13}), -CH$_2$N(R^{s12})S(O)(R^{s13}) and -P(O)(R^{s17})(R^{s17a}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-14}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20b};

R^{s4} is selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

R^{s5} is selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

R^{s6} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -OR^{s12}, -SR^{s12}, -N(R^{s12})(R^{s13}), -C(O)OR^{s12}, -OC(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)OR^{s15}, -N(R^{s14})S(O)$_2$R^{s15}, -C(O)R^{s15}, -S(O)R^{s15}, -OC(O)R^{s15}, -C(O)N(R^{s12})(R^{s13}), -C(O)C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)R^{s15}, -S(O)$_2$R^{s15}, -S(O)$_2$N(R^{s12})(R^{s13}), -S(=O)(=NH)N(R^{s12})(R^{s13}), -CH$_2$C(O)N(R^{s12})(R^{s13}), -CH$_2$N(R^{s14})C(O)R^{s15}, -CH$_2$S(O)$_2$R^{s15}, -CH$_2$S(O)$_2$N(R^{s12})(R^{s13}), -CH$_2$N(R^{s12})S(O)$_2$(R^{s13}), and -P(O)(R^{s17})(R^{s17a}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{s20c};

R^{s7} is selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{1-9}heteroaryl, -OR^{s12}, -SR^{s12}, -N(R^{s12})(R^{s13}), -C(O)OR^{s12}, -OC(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)OR^{s15}, -N(R^{s14})S(O)$_2$R^{s15}, -C(O)R^{s15}, -S(O)R^{s15}, -OC(O)R^{s15}, -C(O)N(R^{s12})(R^{s13}), -C(O)C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)R^{s15}, -S(O)$_2$R^{s15}, -S(O)$_2$N(R^{s12})(R^{s13}), -S(=O)(=NH)N(R^{s12})(R^{s13}), -CH$_2$C(O)N(R^{s12})(R^{s13}), -CH$_2$N(R^{s14})C(O)R^{s15}, -CH$_2$S(O)$_2$R^{s15}, -CH$_2$S(O)$_2$N(R^{s12})(R^{s13}), -CH$_2$N(R^{s12})S(O)$_2$(R^{s13}), and -P(O)(R^{s17})(R^{s17a}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20c};

each R^{s10} is independently selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{s12}, -SR^{s12}, -N(R^{s12})(R^{s13}), -C(O)OR^{s12}, -OC(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)OR^{s15}, -N(R^{s14})S(O)$_2$R^{s15}, -C(O)R^{s15}, -S(O)R^{s15}, -OC(O)R^{s15}, -C(O)N(R^{s12})(R^{s13}), -C(O)C(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)R^{s15}, -S(O)$_2$R^{s15}, -S(O)$_2$N(R^{s12})(R^{s13}), -S(=O)(=NH)N(R^{s12})(R^{s13}), -CH$_2$C(O)N(R^{s12})(R^{s13}), -CH$_2$N(R^{s14})C(O)R^{s15}, -CH$_2$S(O)$_2$R^{s15}, -CH$_2$S(O)$_2$N(R^{s12})(R^{s13}), -CH$_2$N(R^{s12})S(O)$_2$(R^{s13}), and -P(O)(R^{s17})(R^{s17a}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20d};

each R^{s12} is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6} haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20e};

each R^{s13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{s20f};

R^{s13a} is selected from C_{1-6}alkyl and C_{1-6}haloalkyl; or R^{s12} and R^{s13a}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{s20f};

each R^{s14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{s15} is independently selected C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20g};

each R^{s17} and each R^{s17a} are each independently selected from C_{1-6}alkyl and C_{3-6}cycloalkyl, wherein C_{1-6}alkyl and C_{3-6}cycloalkyl are optionally substituted with one, two or three of R^{s20h}; or R^{s17} and R^{s17a} are combined to form a C_{2-9}heterocycloalkyl ring;

each R^{s20a}, R^{s20b}, R^{s20c}, R^{s20d}, R^{s20e}, R^{s20f}, R^{s20g}, and R^{s20h} are each independently selected from halogen, oxo, =NH, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, -$OCH_2C(O)OR^{s22}$, and -$OC(O)R^{s25}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, and -$OC(O)R^{s25}$;

each R^{s21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6}alkyl;

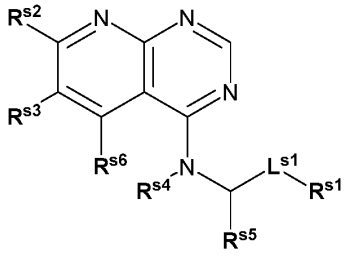
each R^{s22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6}alkyl;

each R^{s23} is independently selected from H and C_{1-6}alkyl;

each R^{s24} is independently selected from H and C_{1-6}alkyl; and

each R^{s25} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl.

[604] In certain aspects, the present disclosure provides a compound of Formula (SIV-1):



(SIV-1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{s1} is a 6-10 membered aryl ring optionally substituted with one or more R^{s10};

L^{s1} is a bond;

R^{s2} is $-OR^{s2a}$ or halogen;

R^{s2a} is selected from C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20a};

R^{s3} is selected from halogen, C_{1-6}alkyl, C_{3-14}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{3-14}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20b};

R^{s4} is selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

R^{s5} is selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

R^{s6} is selected from hydrogen, halogen, -CN, and C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with one, two, or three R^{s20c};

each R^{s10} is independently selected from halogen, -CN, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{s20d};

each R^{s20a}, R^{s20b}, R^{s20c}, and R^{s20d} are each independently selected from halogen, oxo, =NH, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-CH_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, $-CH_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, $-CH_2$-C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

each R^{s21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6}alkyl;

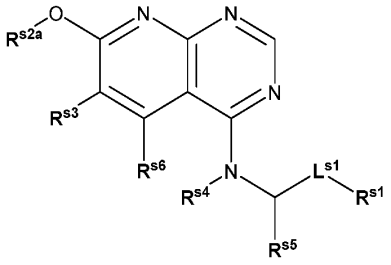
each R^{s22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6}alkyl;

each R^{s23} is independently selected from H and C_{1-6}alkyl;

each R^{s24} is independently selected from H and C_{1-6}alkyl; and

each R^{s25} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl.

[605] In some embodiments, the compound of Formula (SIV-1) is a compound of Formula (SIVa-1):

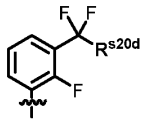
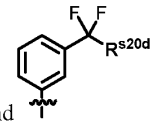
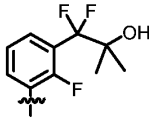
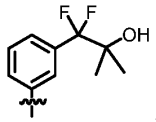
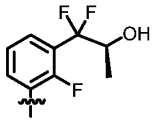
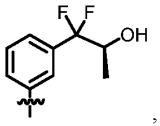
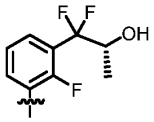
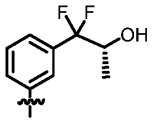


(SIVa-1), or a pharmaceutically acceptable salt or solvate thereof.

[606] In some embodiments, for a compound of Formula (SIV), (SIV-1), or (SIVa-1), R^{s2a} is C_{1-6}alkyl optionally substituted with one, two, or three R^{s20a}. In some embodiments, R^{s2a} is unsubstituted C_{1-6}alkyl. In some embodiments, R^{s2a} is $-CH_3$.

[607] In some embodiments, for a compound of Formula (SIV), (SIV-1), or (SIVa-1), R^{s3} is C_{2-9}heterocycloalkyl optionally substituted with one, two, or three R^{s20b}. In some embodiments, R^{s3} is C_{3-10}cycloalkyl optionally substituted with one, two, or three R^{s20b}. In some embodiments, R^{s3} is C_{3-4}cycloalkyl optionally substituted with one R^{s20b}. In some embodiments, R^{s20b} is -CN or halogen. In some embodiments, R^{s3} is or .

[608] In some embodiments, for a compound of Formula (SIV), (SIV-1), or (SIVa-1), R^{s6} is selected from hydrogen, halogen, and unsubstituted C_{1-6}alkyl. In some embodiments, R^{s6} is hydrogen. In some embodiments, R^{s5} is C_{1-6}alkyl. In some embodiments, R^{s5} is $-CH_3$. In some embodiments, R^{s4} is hydrogen.

[609] In some embodiments, for a compound of Formula (SIV), (SIV-1), or (SIVa-1), R^{s1} is phenyl substituted with one or more R^{s10}. In some embodiments, R^{s10} is independently selected from halogen and C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with one, two, or three R^{s20d}. In some embodiments, each R^{s10} is independently selected from halogen and C_{1-6}alkyl, wherein C_{1-6}alkyl is substituted with one, two, or three R^{s20d}, and each R^{s20d} is halogen or -OH. In some embodiments, R^{s1} is independently selected from  and  . In some embodiments, R^{s20d} is C_{1-6}alkyl optionally substituted with one, two, or three groups independently selected from F and -OH. In some embodiments, R^{s20d} is C_{1-3}alkyl substituted with one -OH. In some embodiments, R^{s1} is selected from  ,  ,  ,  ,  , and  .

[610] In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate

thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-A), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-B), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-B1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-B2), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-C), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-C1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-C2), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-C3), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-D), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-D1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-D2), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-E), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SI-E1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SII-B), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SII-C), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SIII), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SIV), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SIV-1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Formula (SIVa-1), or an embodiment thereof, or a pharmaceutically acceptable salt or solvate thereof.

[611] In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Table 2a, or a pharmaceutically acceptable salt or solvate thereof. In embodiments of any one of the methods, kits, or pharmaceutical compositions described herein, the SOS1 inhibitor is a compound of Table 2b, or a pharmaceutically acceptable salt or solvate thereof.

[612] SOS1 inhibitors suitable for use in the subject methods—including the synergistic inhibition of proliferation of KRAS-mediated cancer cells in combination with a KRAS inhibitor—include compounds of Formula (SI); Formula (SI-A); Formula (SI-B); Formula (SI-1), encompassing Compound A; Formula (SI-B1); Formula (SI-B2); Formula (SI-C); Formula (SI-C1); Formula (SI-C2); Formula (SI-C3); Formula (SI-D); Formula (SI-D1); Formula (SI-D2); Formula (SI-E); Formula (SI-E1); Formula (SII-B); Formula (SII-C); and Formula (SIII). Exemplary SOS1 inhibitors include, but are not limited to, compounds selected from Table 2a (including Compound A) and Table 2b, or a salt or solvate thereof.

[613] In some embodiments, a compound disclosed herein, such as a compound of Formula (SI), (SI-A), (SI-B), (SI-1), (SI-B1), (SI-B2), (SI-C), (SI-C1), (SI-C2), (SI-C3), (SI-D), (SI-D1), (SI-D2), (SI-E), (SI-E1), (SII-B), (SII-C), (SIII), (SIV), (SIV-1), or (SIVa-1), is provided as a substantially pure stereoisomer. In some embodiments, the stereoisomer is provided in at least 80% enantiomeric excess, such as at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.9% enantiomeric excess.

[614] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[615] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases or inorganic or organic acids to form a pharmaceutically acceptable salt. In some embodiments, such salts are prepared in situ during the final isolation and purification of the compounds described herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[616] In some embodiments, the compounds described herein exist as solvates. In some embodiments are methods of treating diseases by administering such solvates. Further described herein are methods of treating diseases by administering such solvates as pharmaceutical compositions.

[617] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran, or MeOH. In addition, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[618] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques known in the art. Materials used herein are either commercially available or prepared by synthetic methods generally known in the art. These schemes are not limited to the compounds listed in the examples or by any particular substituents, which are employed for illustrative purposes. Although various steps are described and depicted

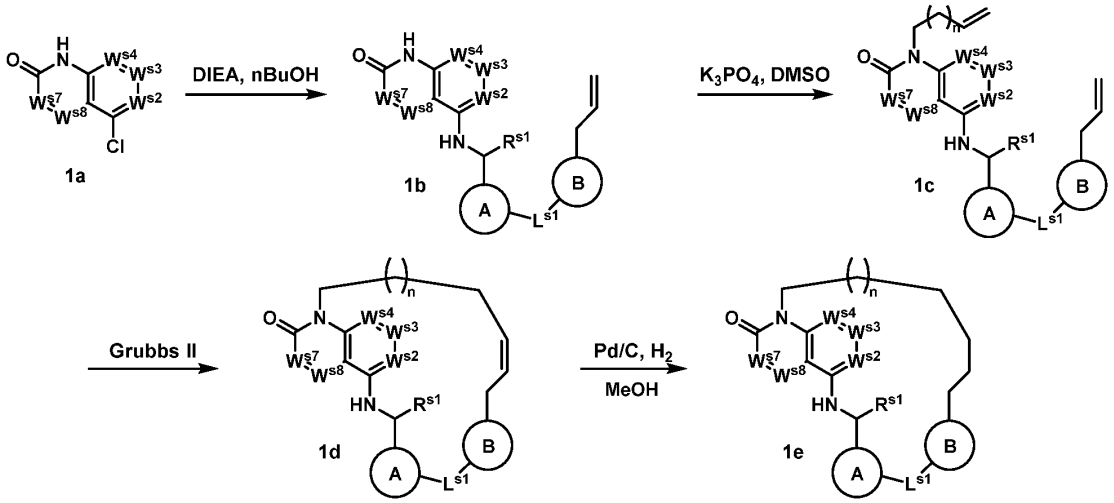
in **Schemes 1-16**, the steps in some cases may be performed in a different order than the order shown in **Schemes 1-16**. Various modifications to these synthetic reaction schemes may be made and will be suggested to one skilled in the art having referred to the present disclosure. Numberings or R groups in each scheme typically have the same meanings as those defined elsewhere herein unless otherwise indicated.

[619] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10 °C to 200 °C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, e.g., taking place at about atmospheric pressure within a temperature range of about -10 °C to about 110 °C over a period of about 1 to about 24 hours; reactions left to run overnight average a period of about 16 hours.

[620] Synthetic procedures for certain compounds may be found in PCT/US2023/066569, U.S. App. No. 18/311,850, PCT/US2023/066570, U.S. App. No. 18/311,853, each of which is incorporated by reference in its entirety, including any compounds, formulas, recitations of compound variables, and synthetic methods disclosed therein.

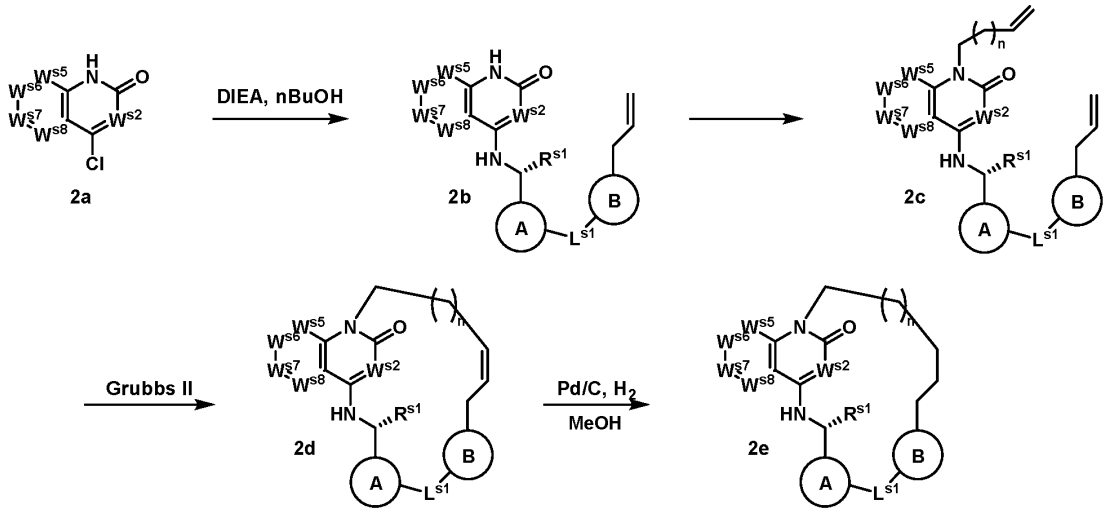
[621] In general, compounds of the disclosure may be prepared by the following reaction schemes:

Scheme 1



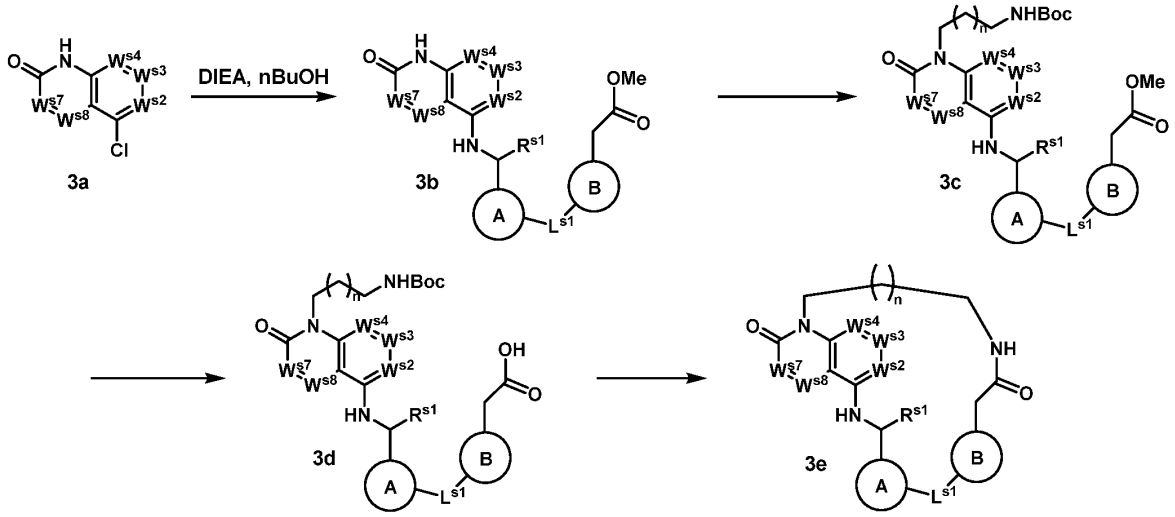
[622] In some embodiments, a compound of Formula **1e** may be prepared according to **Scheme 1**. For example, heteroaryl amine **1b** can be formed from chloride **1a** via a nucleophilic aromatic substitution reaction. Substitution of the lactam can proceed under basic conditions to give diene **1c**, which can undergo a cross metathesis reaction—such as Grubbs cross metathesis reaction—to form macrocycle **1d**. Optionally, **1d** may be subjected to one or more subsequent reactions, such as a hydrogenation reaction, to provide a compound of Formula **1e**.

Scheme 2



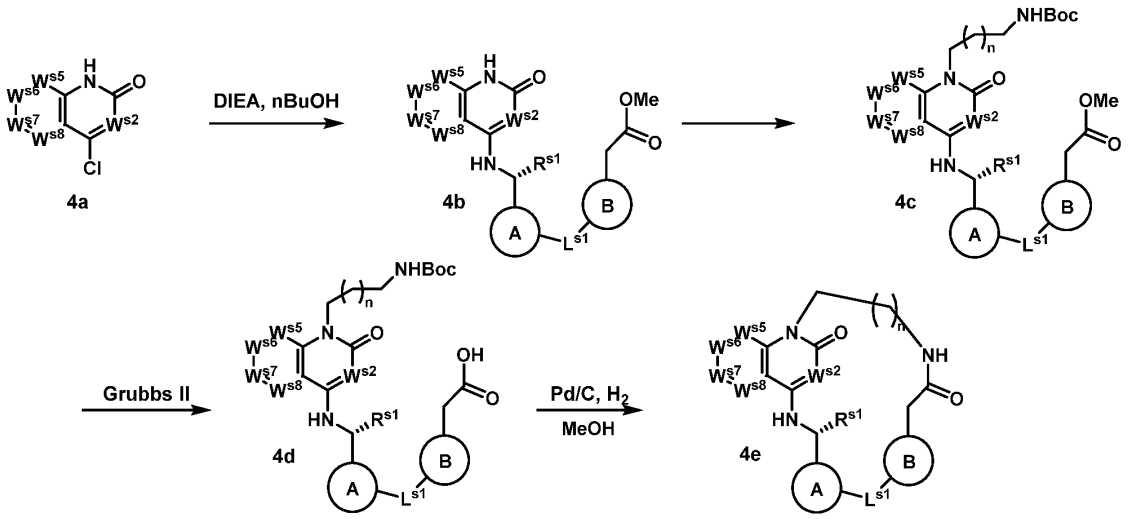
[623] Similarly, in some embodiments, a compound of Formula **2e** may be prepared according to **Scheme 2**. For example, heteroaryl amine **2b** can be formed from chloride **2a** via a nucleophilic aromatic substitution reaction. Substitution of the lactam can proceed under basic conditions to give diene **2c**, which can undergo a cross metathesis reaction—such as Grubbs cross metathesis reaction—to form macrocycle **2d**. Optionally, **2d** may be subjected to one or more subsequent reactions, such as a hydrogenation reaction, to provide a compound of Formula **2e**.

Scheme 3



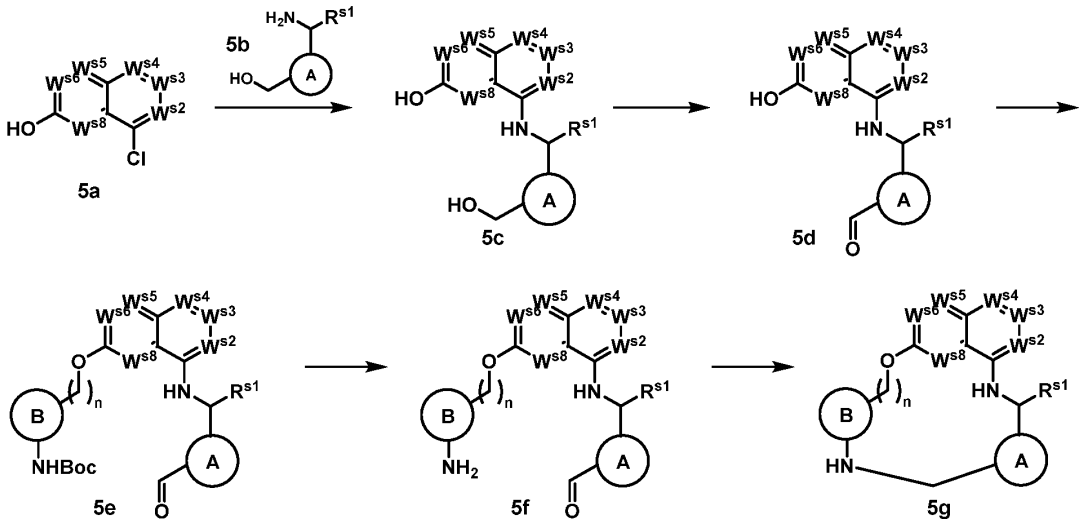
[624] In some embodiments, a compound of Formula **3e** may be prepared according to **Scheme 3**. For example, heteroaryl amine **3b** can be formed from chloride **3a** via a substitution reaction. Substitution of the lactam can give protected amine **3c**. Hydrolysis of the ester can form carboxylic acid **3d**, which can undergo deprotection and peptide coupling reactions to afford macrocycle of Formula **3e**.

Scheme 4



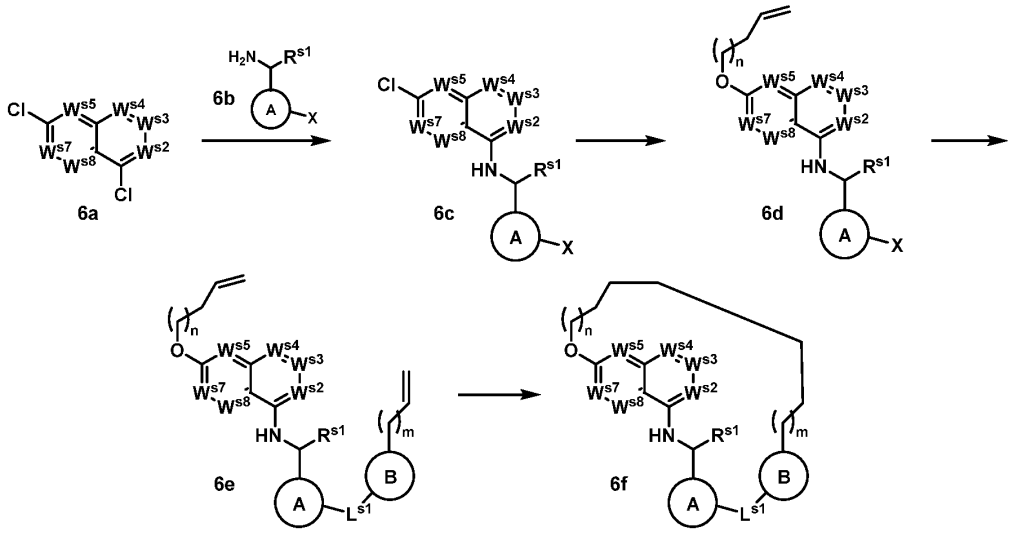
[625] Similarly, in some embodiments, a compound of Formula **4e** may be prepared according to **Scheme 4**. For example, heteroaryl amine **4b** can be formed from chloride **4a** via a substitution reaction. Substitution of the lactam can give protected amine **4c**. Hydrolysis of the ester can form carboxylic acid **4d**, which can undergo deprotection and peptide coupling reactions to afford a macrocycle of Formula **4e**.

Scheme 5



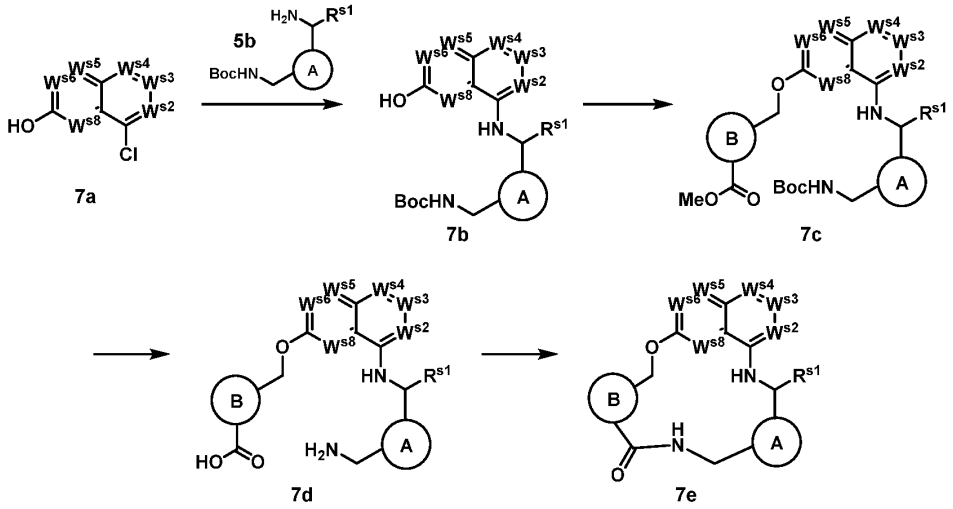
[626] In some embodiments, a compound of Formula **5g** may be prepared according to **Scheme 5**. For example, heteroaryl amine **3c** can be formed by coupling chloride **5a** with amine **5b**. Oxidation of the alcohol can give aldehyde **5d**, which can be followed with substitution of the phenol to give **5e**. Removal of the amine protecting group can afford **5f**, which can undergo a reductive amination to form a macrocycle of Formula **5g**.

Scheme 6



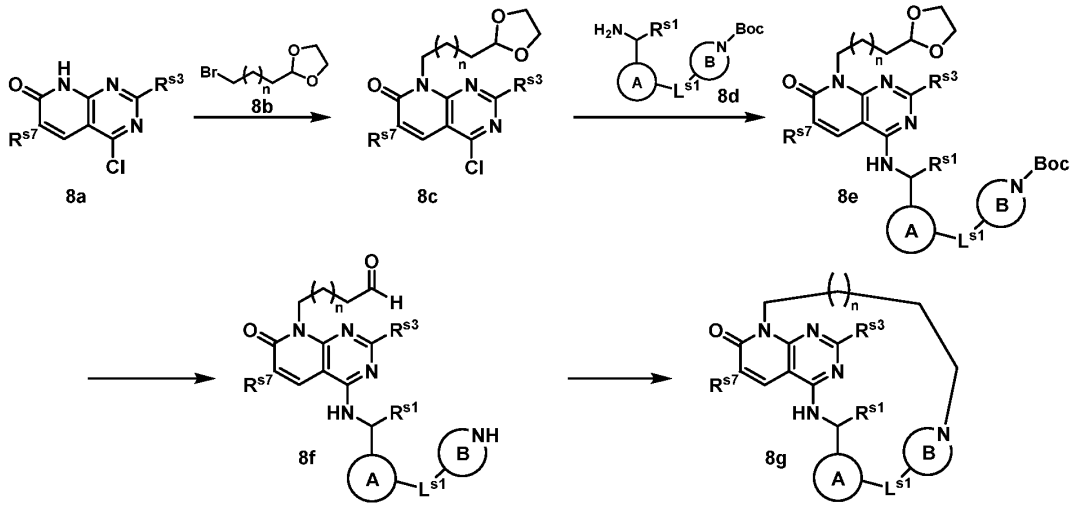
[627] In some embodiments, a compound of Formula **6f** may be prepared according to **Scheme 6**. For example, heteroaryl amine **6c** can be formed by coupling chloride **1a** with amine **6b**. Substitution of the phenol to olefin **6d** can be followed by installation of a second olefin to give diene **6e**. A cross metathesis reaction—such as Grubbs cross metathesis reaction—can be followed by hydrogenation of the resulting double bond to provide a macrocycle of Formula **6f**.

Scheme 7



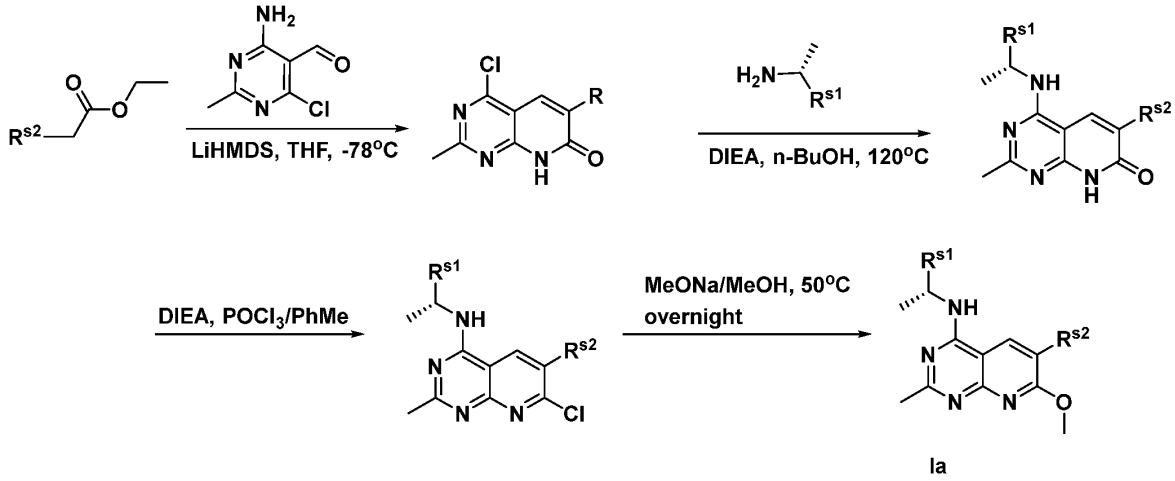
[628] In some embodiments, a compound of Formula **7e** may be prepared according to **Scheme 7**. For example, heteroaryl amine **7b** can be formed by coupling chloride **7a** with amine **5b**. Substitution of the phenol can give **7c**. Ester hydrolysis and deprotection of the amine can give **7d**, which can be cyclized to form a macrocycle of Formula **7e** via a peptide coupling reaction.

Scheme 8

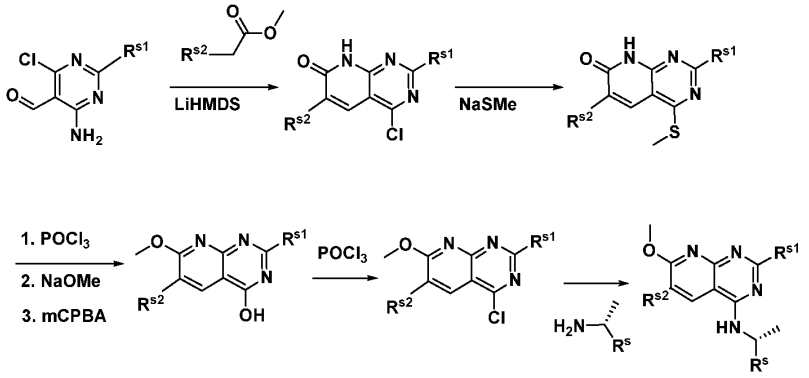


[629] In some embodiments, a compound of Formula **8g** may be prepared according to **Scheme 8**. For example, substitution of lactam **8a** with a suitable bromo dioxolane (**8b**) can give acetal **8c**. Nucleophilic aromatic substitution with amine **8d** can provide heteroaryl amine **8e**, which can be treated with a suitable acid, such as HCl, to remove the Boc protecting group and reveal the aldehyde. Finally, cyclization of **8f** can proceed via reductive amination conditions to give a macrocycle of Formula **8g**.

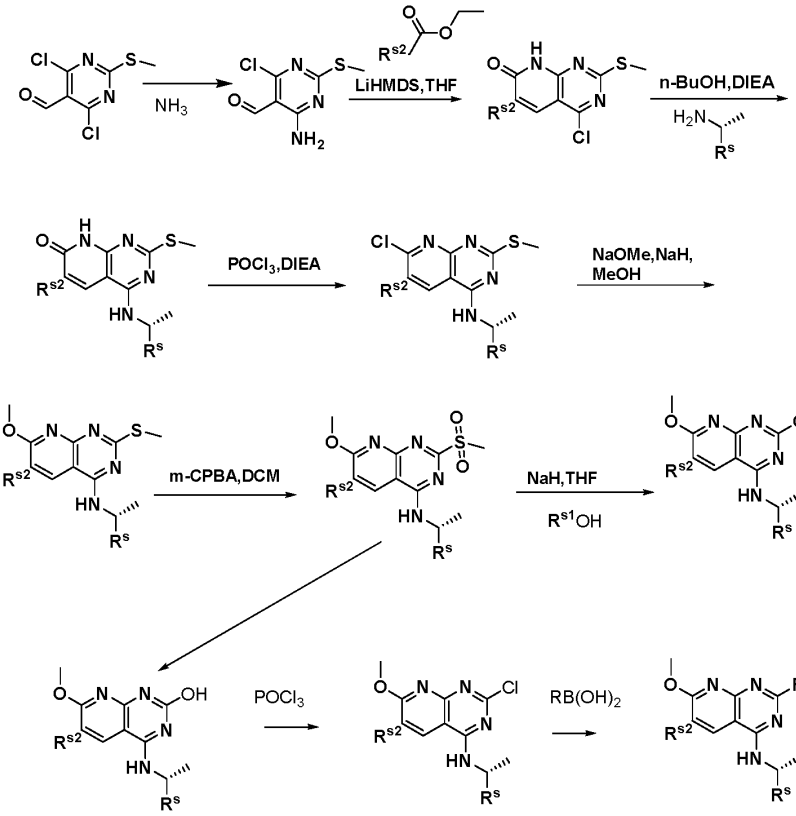
Scheme 9



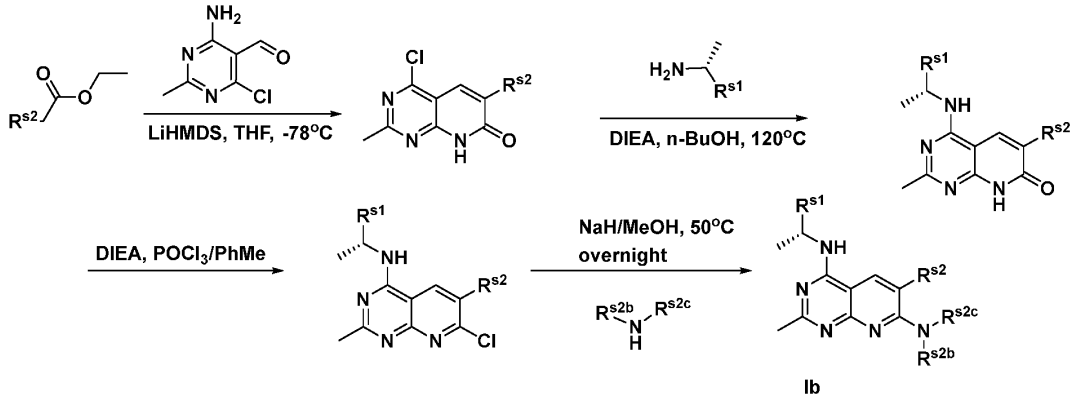
Scheme 10



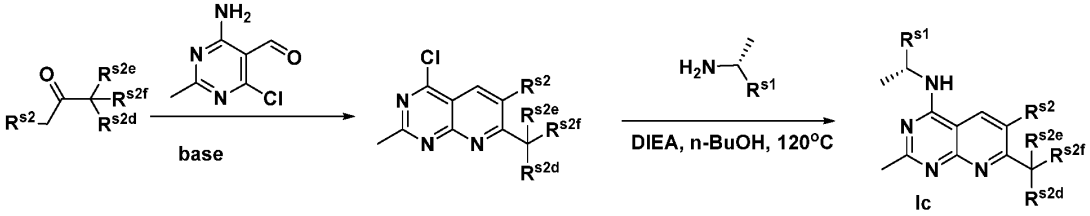
Scheme 11



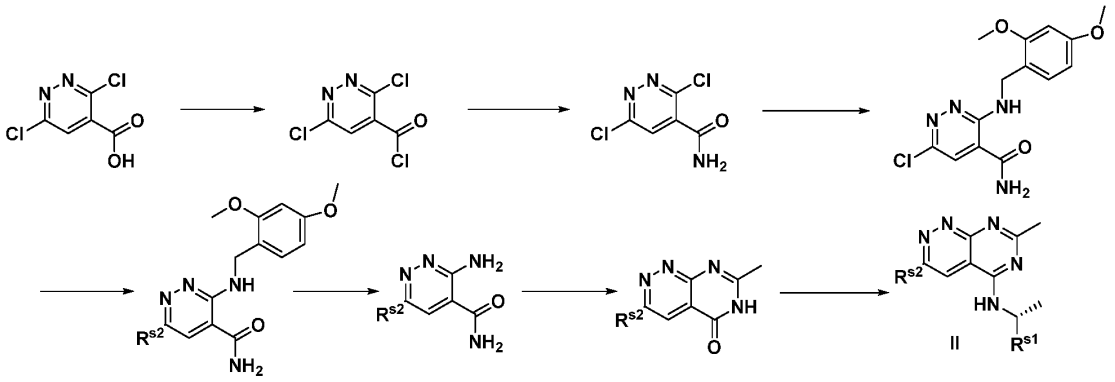
Scheme 12



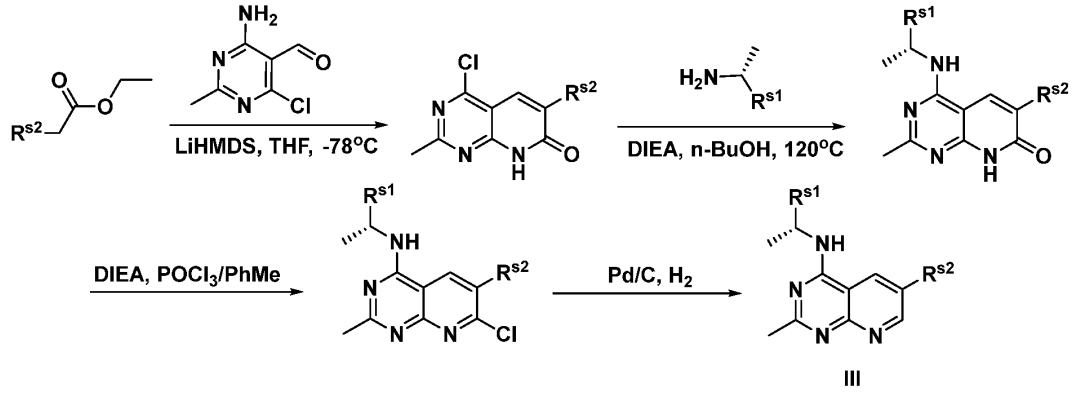
Scheme 13



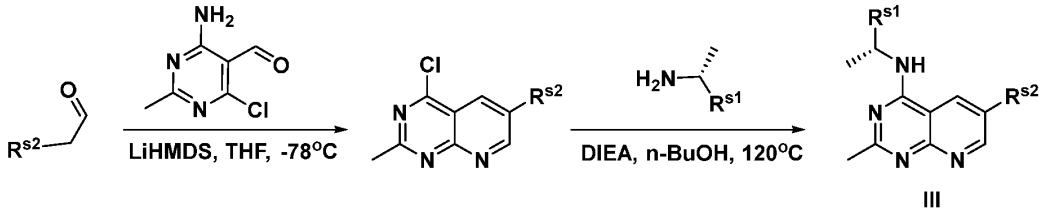
Scheme 14



Scheme 15



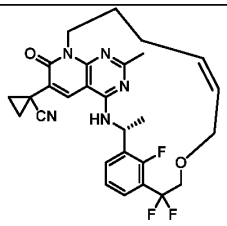
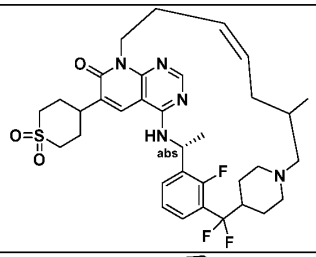
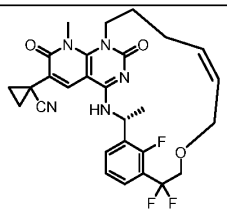
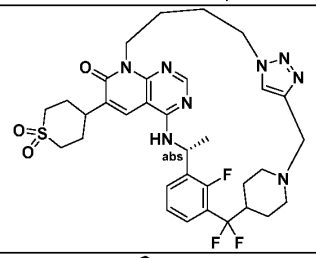
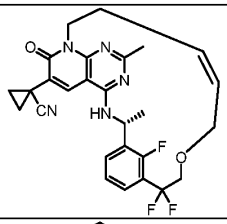
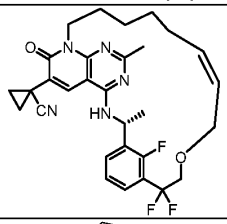
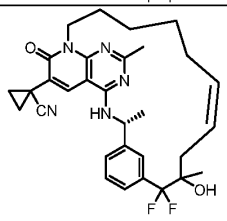
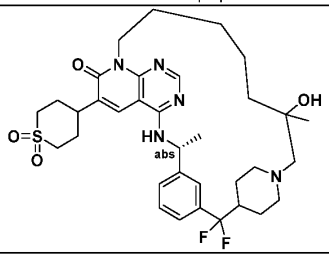
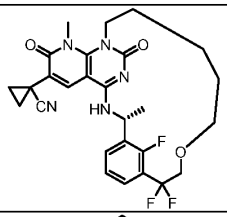
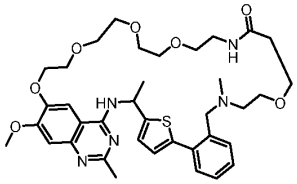
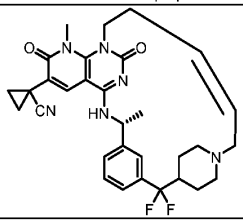
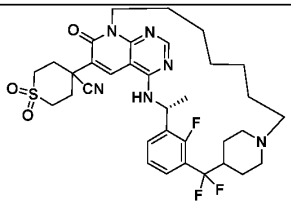
Scheme 16

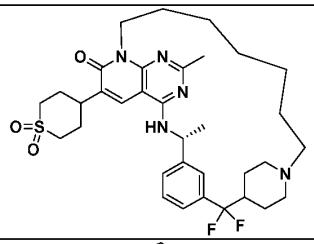
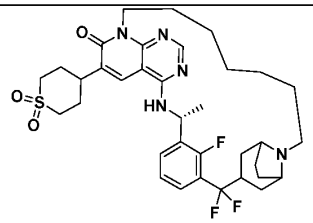
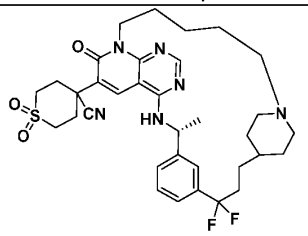
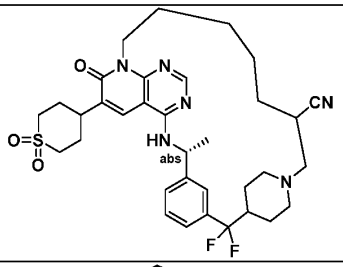
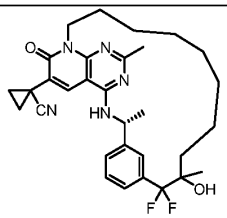
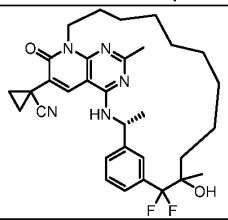
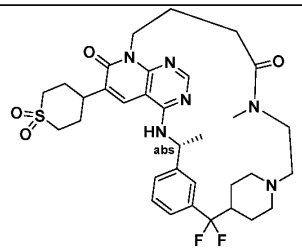
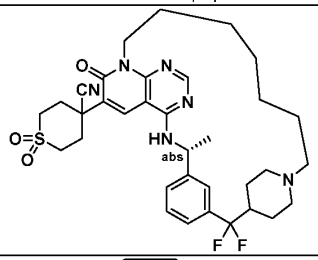
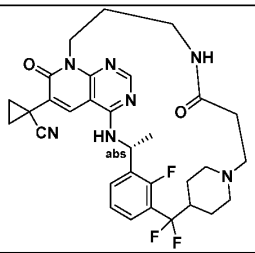
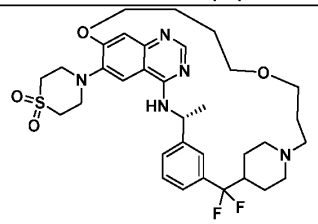
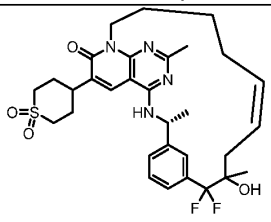
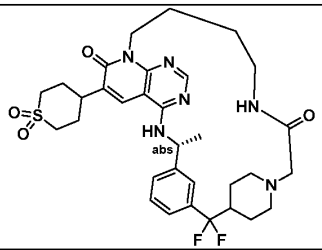
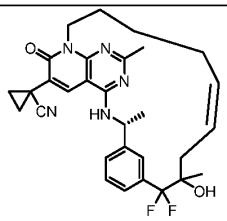
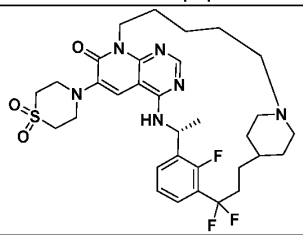


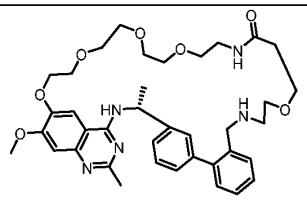
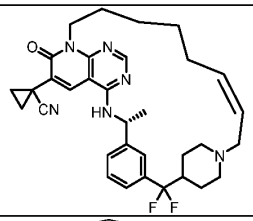
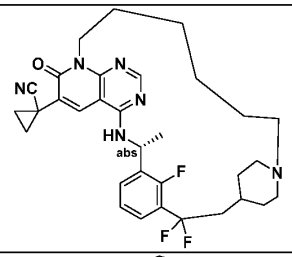
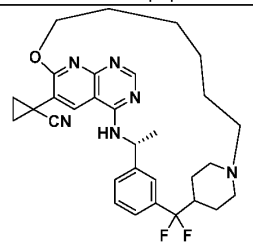
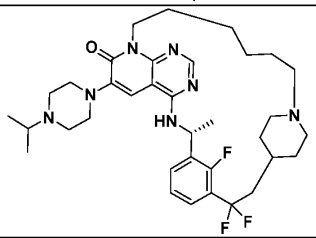
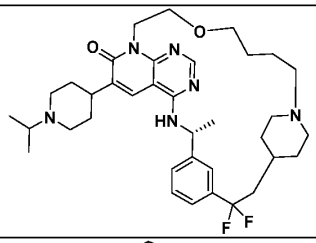
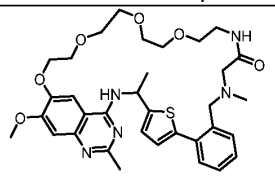
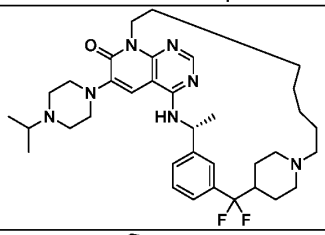
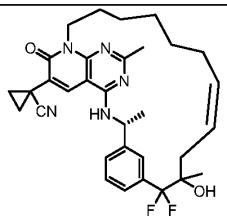
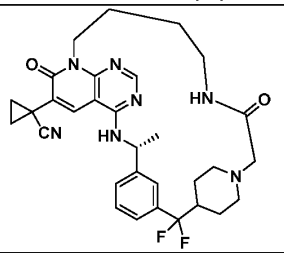
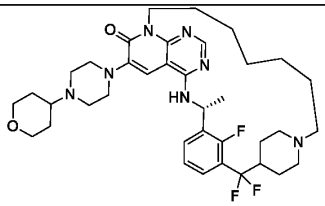
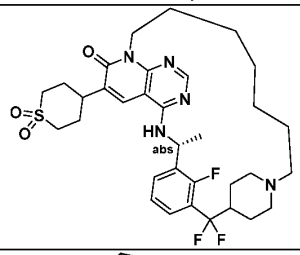
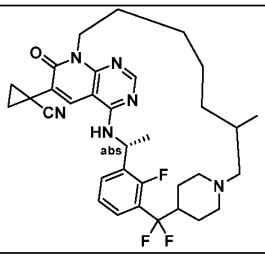
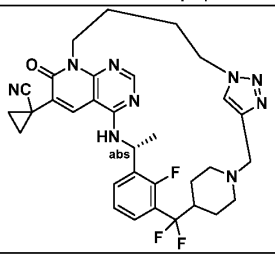
[630] Synthetic procedures for certain compounds may be found in PCT/US2022/018584, U.S. Pat. No. 11,648,254, PCT/US2023/065963, and U.S. App. No. 18/328,109, each of which is incorporated by reference in its entirety, including any compounds, formulas, recitations of compound variables, and synthetic methods disclosed therein. In some embodiments, a SOS1 inhibitor of the present disclosure is a compound described in U.S. Pat. No. 11,648,254, which is incorporated herein by reference in its entirety.

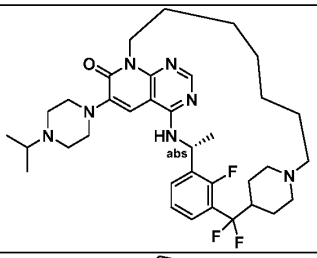
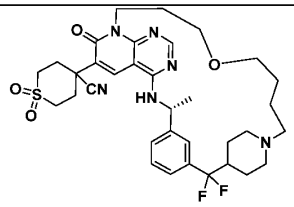
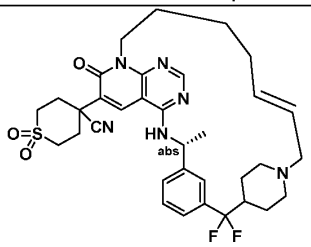
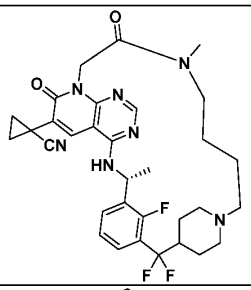
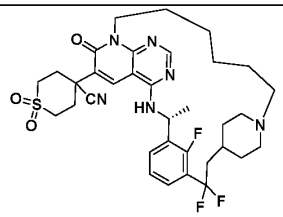
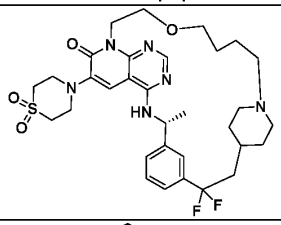
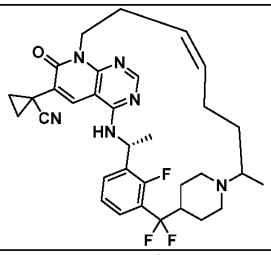
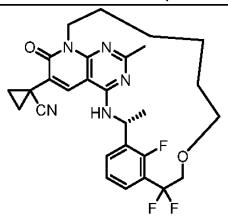
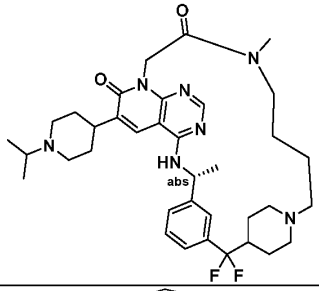
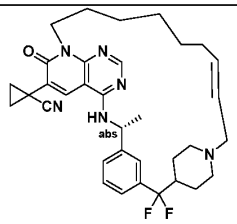
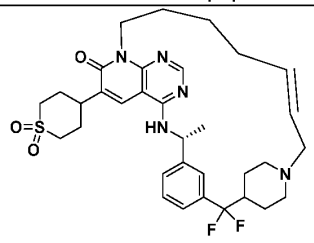
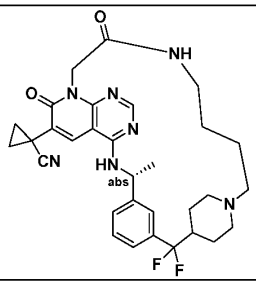
[631] In some embodiments, a compound of the present disclosure, for example, a compound of a formula given in **Table 2a** or **2b**, was synthesized according to one of the general routes outlined in **Schemes 1-16** or by methods generally known in the art. In some embodiments, exemplary compounds may include, but are not limited to, a compound selected from **Table 2a** or **2b**, or a salt or solvate thereof.

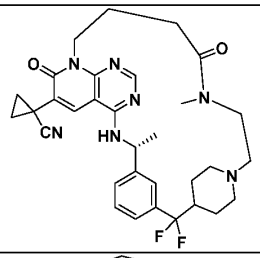
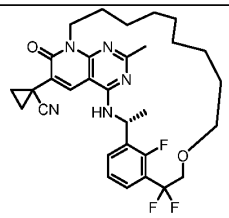
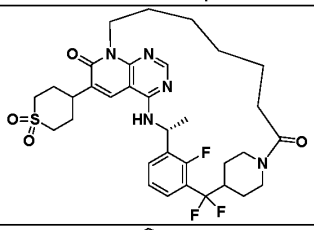
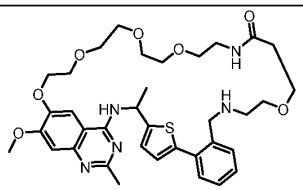
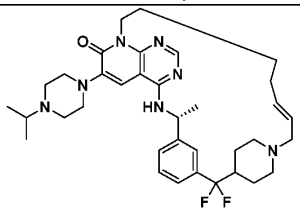
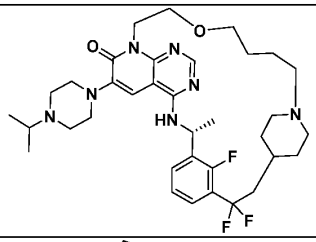
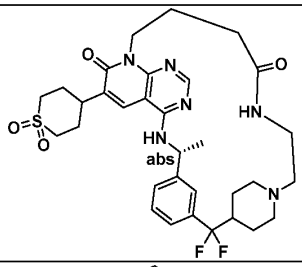
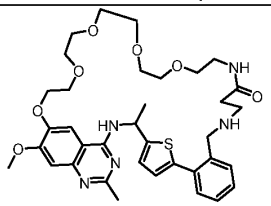
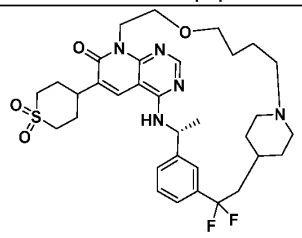
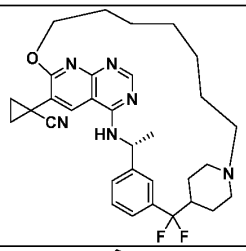
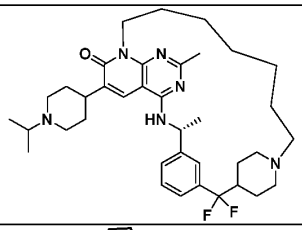
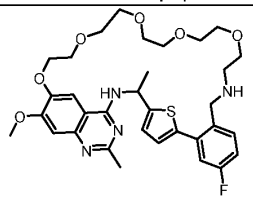
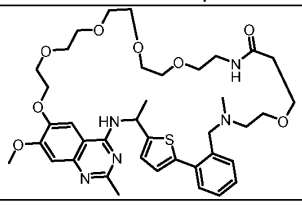
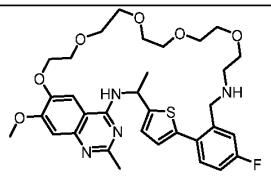
Table 2a

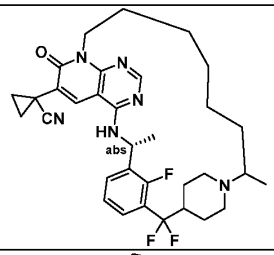
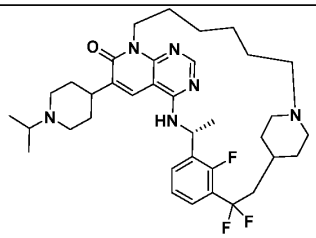
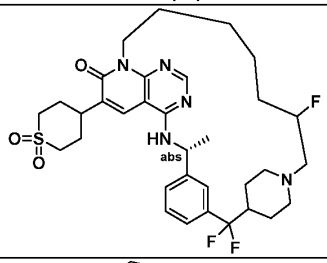
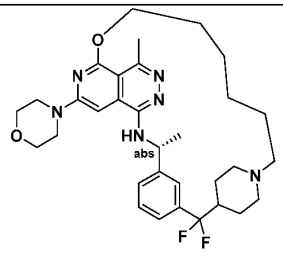
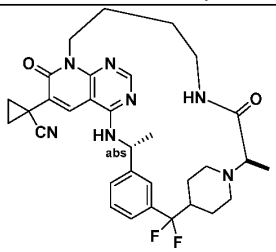
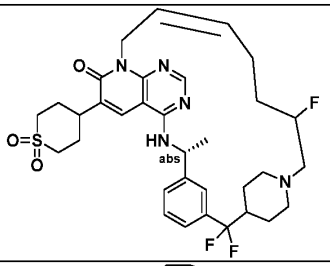
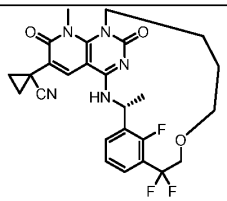
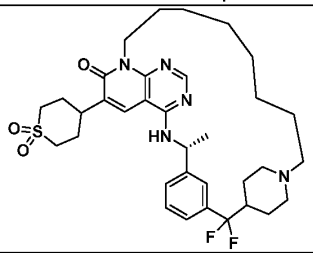
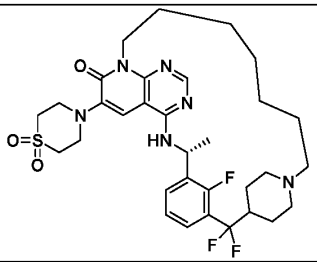
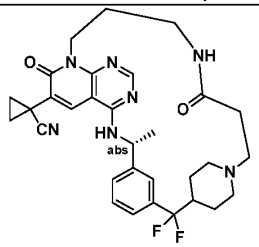
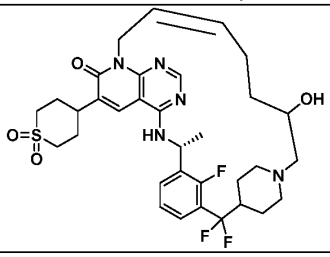
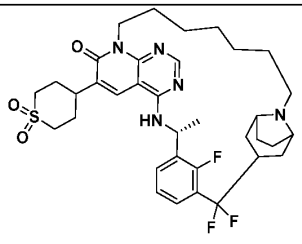
No.	Structure	$[M+H]^+$	No.	Structure	$[M+H]^+$
S1		524.4	S107		658.2
S2		540.4	S108		685.2
S3		510.4	S109		552.4
S4		548.3	S110		658.3
S5		528.4	S111		708.3
S6		561.4	S112		671.5

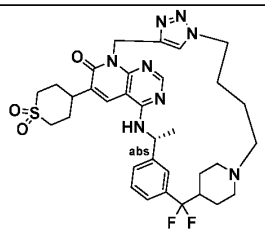
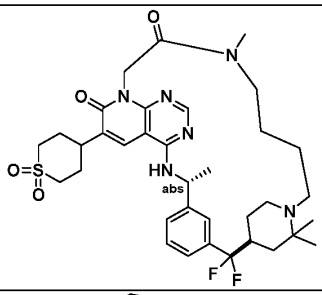
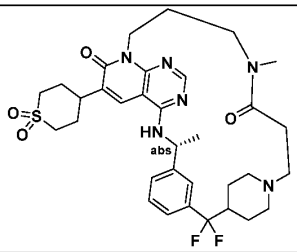
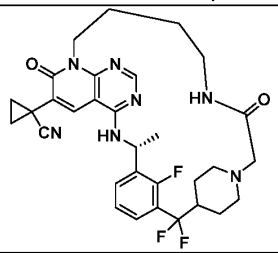
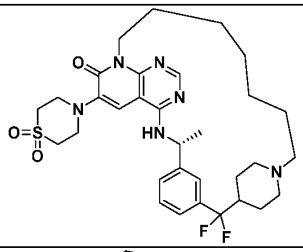
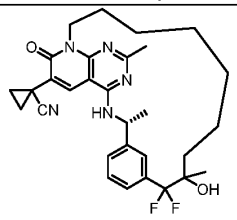
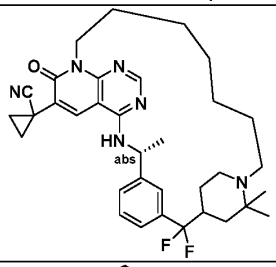
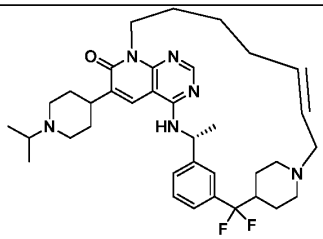
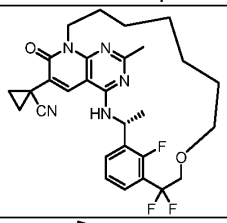
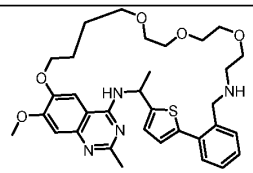
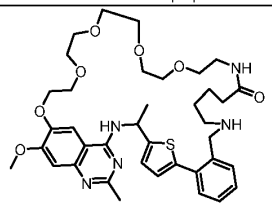
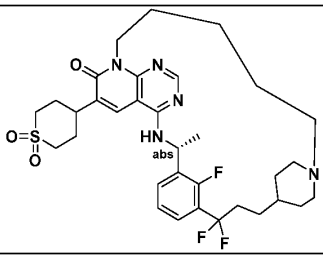
S7		644.5	S113		672.3
S8		653.3	S114		653.2
S9		550.4	S115		564.4
S10		657.4	S116		653.4
S11		594.5	S117		644.4
S12		601.4	S118		643.3
S13		534.4	S119		647.3

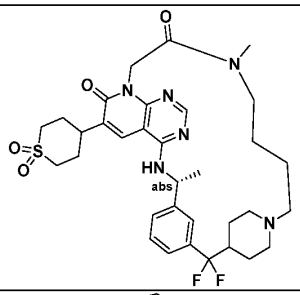
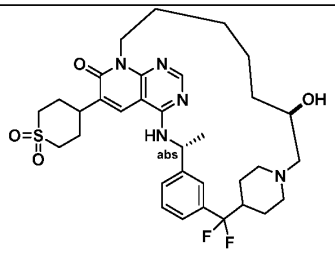
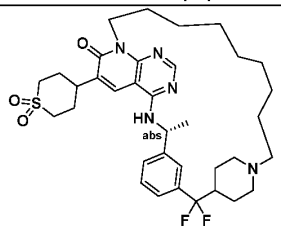
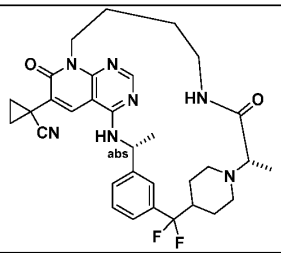
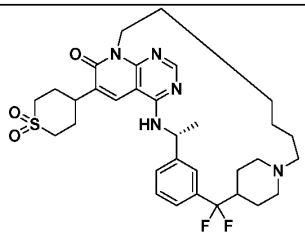
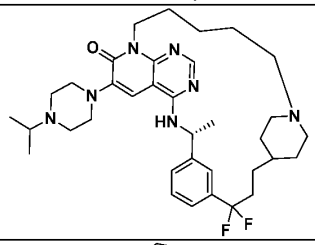
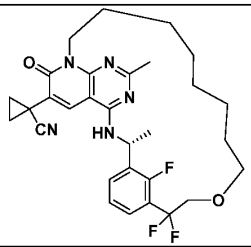
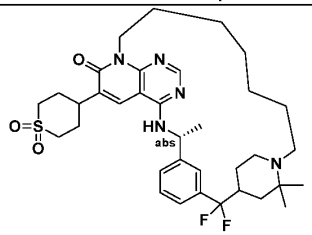
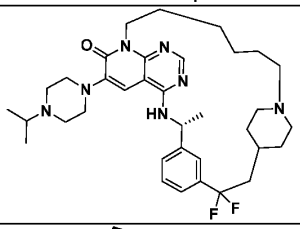
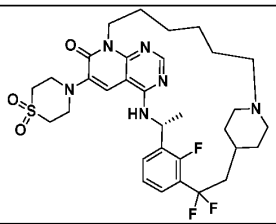
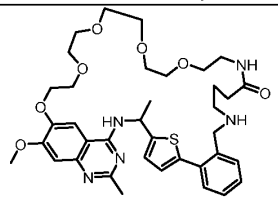
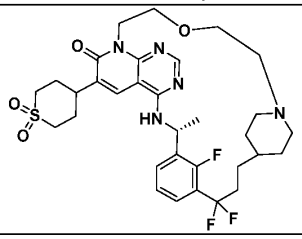
S14		688.4	S120		573.4
S15		579.4	S121		547.3
S16		640.8	S122		637.5
S17		650.3	S123		622.3
S18		562.4	S124		576.3
S19		682.5	S125		646.3
S20		593.4	S126		618.4

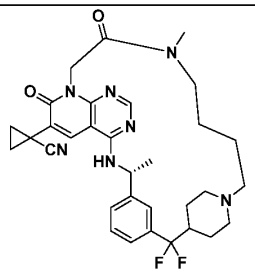
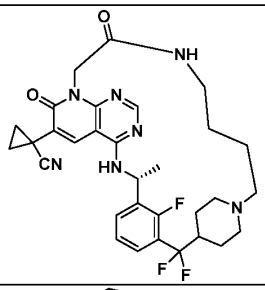
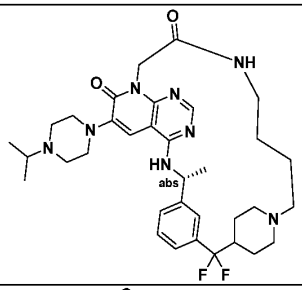
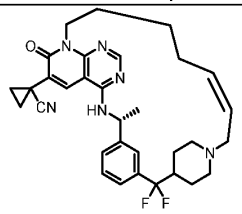
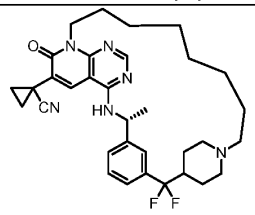
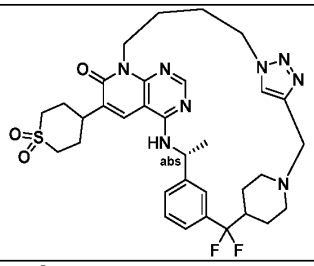
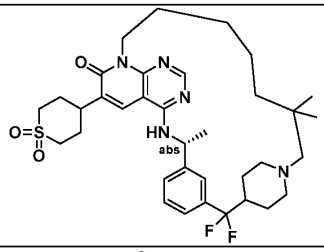
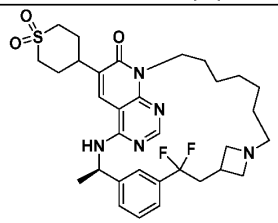
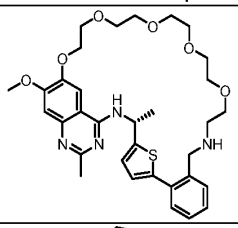
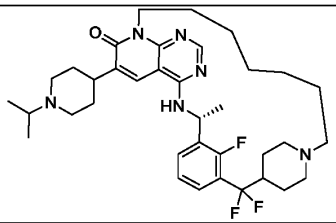
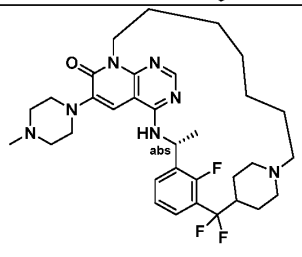
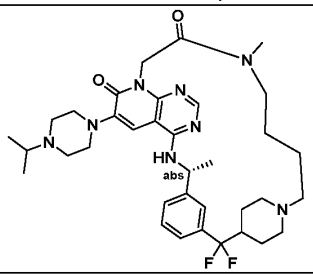
S21		640.3	S127		669.3
S22		651.3	S128		608.4
S23		671.3	S129		645.4
S24		591.5	S130		526.4
S25		650.3	S131		587.3
S26		626.4	S132		576.7

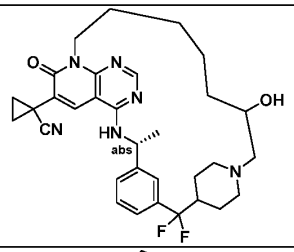
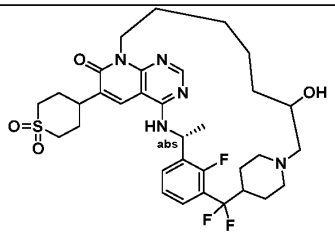
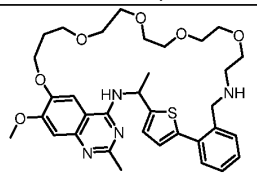
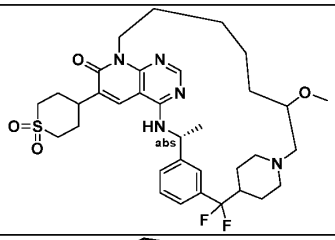
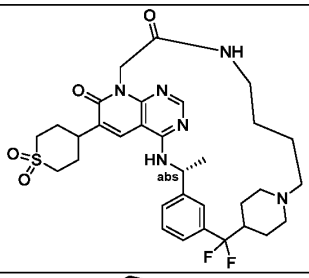
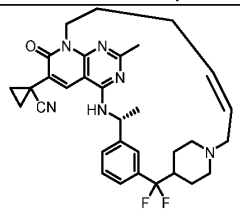
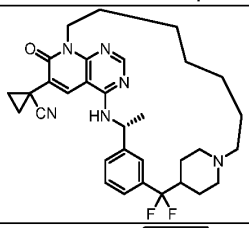
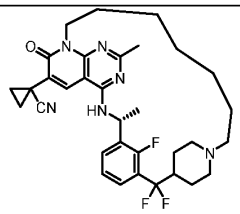
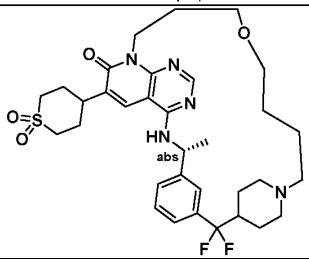
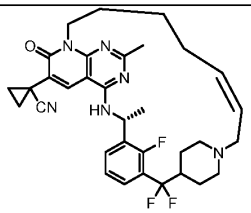
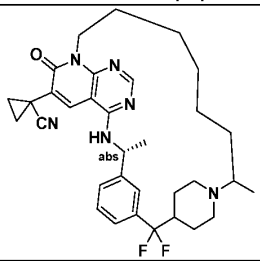
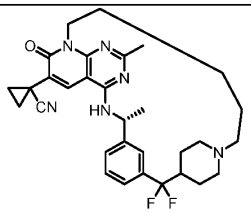
S27		590.3	S133		568.5
S28		660.2	S134		694.3
S29		620.3	S135		656.7
S30		643.4	S136		694.3
S31		664.5	S137		561.4
S32		635.6	S138		641.3
S33		752.4	S139		641.3

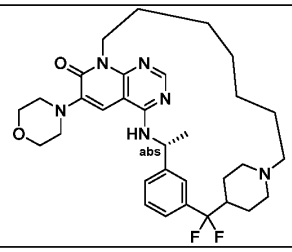
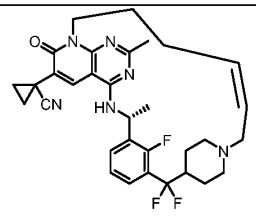
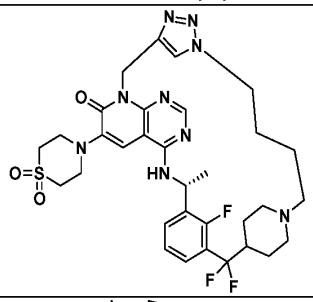
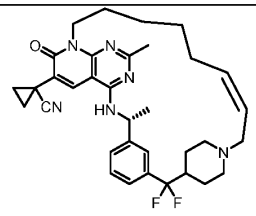
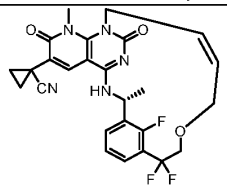
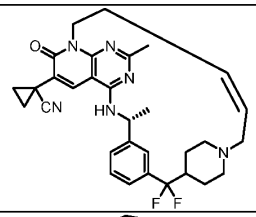
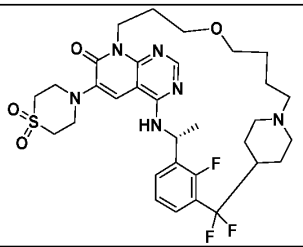
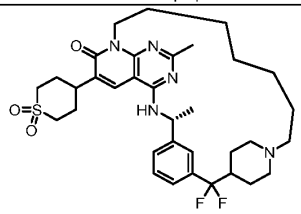
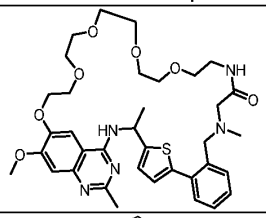
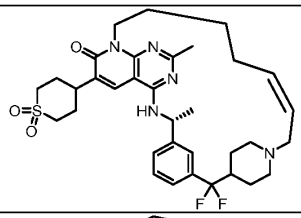
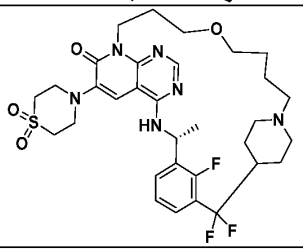
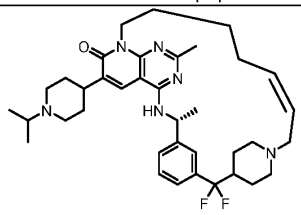
S34		593.4	S140		639.3
S35		646.4	S141		581.2
S36		590.3	S142		644.2
S37		514.3	S143		642.4
S38		647.6	S144		576.3
S39		660.4	S145		672.3

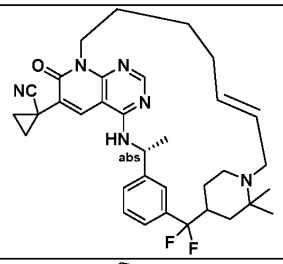
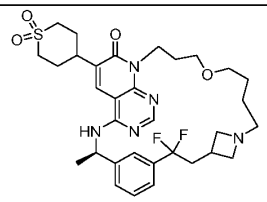
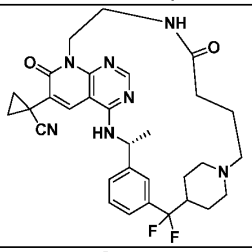
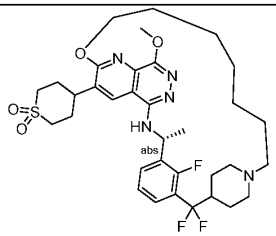
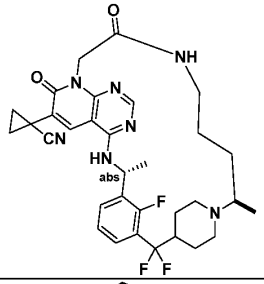
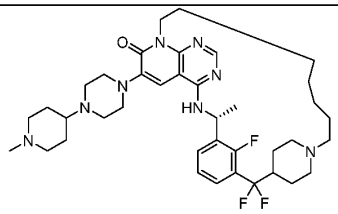
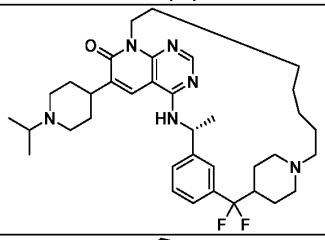
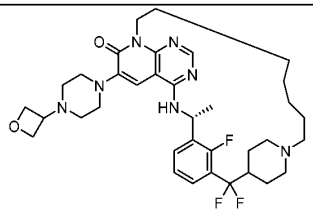
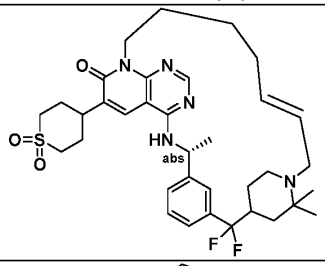
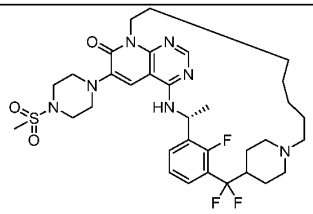
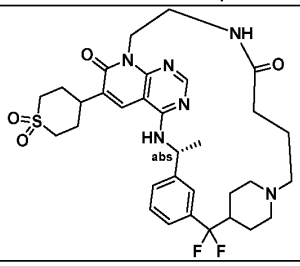
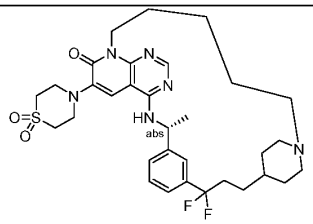
S40		667.3	S146		685.3
S41		657.4	S147		594.3
S42		629.3	S148		536.4
S43		589.3	S149		619.4
S44		540.4	S150		607.3
S45		722.4	S151		646.2

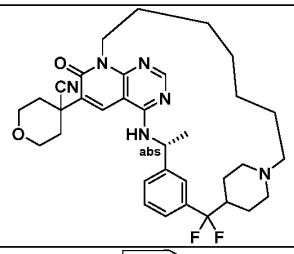
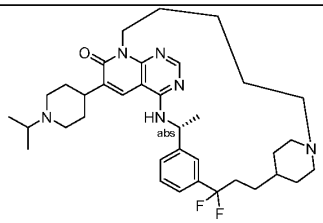
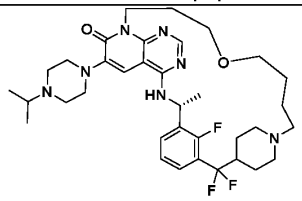
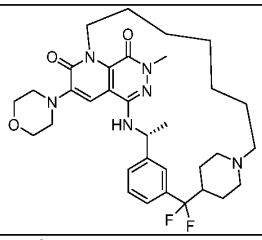
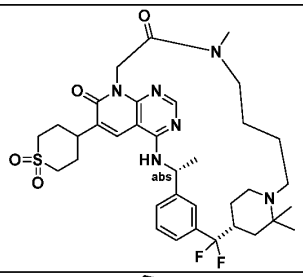
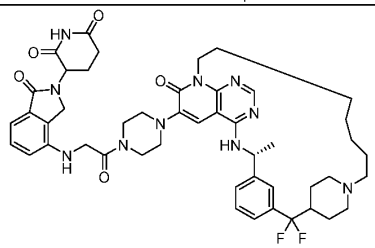
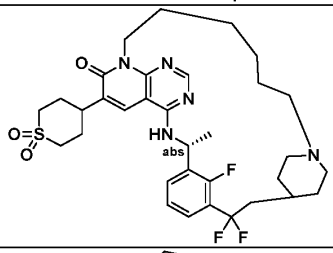
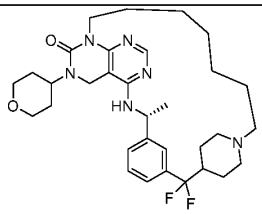
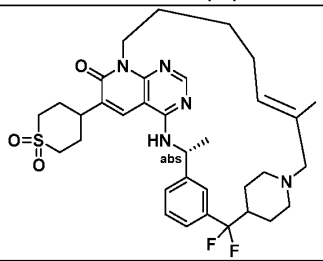
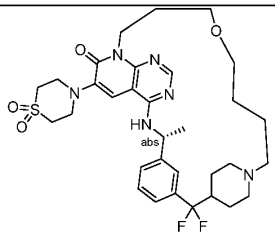
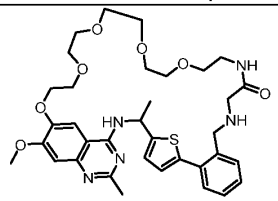
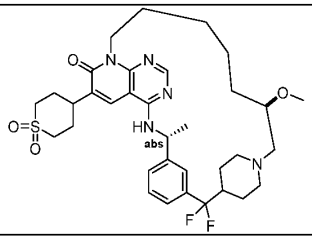
S46		657.3	S152		644.2
S47		656.3	S153		590.3
S48		614.4	S154		622.4
S49		554.3	S155		656.3
S50		622.4	S156		646.8
S51		708.3	S157		648.6

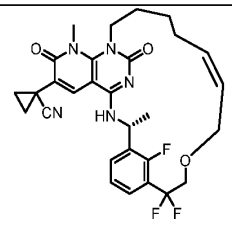
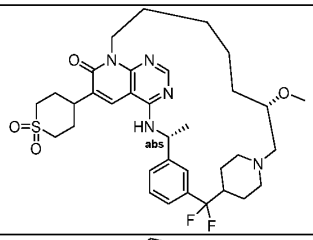
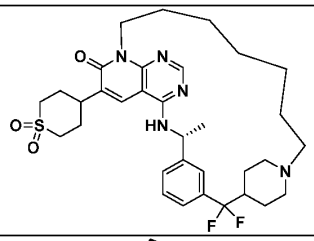
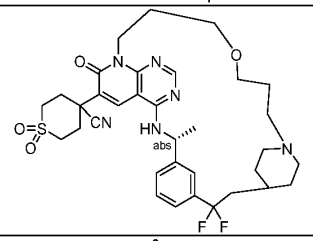
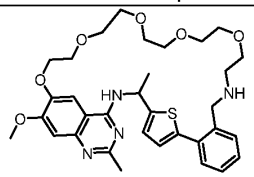
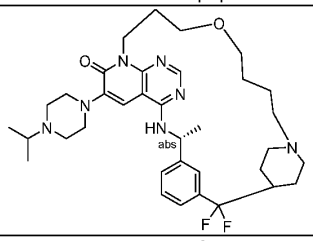
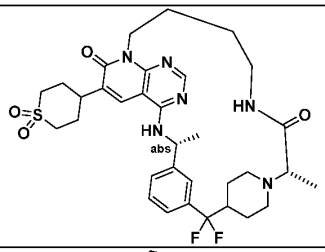
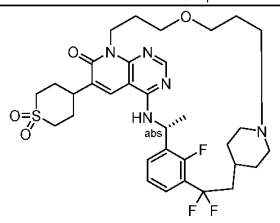
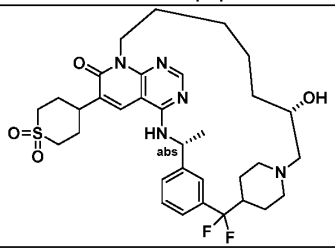
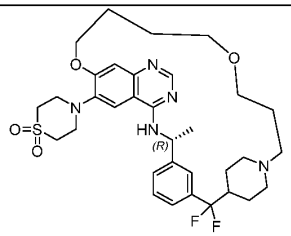
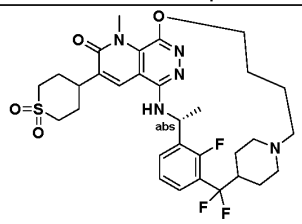
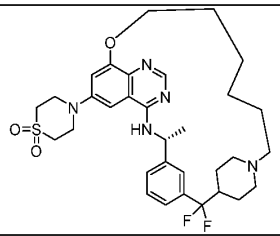
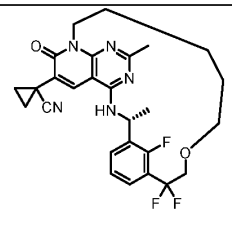
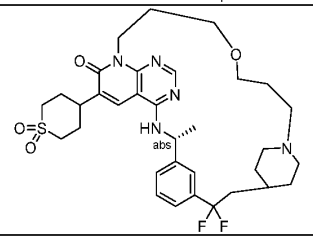
S52		590.3	S158		594.7
S53		637.2	S159		559.4
S54		575.4	S160		667.3
S55		656.6	S161		614.3
S56		623.2	S162		639.7
S57		612.3	S163		651.3

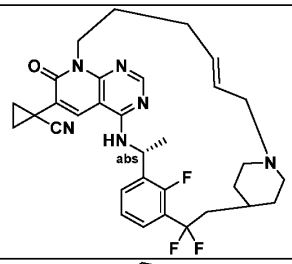
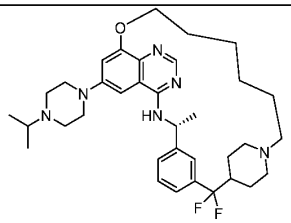
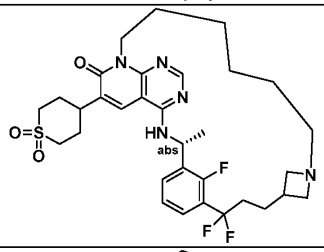
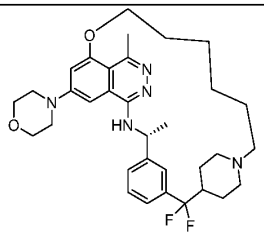
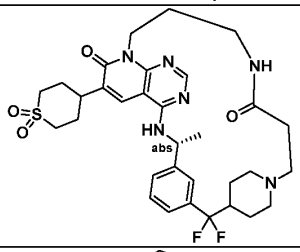
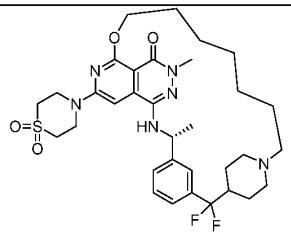
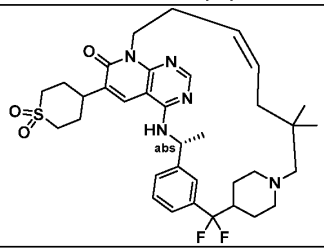
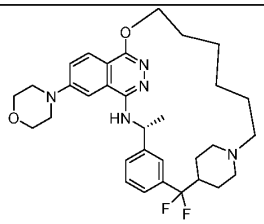
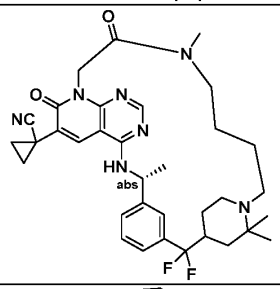
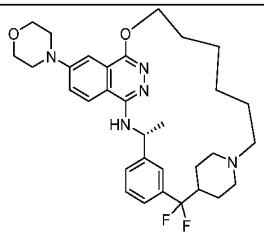
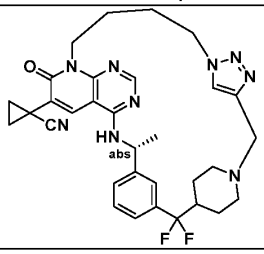
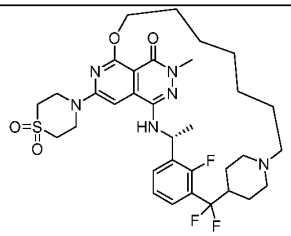
S58		577.3	S164		662.4
S59		637.3	S165		658.3
S60		643.3	S166		559.5
S61		561.5	S167		593.5
S62		644.5	S168		591.5
S63		575.3	S169		547.4

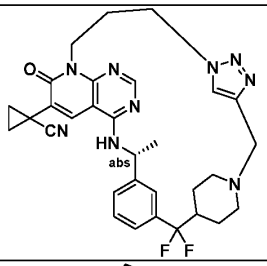
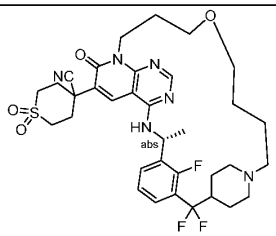
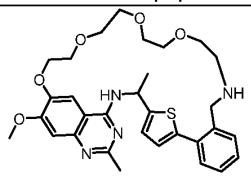
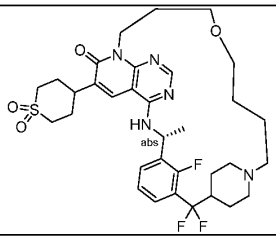
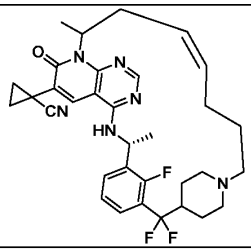
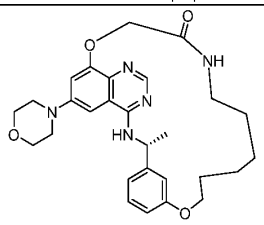
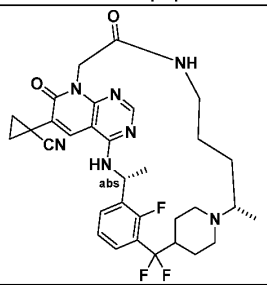
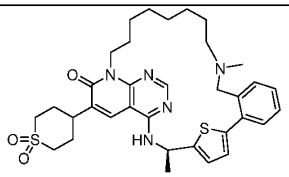
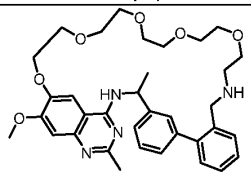
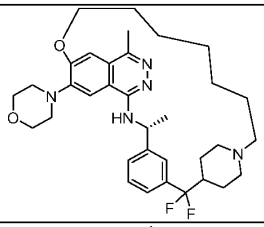
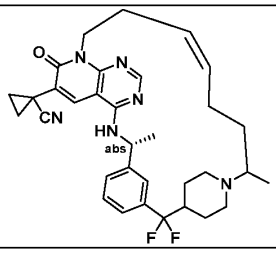
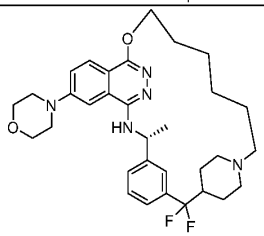
S64		581.3	S170		577.5
S65		686.2	S171		587.5
S66		512.3	S172		545.4
S67		640.4	S173		642.5
S68		694.3	S174		640.5
S69		663.3	S175		633.5

S70		587.4	S176		630.4
S71		576.3	S177		676.3
S72		608.3	S178		695.5
S73		621.6	S179		654.3
S74		654.3	S180		676.4
S75		643.2	S181		629.3

S76		605.2	S182		621.4
S77		656.6	S183		611.5
S78		685.3	S184		879.7
S79		646.1	S185		583.5
S80		640.3	S186		645.3
S81		680.3	S187		658.3

S82		554.4	S188		658.6
S83		628.3	S189		669.3
S84		623.3	S190		638.4
S85		657.3	S191		662.3
S86		644.3	S192		644.4
S87		634.2	S193		614.6
S88		512.4	S194		644.3

S89		577.2	S195		607.5
S90		632.2	S196		580.5
S91		643.2	S197		659.3
S92		654.4	S198		
S93		618.3	S200		
S94		600.3	S201		

S95		586.4	S202		687.3
S96		579.3	S203		662.3
S97		591.5	S204		506.4
S98		608.3	S205		634.5
S99		617.4	S206		594.5
S100		573.3	S207		566.2

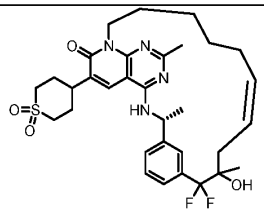
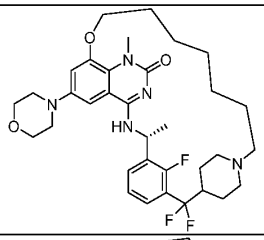
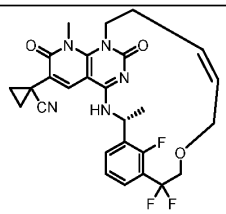
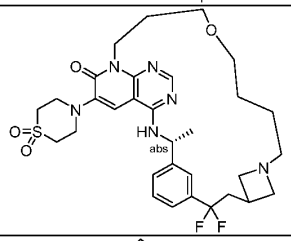
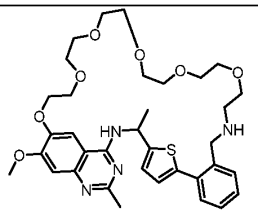
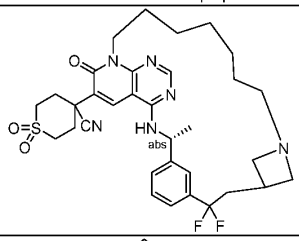
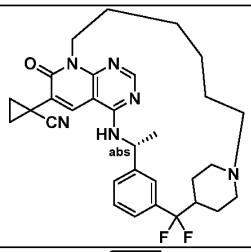
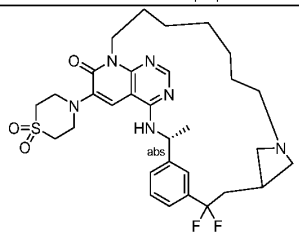
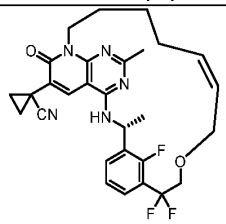
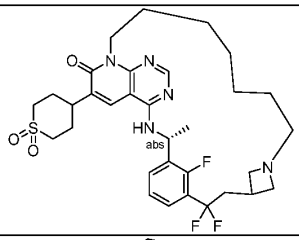
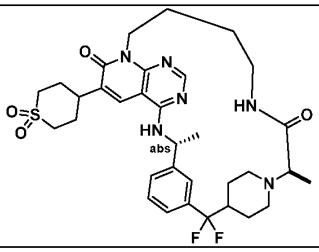
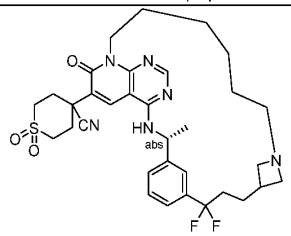
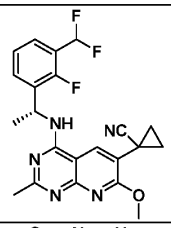
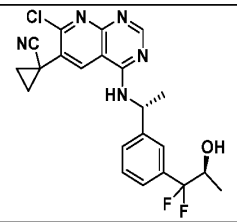
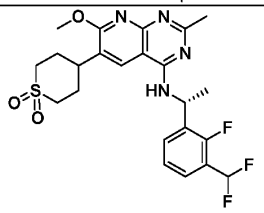
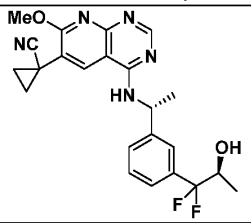
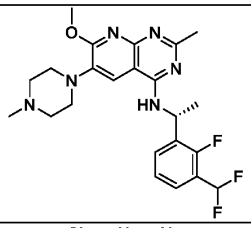
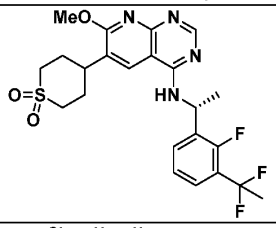
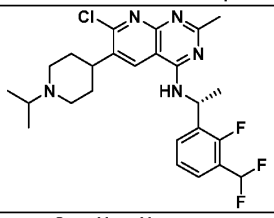
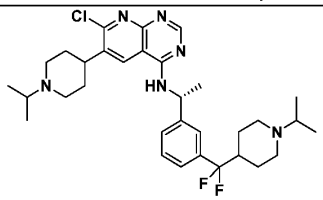
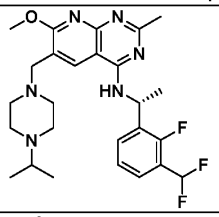
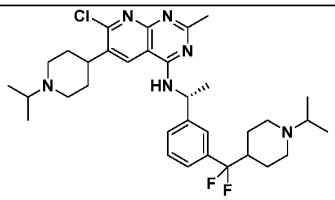
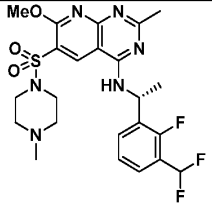
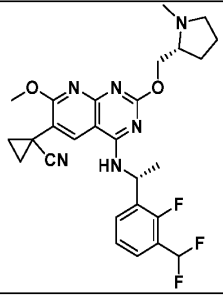
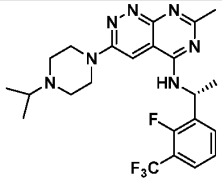
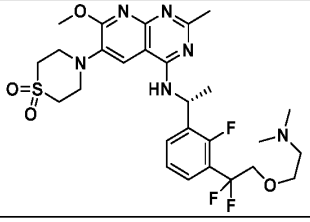
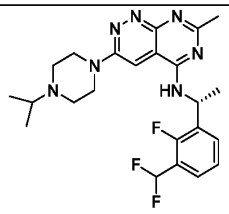
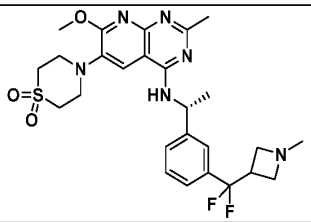
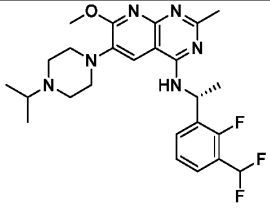
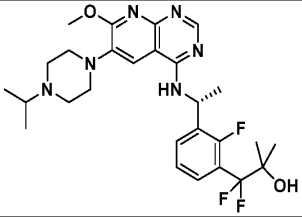
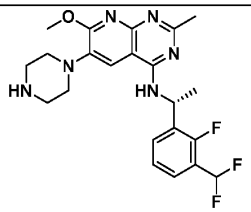
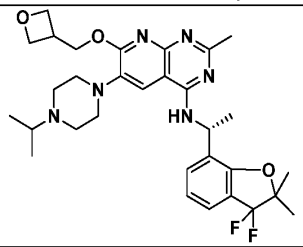
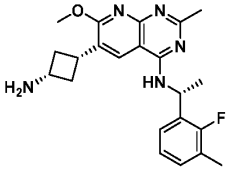
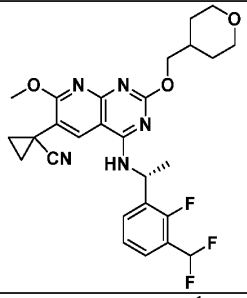
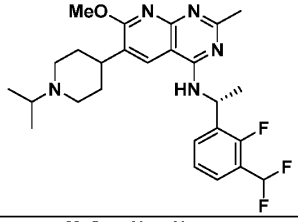
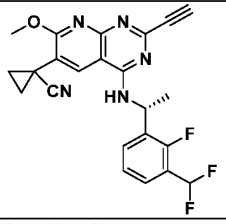
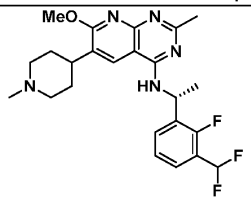
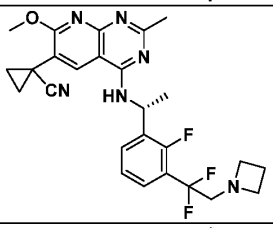
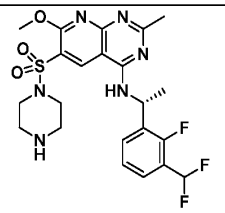
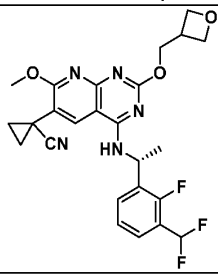
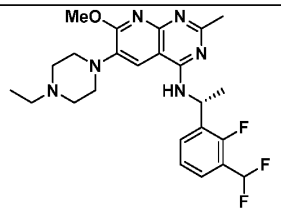
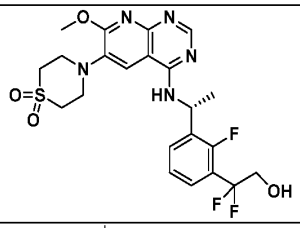
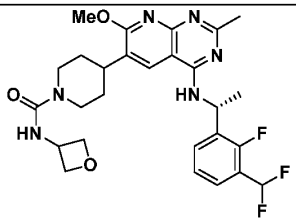
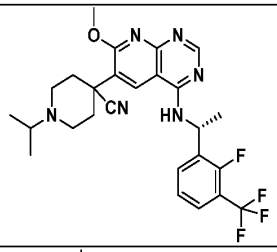
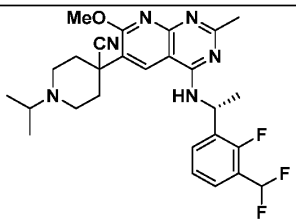
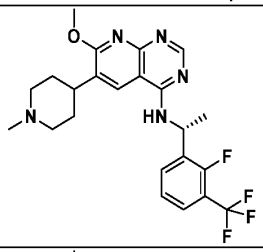
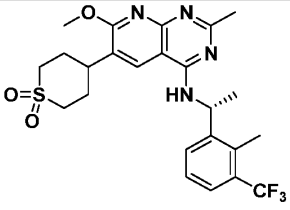
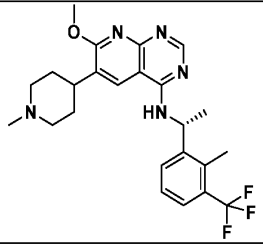
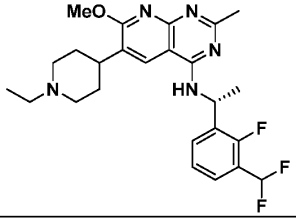
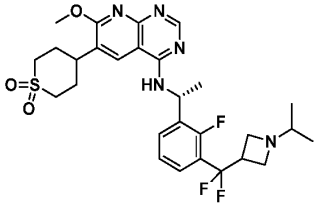
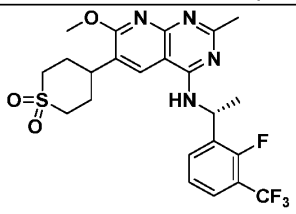
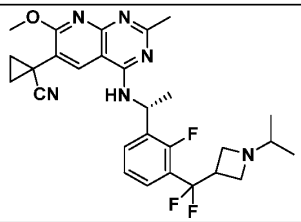
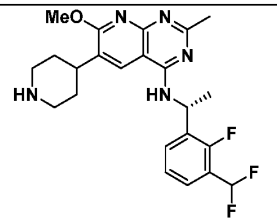
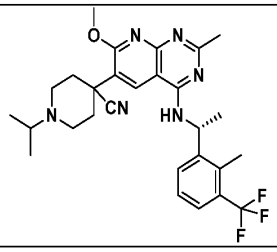
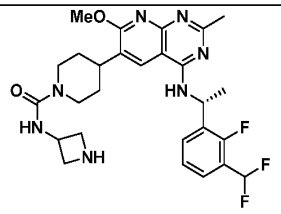
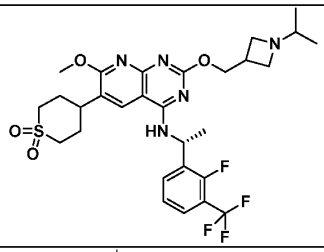
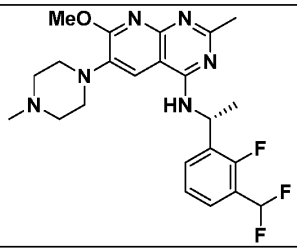
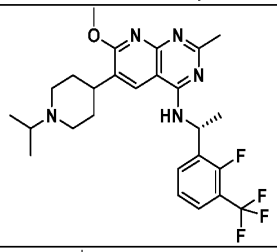
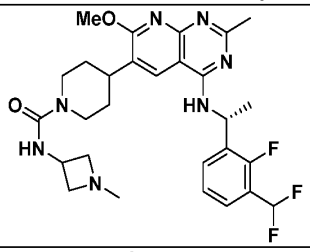
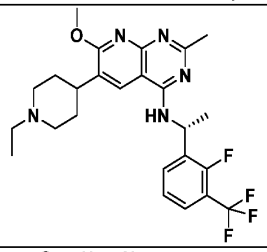
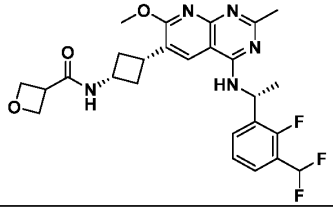
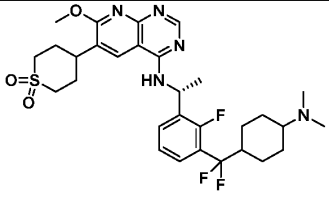
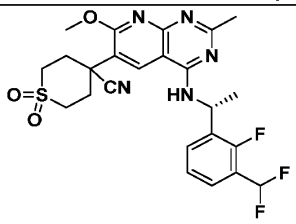
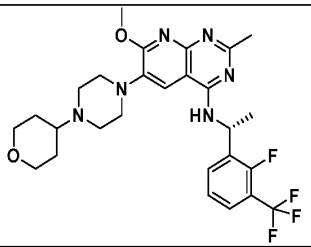
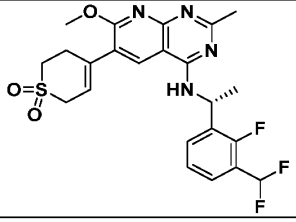
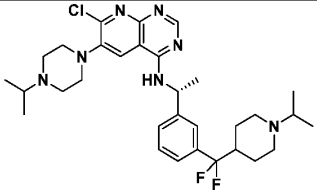
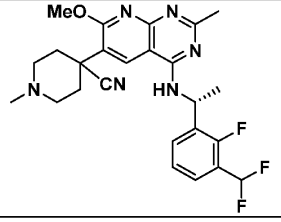
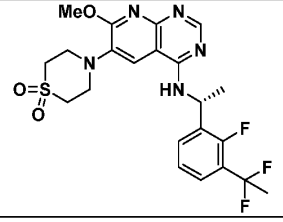
S101		615.4	S208		628.4
S102		526.4	S209		631.6
S103		667.3	S210		639.5
S104		547.3	S211		615.3
S105		538.4	S212		632.0
S106		657.3	S213		639.2

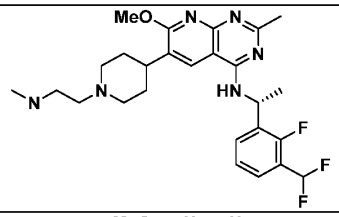
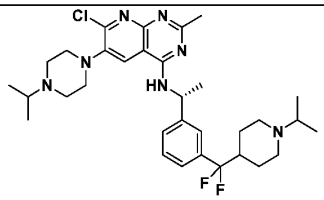
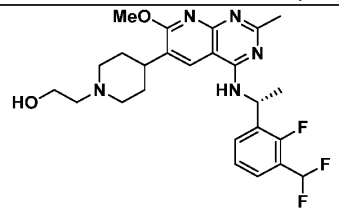
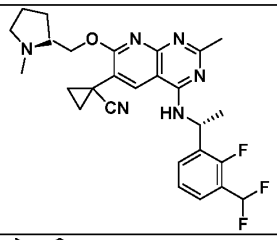
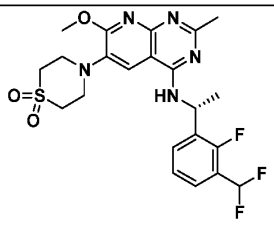
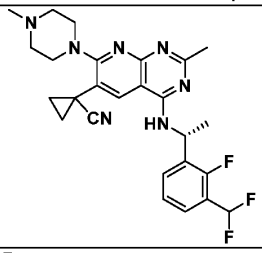
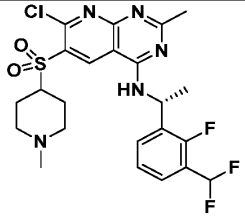
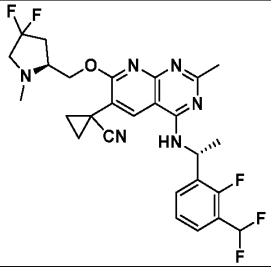
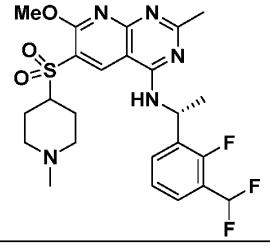
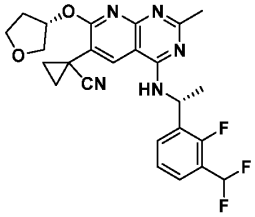
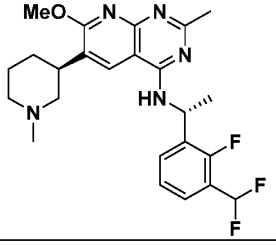
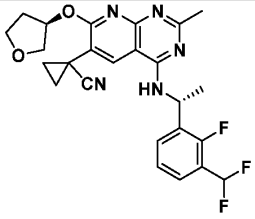
Table 2b

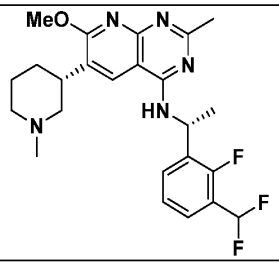
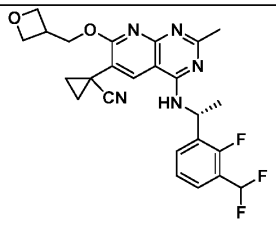
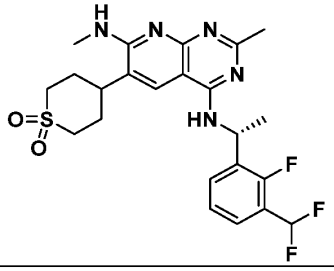
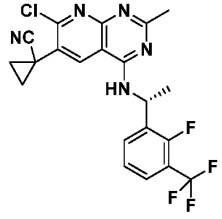
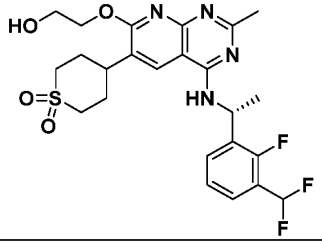
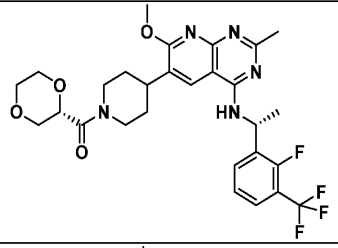
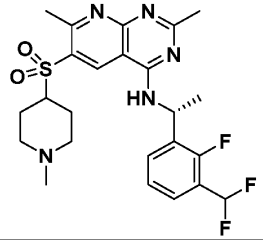
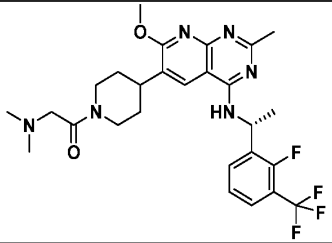
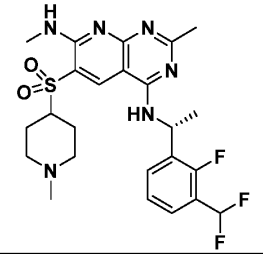
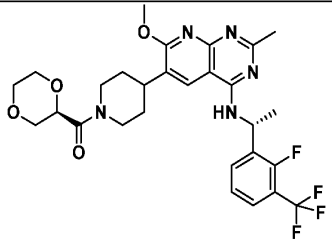
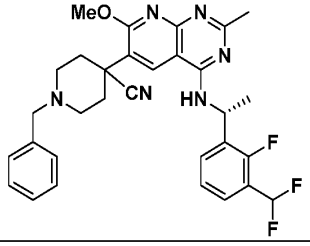
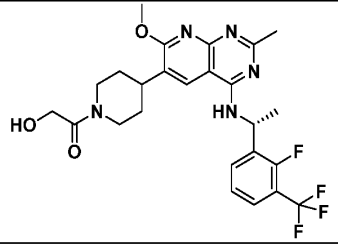
No.	Structure	[M+H]+	No.	Structure	[M+H]+
S1101		428.9	S1265		444.
S1102		495	S1266		440.2
S1103		461.2	S1267		495.3
S1104		492	S1268		585.3
S1105		503	S1269		599.6
S1106		525	S1270		527.5
S1107		478	S1271		596.5

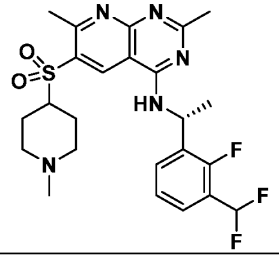
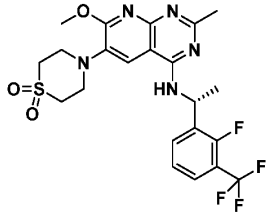
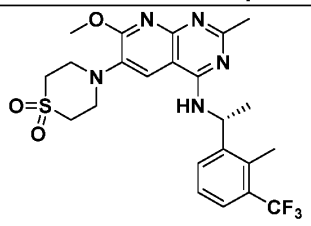
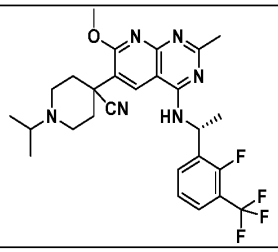
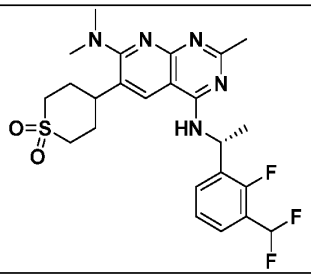
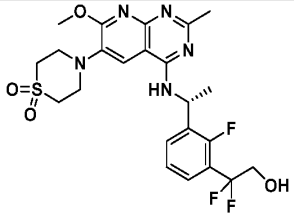
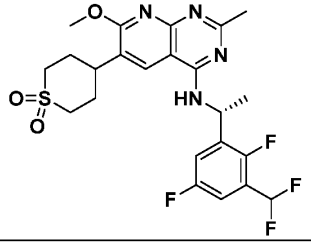
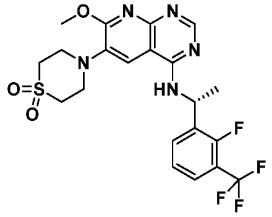
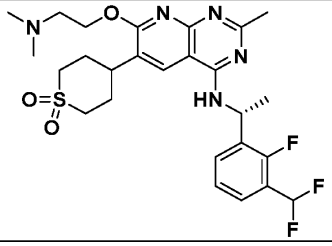
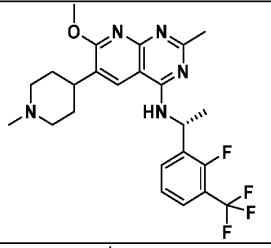
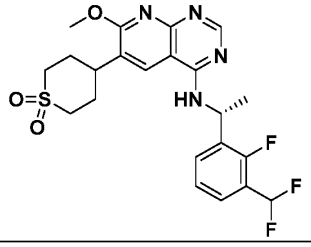
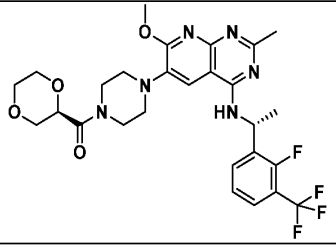
S1108		460	S1272		546.4
S1109		489.3	S1273		533.5
S1110		447.4	S1274		583.6
S1111		396.4	S1275		528.8
S1112		488.5	S1276		438.3
S1113		460.4	S1277		497.4
S1114		511.4	S1278		500.4

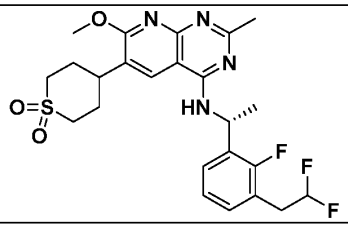
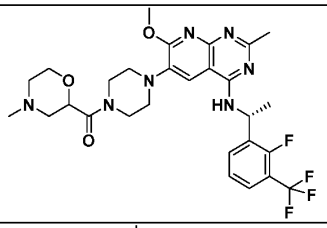
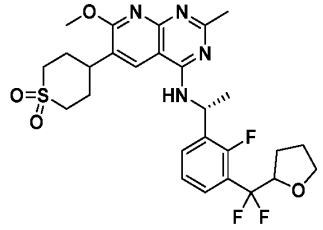
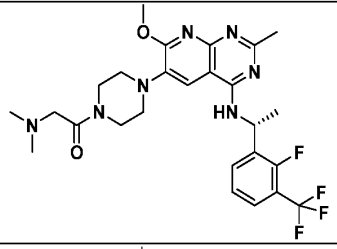
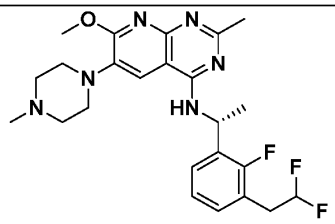
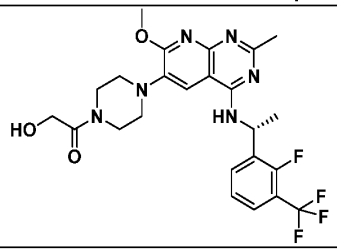
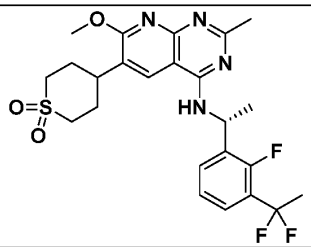
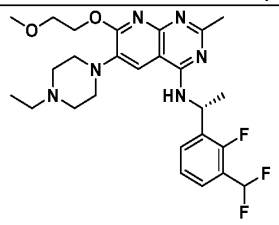
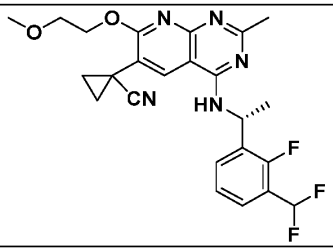
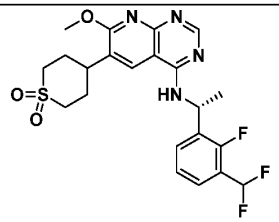
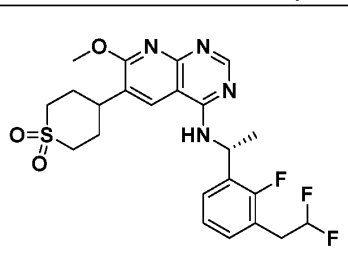
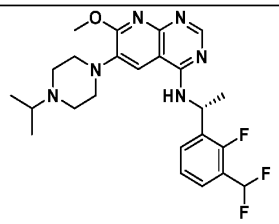
S1115		475.4	S1279		512.3
S1116		546.0	S1280		517.4
S1117		513.4	S1281		464.3
S1118		509.9	S1282		460.3
S1119		474.5	S1283		578.4
S1120		513.8	S1284		525.4
S1121		446.4	S1285		527.4

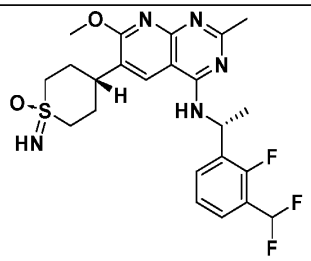
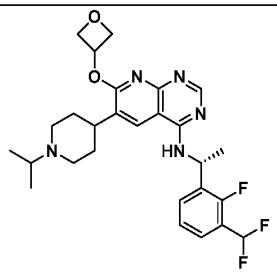
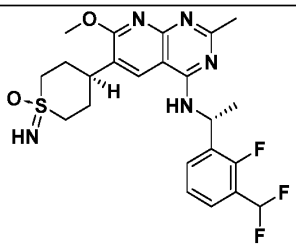
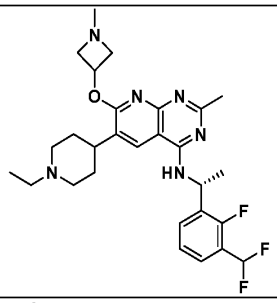
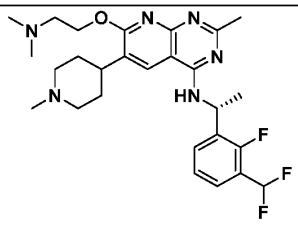
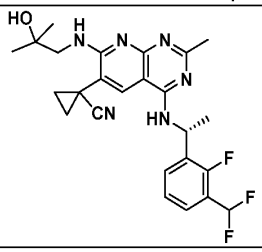
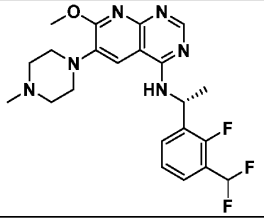
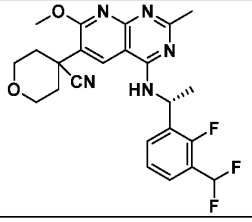
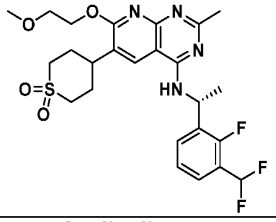
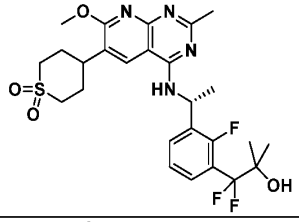
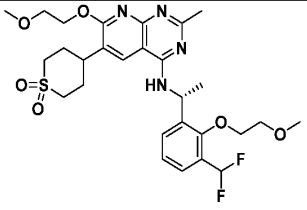
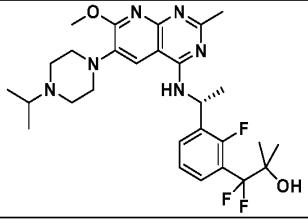
S1122		544.6	S1286		626.4
S1123		475.9	S1287		506.5
S1124		558.6	S1288		492.4
S1125		516.9	S1289		606
S1126		520.8	S1290		549.4
S1127		493.8	S1291		586.5
S1128		485.5	S1292		496.4

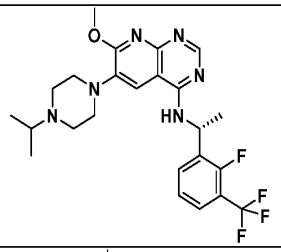
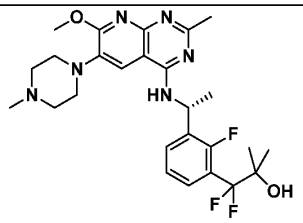
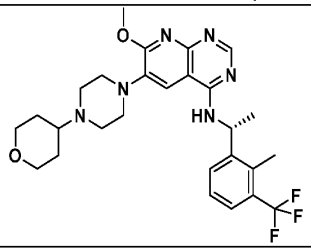
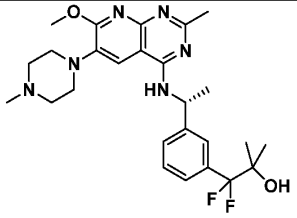
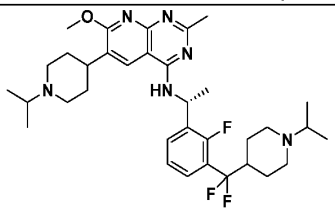
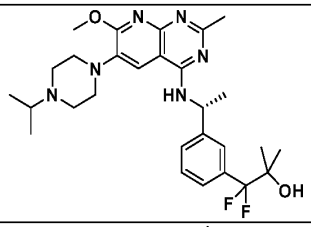
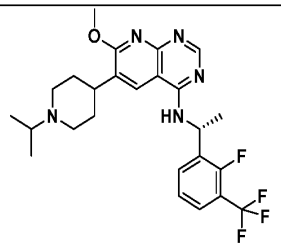
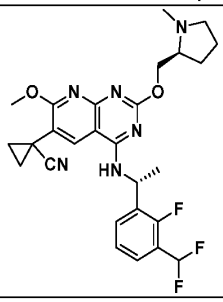
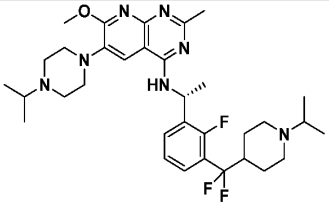
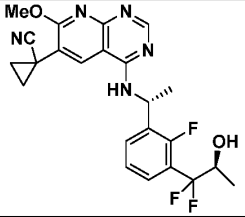
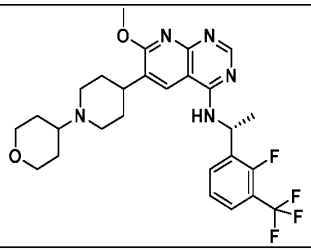
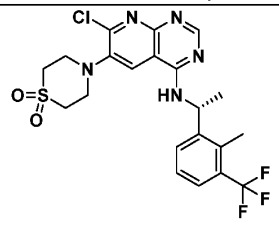
S1129		503.5	S1293		600.6
S1130		490.4	S1294		511.4
S1131		496.8	S1295		496.3
S1132		528.9	S1296		547.2
S1133		524.4	S1297		483.3
S1134		460.4	S1298		483.3

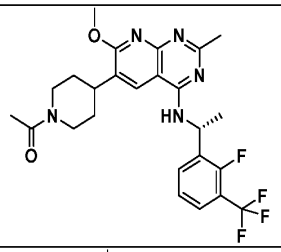
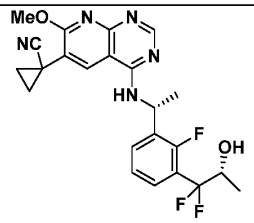
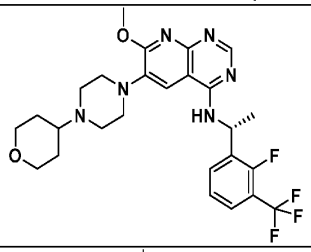
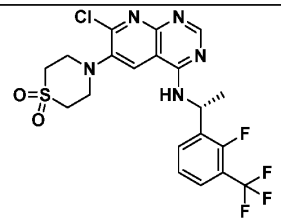
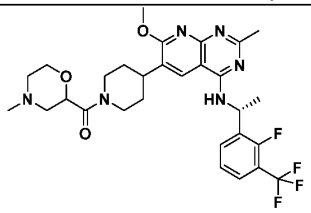
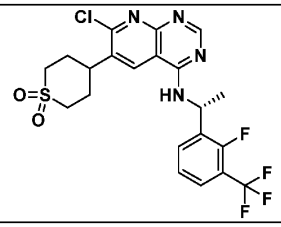
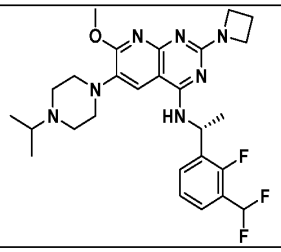
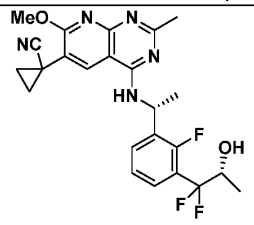
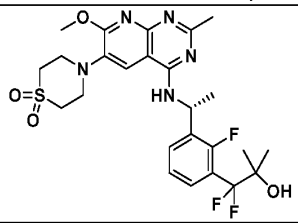
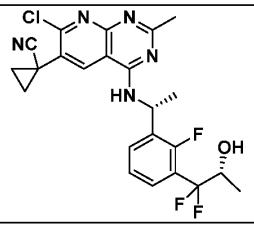
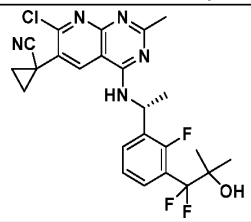
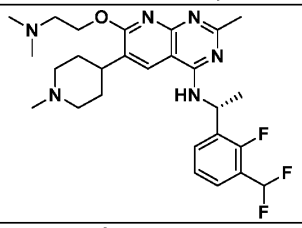
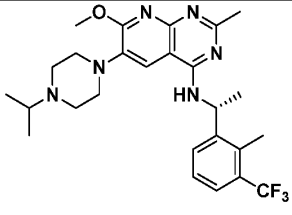
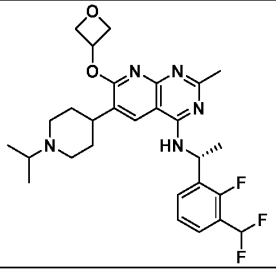
S1135		460.4	S1299		484.7
S1136		494.8	S1300		450.5
S1137		525.8	S1301		578.8
S1138		494.4	S1302		549.4
S1139		523.5	S1303		578.4
S1140		561.5	S1304		522.8

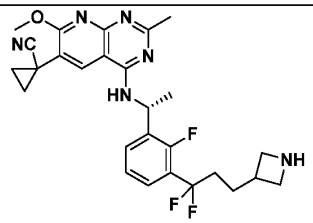
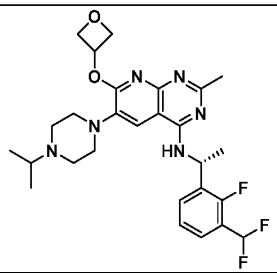
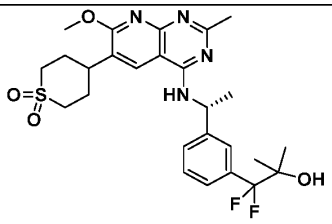
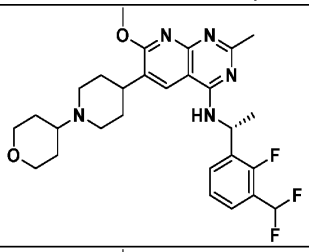
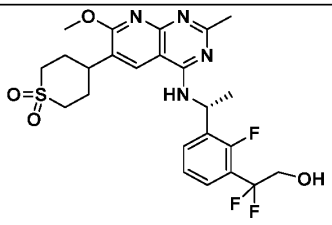
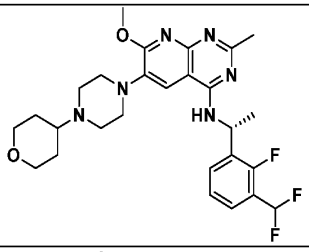
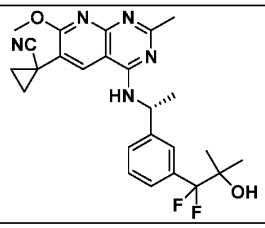
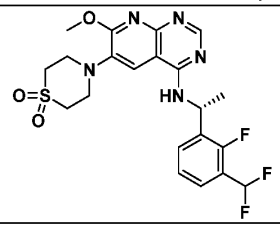
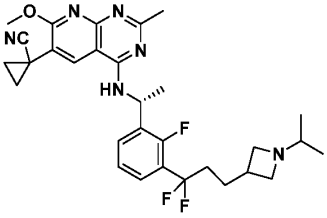
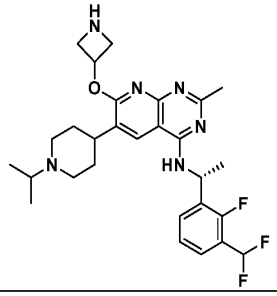
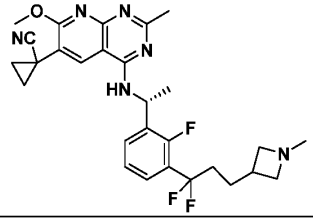
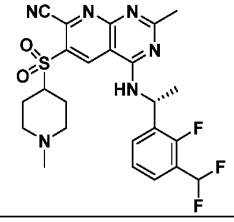
S1141		508.4	S1305		514.3
S1142		510.5	S1306		531.4
S1143		508.8	S1307		526.7
S1144		513.9	S1308		500.6
S1145		552.9	S1309		478.3
S1146		481.4	S1310		579.4

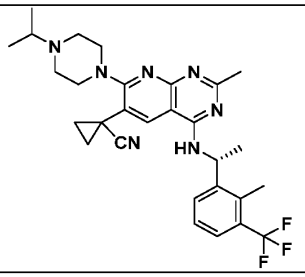
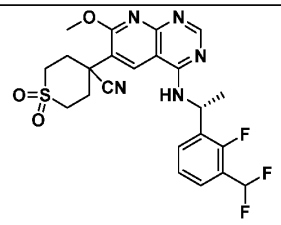
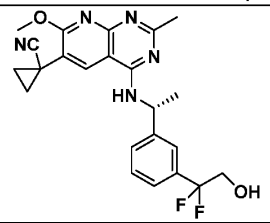
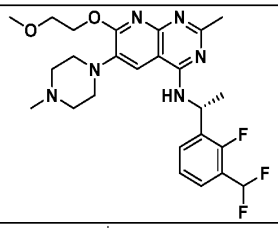
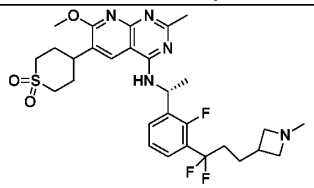
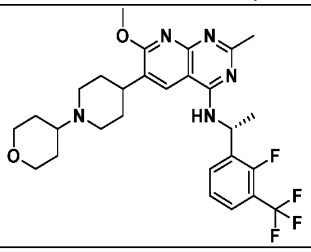
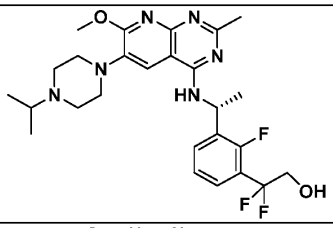
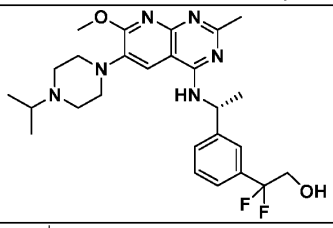
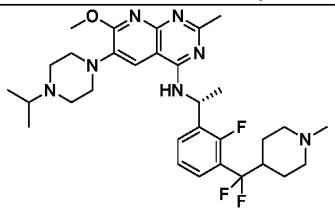
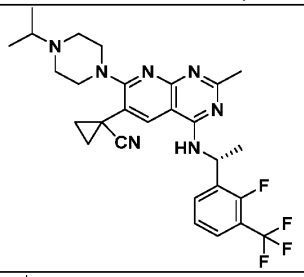
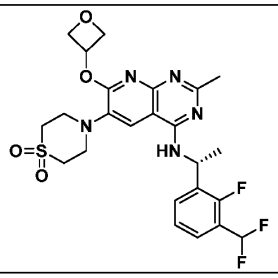
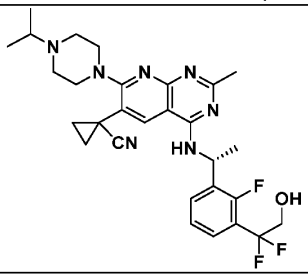
S1147		509.8	S1311		592.4
S1148		565.9	S1312		550.4
S1149		475.5	S1313		523.4
S1150		509.9	S1314		519.5
S1151		472.9	S1315		481.3
S1152		495.8	S1316		475.4

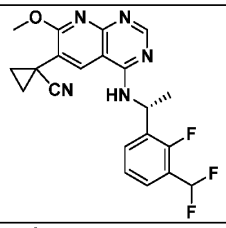
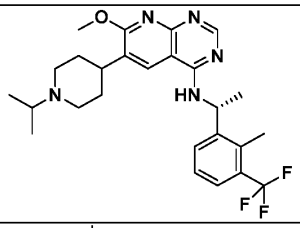
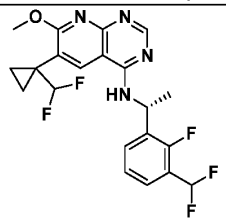
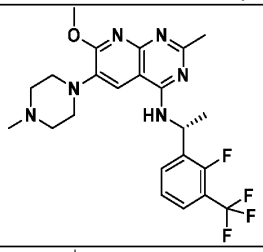
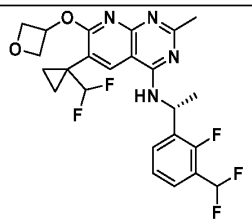
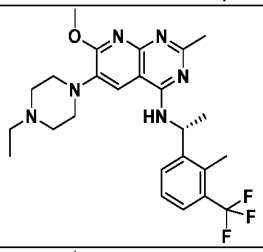
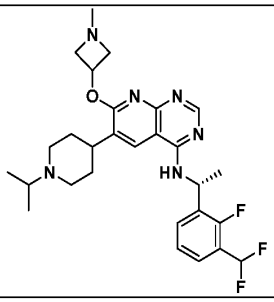
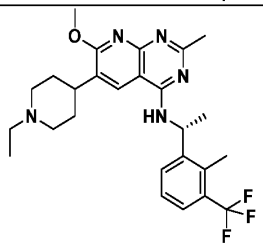
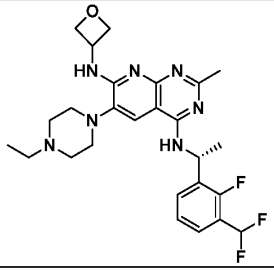
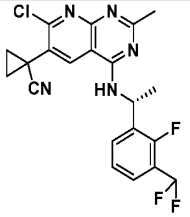
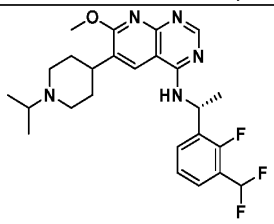
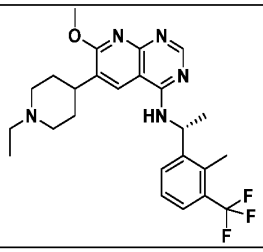
S1153		494.8	S1317		516.5
S1154		494.8	S1318		529.5
S1155		517.5	S1319		485.3
S1156		447.3	S1320		472.6
S1157		539.8	S1321		553.3
S1158		595.9	S1322		547.5

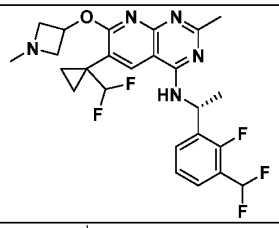
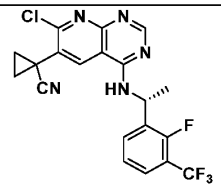
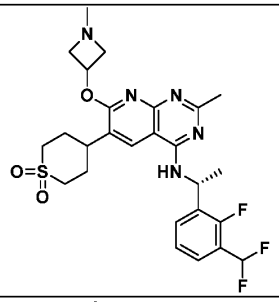
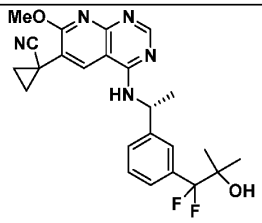
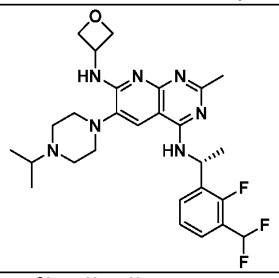
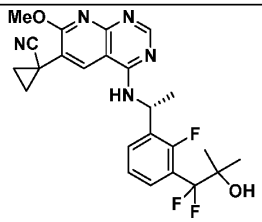
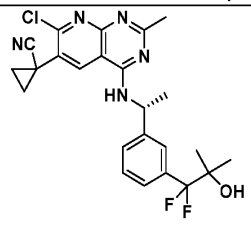
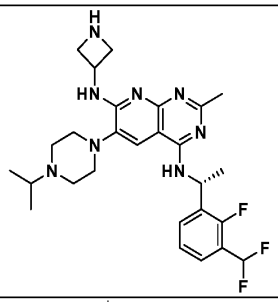
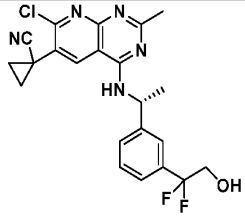
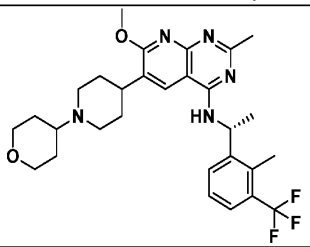
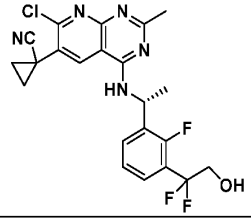
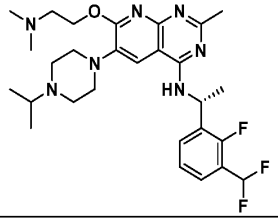
S1159		493.4	S1323		519.4
S1160		531.4	S1324		501.5
S1161		613.6	S1325		529.5
S1162		492.4	S1326		527.5
S1163		614.5	S1327		458.7
S1164		534.5	S1328		500.2

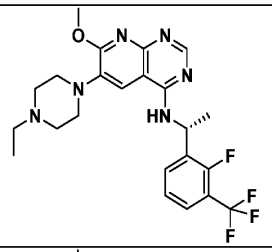
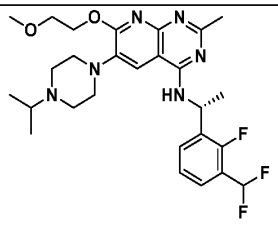
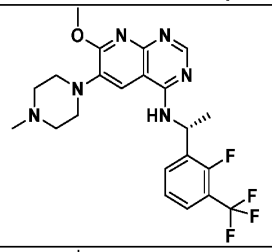
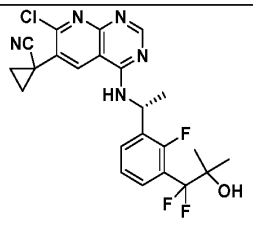
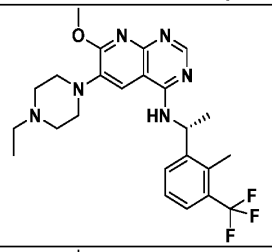
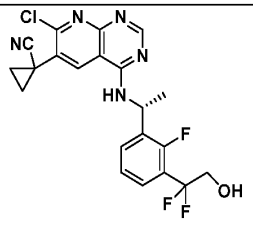
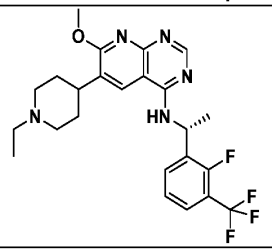
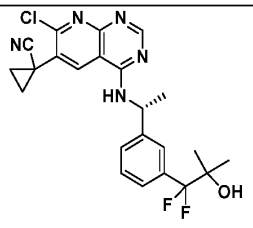
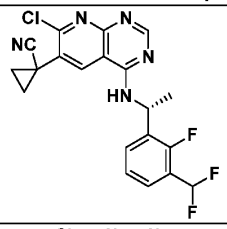
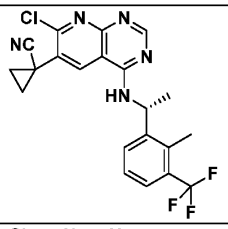
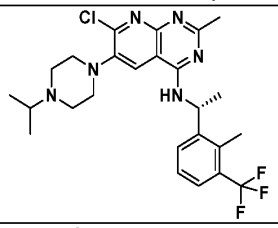
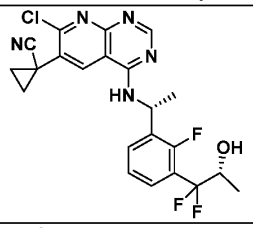
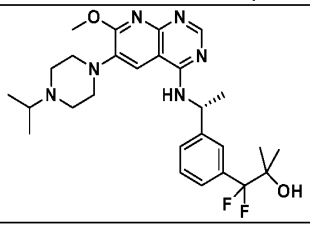
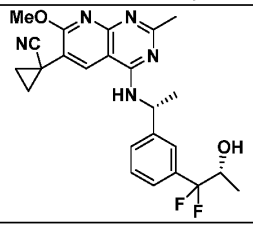
S1165		506.8	S1329		458.7
S1166		535.4	S1330		504.2
S1167		591.4	S1331		503.2
S1168		530.45	S1332		472.3
S1169		554.4	S1333		476.3
S1170		490.3	S1334		517.5
S1171		503.3	S1335		530.5

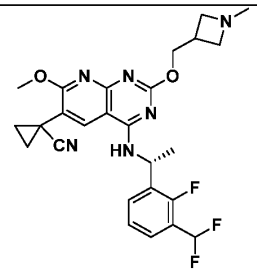
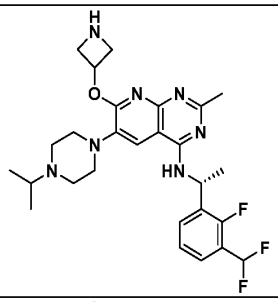
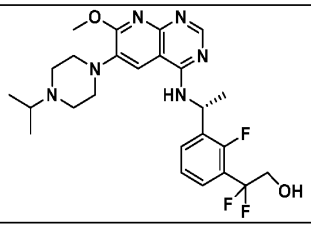
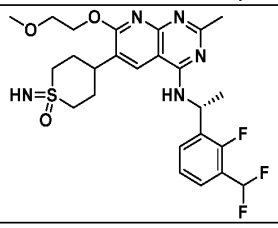
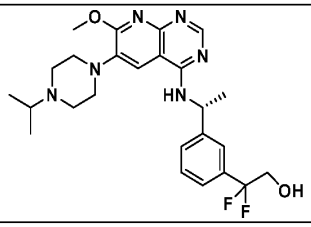
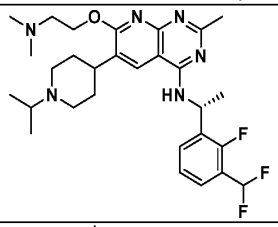
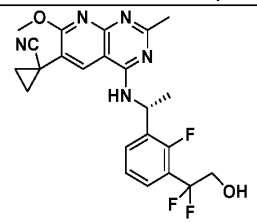
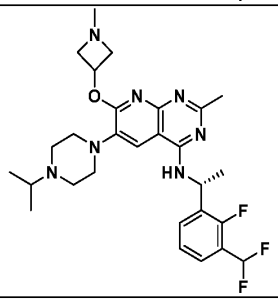
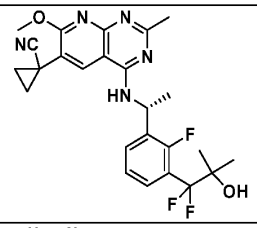
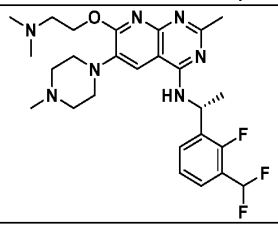
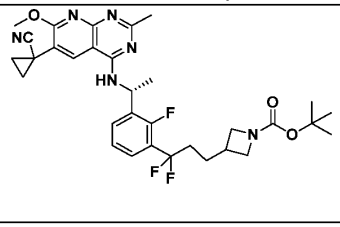
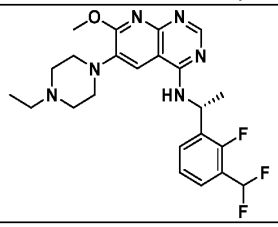
S1172		511.35	S1336		531.5
S1173		535.6	S1337		530.5
S1174		525.6	S1338		531.5
S1175		468.6	S1339		482.3
S1176		553.4	S1340		529.5
S1177		525.3	S1341		519.4

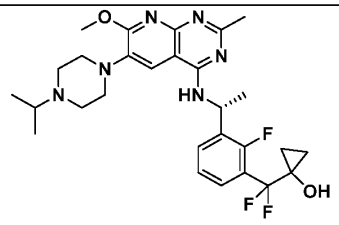
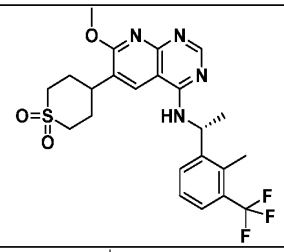
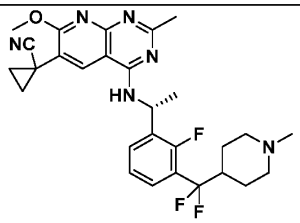
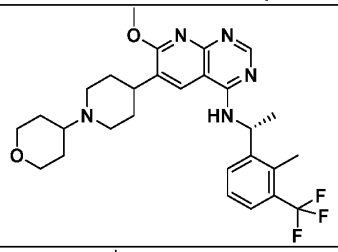
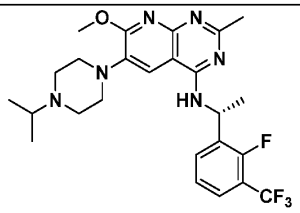
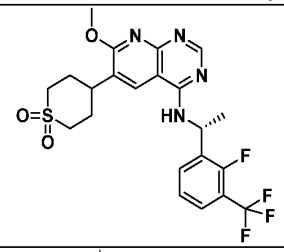
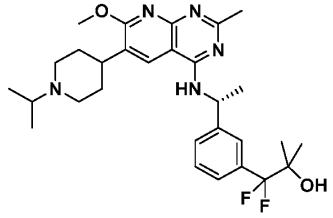
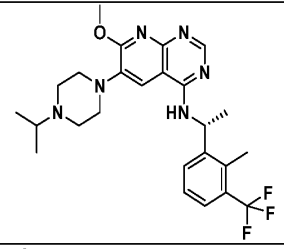
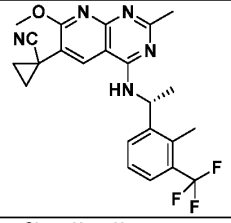
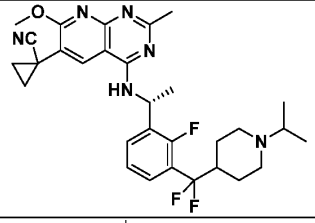
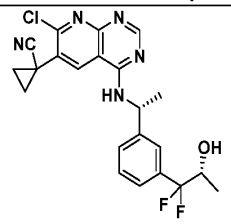
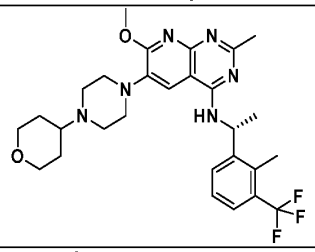
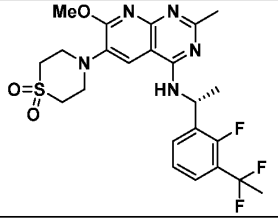
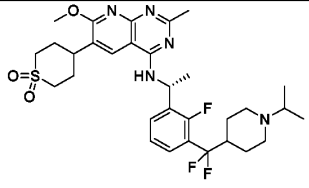
S1178		538.4	S1342		506.3
S1179		440.6	S1343		505.5
S1180		592.4	S1344		548.5
S1181		519.3	S1345		501.4
S1182		586.5	S1346		542.4
S1183		538.4	S1347		554.4

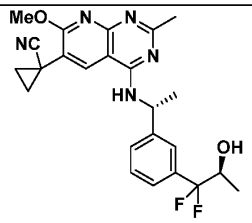
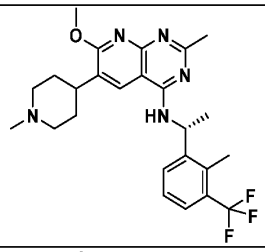
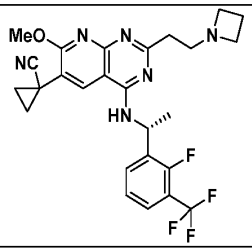
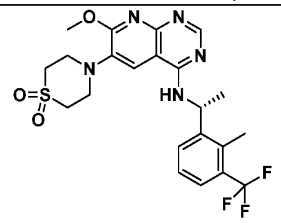
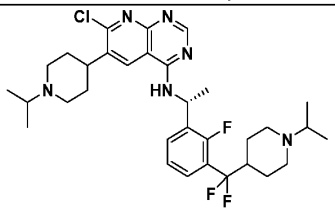
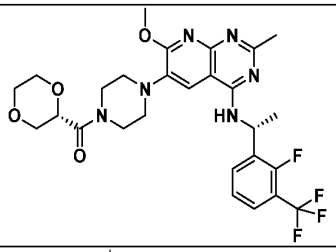
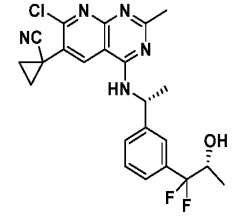
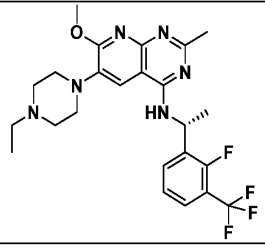
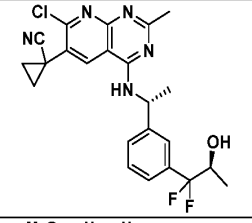
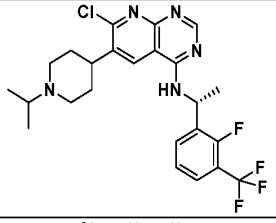
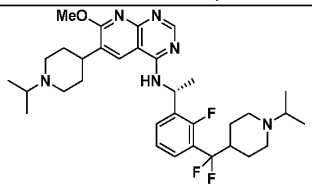
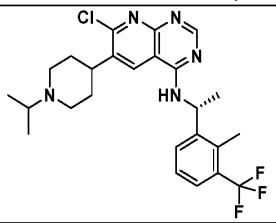
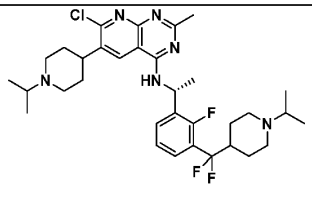
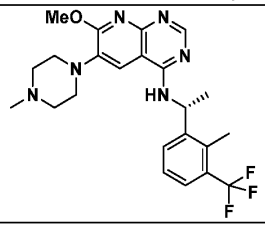
S1184		414.7	S1348		488.3
S1185		439.65	S1349		479.3
S1186		495.8	S1350		489.4
S1187		529.9	S1351		488.4
S1188		516.5	S1352		432.3
S1189		474.5	S1353		474.3

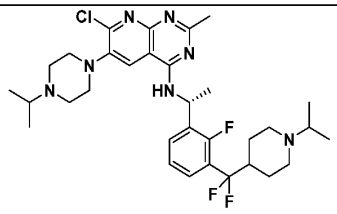
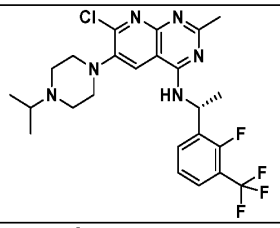
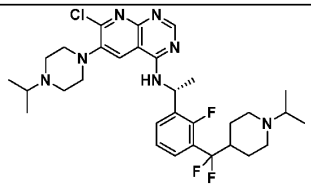
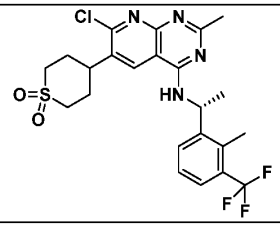
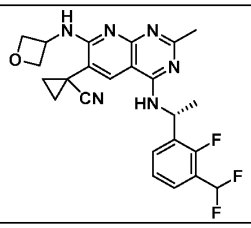
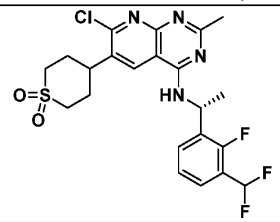
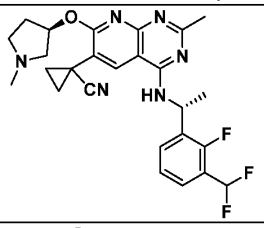
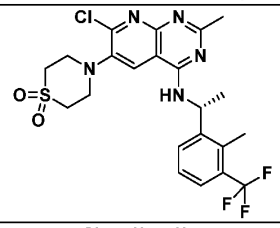
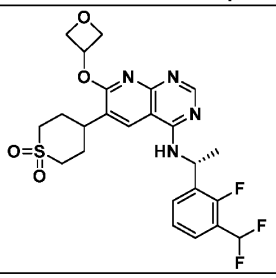
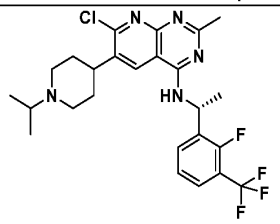
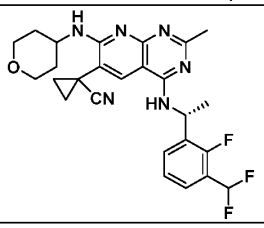
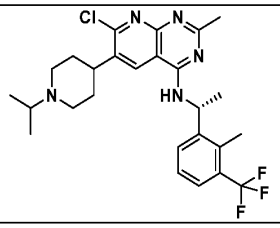
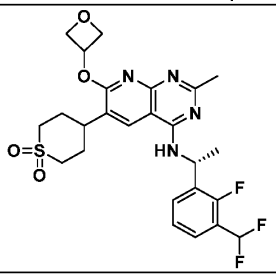
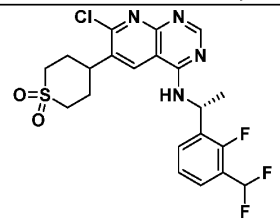
S1190		508.3	S1354		436.5
S1191		550.4	S1355		454.7
S1192		530.5	S1356		472.7
S1193		472.3	S1357		529.3
S1194		444.2	S1358		544.5
S1195		462.3	S1359		546.3

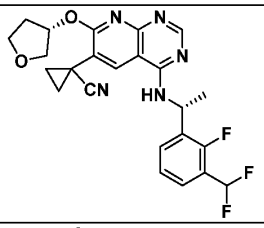
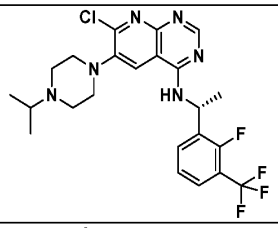
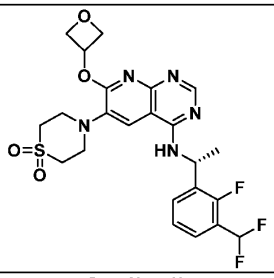
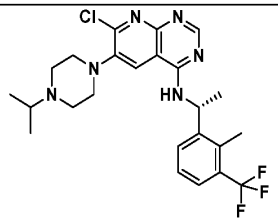
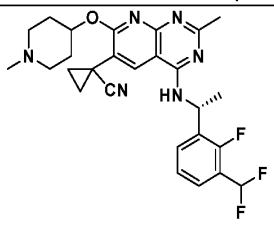
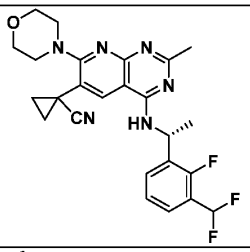
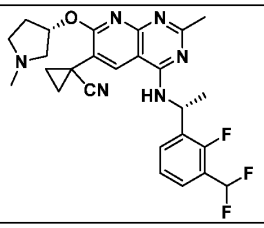
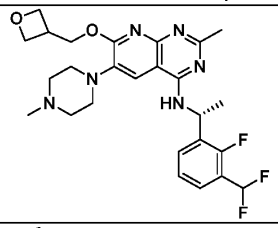
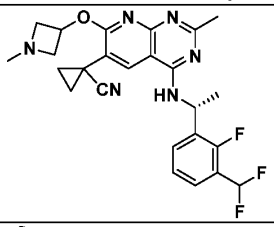
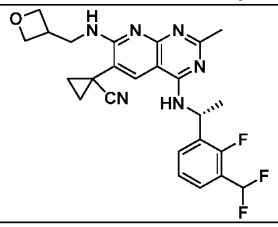
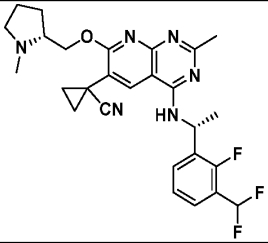
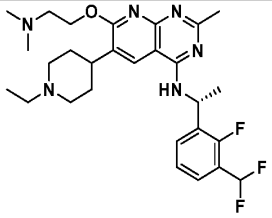
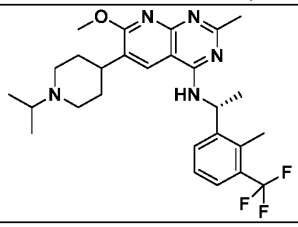
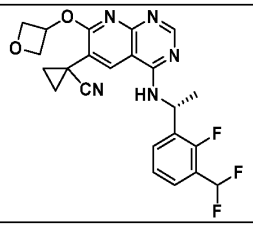
S1196		479.3	S1360		533.5
S1197		465.3	S1361		476.2
S1198		475.4	S1362		448.2
S1199		478.4	S1363		458.3
S1200		418.4	S1364		432.2
S1201		507.3	S1365		462.2
S1202		515.5	S1366		454.3

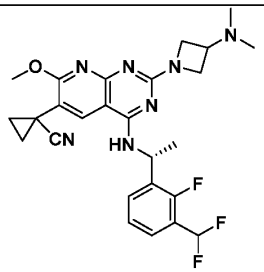
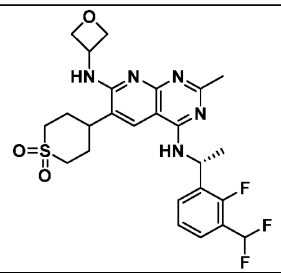
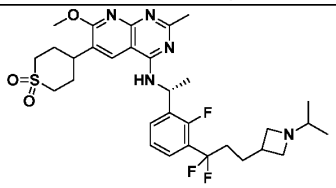
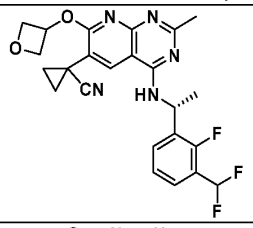
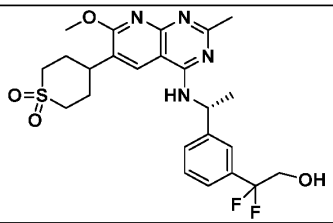
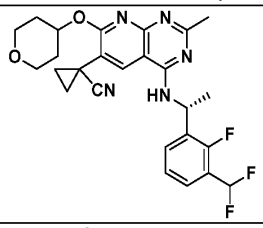
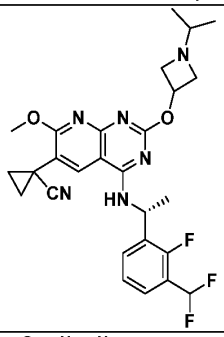
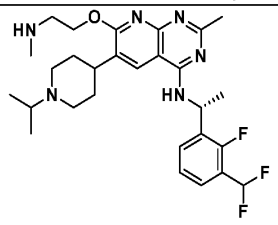
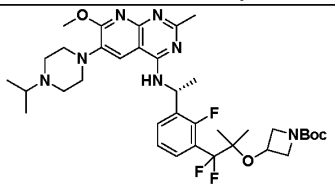
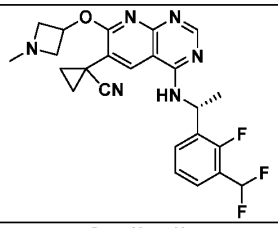
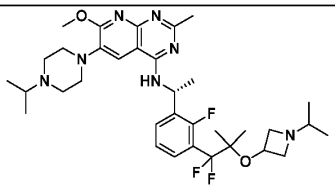
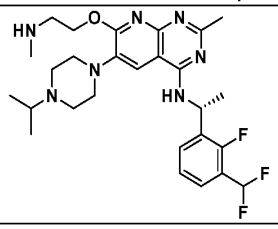
S1203		513.4	S1367		530.5
S1204		505.5	S1368		538.5
S1205		487.4	S1369		545.6
S1206		458.7	S1370		544.5
S1207		486.8	S1371		518.5
S1208		611.5	S1372		461.3

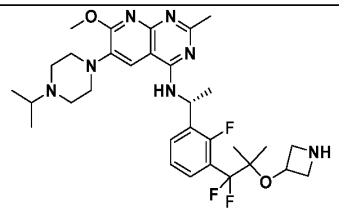
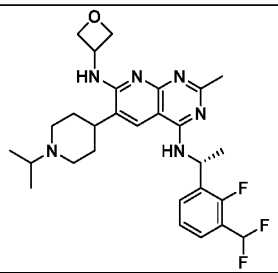
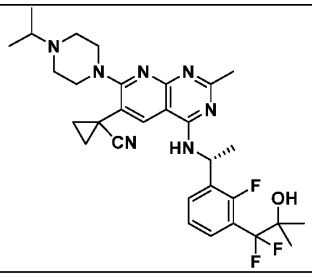
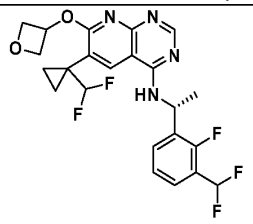
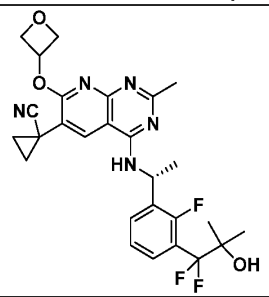
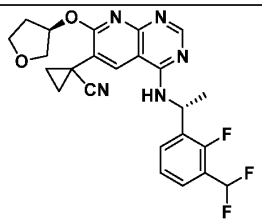
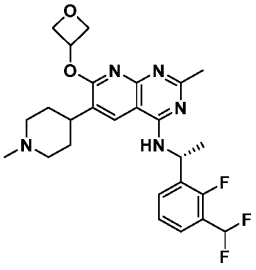
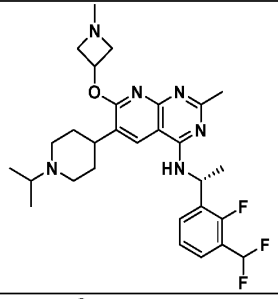
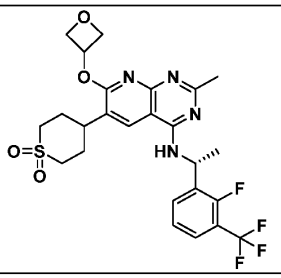
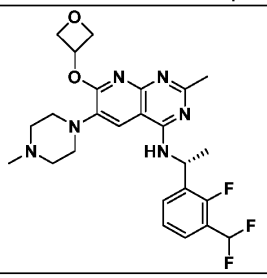
S1209		545.5	S1373		530.4
S1210		525.5	S1374		495.3
S1211		507.4	S1375		499.3
S1212		528.5	S1376		489.4
S1213		442.7	S1377		533.4
S1214		444.3	S1378		545.4
S1215		510.3	S1379		620.5

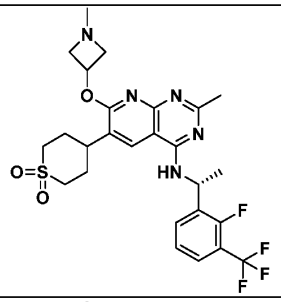
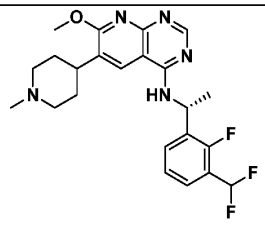
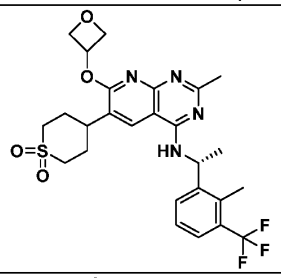
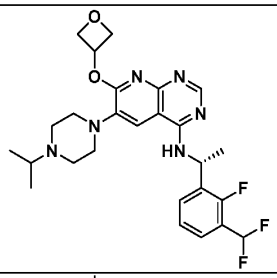
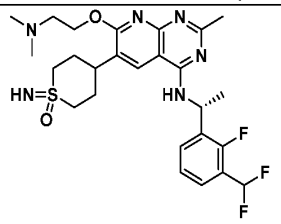
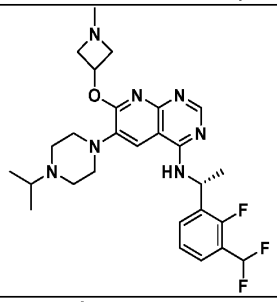
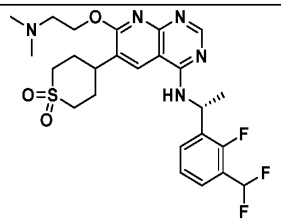
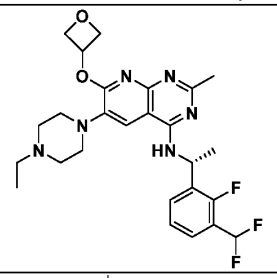
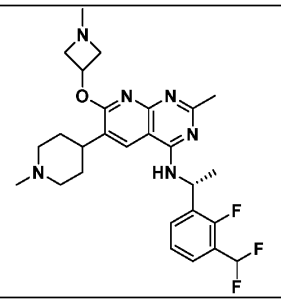
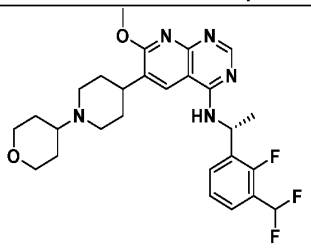
S1216		454.3	S1380		474.4
S1217		497.4	S1381		496.7
S1218		603.5	S1382		579.4
S1219		458.2	S1383		493.3
S1220		458.2	S1384		496.4
S1221		599.5	S1385		492.4
S1222		617.6	S1386		461.4

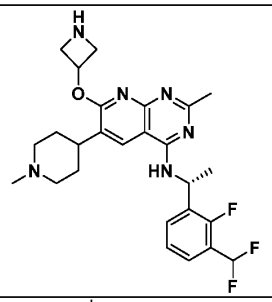
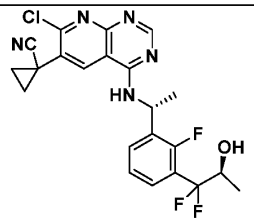
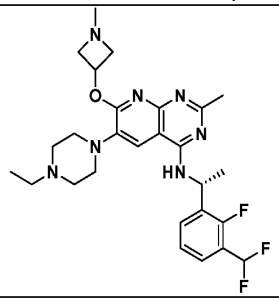
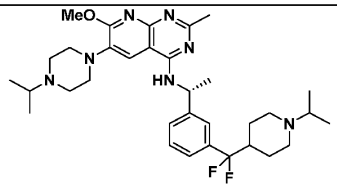
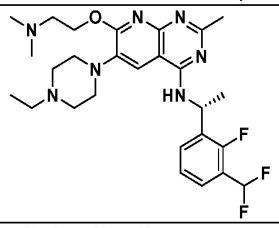
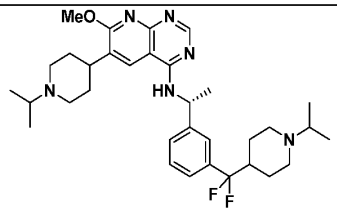
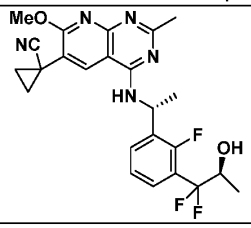
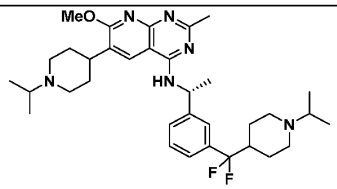
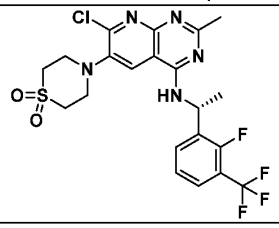
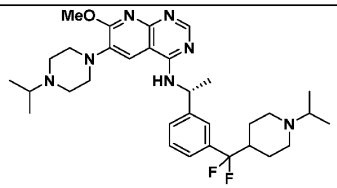
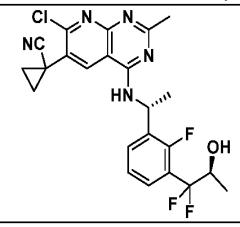
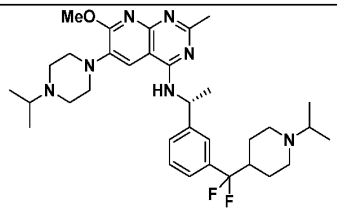
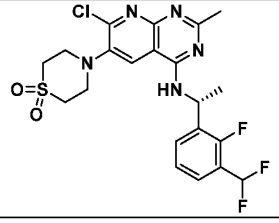
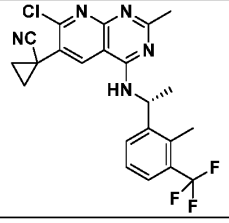
S1223		618.6	S1387		511.6
S1224		604.5	S1388		513.2
S1225		469.25	S1389		499.3
S1226		497.4	S1390		514.3
S1227		523.8	S1391		510.3
S1228		497.3	S1392		506.4
S1229		537.3	S1393		485.2

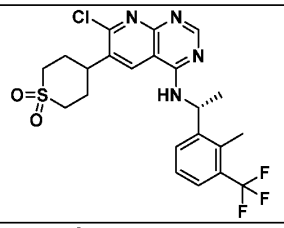
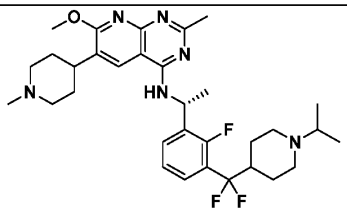
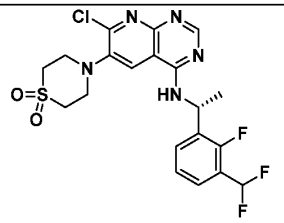
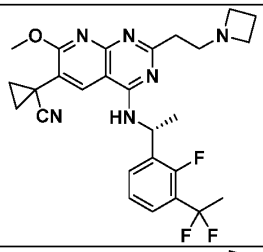
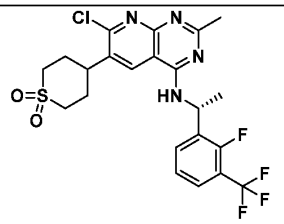
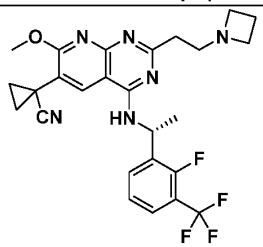
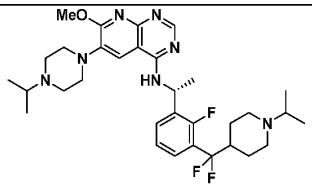
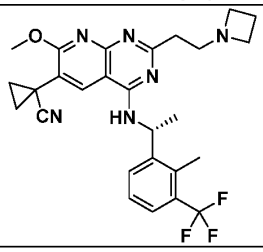
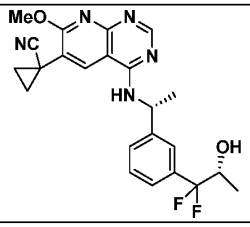
S1230		470.7	S1394		497.4
S1231		524.3	S1395		493.3
S1232		511.3	S1396		483.7
S1233		497.4	S1397		517.4
S1234		483.3	S1398		483.3
S1235		511.4	S1399		531.5
S1236		502.3	S1400		456.7

S1237		512.3	S1401		536.5
S1238		620.4	S1402		470.4
S1239		507.6	S1403		498.3
S1240		527.3	S1404		531.4
S1241		702.6	S1405		469.3
S1242		644.5	S1406		532.5

S1243		602.5	S1407		529.4
S1244		582.5	S1408		481.2
S1245		528.7	S1409		470.7
S1246		502.5	S1410		543.5
S1247		555.8	S1411		503.5

S1248		568.5	S1412		446.3
S1249		551.5	S1413		517.4
S1250		551.5	S1414		530.5
S1251		538.5	S1415		517.5
S1252		515.5	S1416		516.5

S1253		501.5	S1417		462.3
S1254		530.5	S1418		596
S1255		532.5	S1419		580
S1256		472.3	S1420		595
S1257		518.3	S1421		582
S1258		476.3	S1422		596
S1259		500.3	S1423		446.2

S1260		499.3	S1424		585.5
S1261		486.2	S1425		511.4
S1262		517.3	S1426		515.4
S1263		600.3	S1427		511.4
S1264		440.3			

[632] In some embodiments, the compounds of the present disclosure exhibit one or more functional characteristics described herein. For example, a subject compound is capable of reducing Ras signaling output. In some instances, a subject compound is capable of disrupting a Ras-SOS interaction, including disrupting interaction or binding between a mutant Kras (e.g., Kras G12C) and SOS1, or between a wildtype Kras and SOS1, thereby reducing Ras signaling output. In some embodiments, a subject compound binds specifically to a SOS protein, including SOS1.

[633] A reduction in Ras signaling output can be evidenced by one or more members of the following: (i) an increase in steady state level of GDP-bound Ras protein; (ii) a reduction in steady state level of GTP-bound Ras protein; (iii) a reduction of phosphorylated AKTs473, (iv) a reduction of phosphorylated ERKT202/y204, (v) a reduction of phosphorylated S6S235/236, (vi) reduction (e.g., inhibition) of cell growth of Ras-driven tumor cells (e.g., those derived from a tumor cell line disclosed herein), and (vii) an interference or disruption of the interaction or binding between a SOS protein (e.g., SOS1) with a Ras protein such as a wildtype or a mutant Ras. In some cases, the reduction in Ras signaling output can be evidenced by two, three, four, five, six, or all of (i)-(vii) above.

[634] It shall be understood that different aspects of the invention can be appreciated individually, collectively, or in combination with each other. Various aspects of the invention described herein may be applied to any of the particular applications disclosed herein. The compositions of matter including compounds of any formulae disclosed herein in the compounds section of the present disclosure may be utilized in the methods section including methods of use and production disclosed herein, or vice versa.

[635] Additional Embodiments

Embodiment 1. A method of reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS protein overexpression, the method comprising administering to the cells (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

Embodiment 2. The method of embodiment 1, wherein the cancer cells are non-small cell lung cancer cells, colorectal cancer cells, or pancreatic cancer cells.

Embodiment 3. A method of downregulating KRAS signaling output in a plurality of cancer cells, comprising:

(i) assessing KRAS mutation status in a biological sample comprising nucleic acid from the subject; and

(ii) administering an effective dose of (a) a SOS1 inhibitor and an effective dose of (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), if a KRAS mutation is detected in the sample, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

Embodiment 4. A method of treating cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

Embodiment 5. The method of embodiment 4, wherein the cancer is a mutant KRAS-mediated cancer.

Embodiment 6. The method of any one of embodiments 1 to 5, wherein the KRAS inhibitor is a compound, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3).

Embodiment 7. The method of any one of the preceding embodiments, wherein the administration of (a) and (b) synergistically reduces proliferation of the cancer cells with a synergistic value of at least 0.05 as ascertained by Bliss independence criterion.

Embodiment 8. A method of treating an mutant KRAS-mediated cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), wherein (a) is administered prior to, concurrently with, or subsequent to administering (b), and wherein the administration of (a) and (b) synergistically reduces proliferation of the cancer cells with a synergistic value of at least 0.05 as ascertained by Bliss independence criterion.

Embodiment 9. The method of embodiment 7 or 8, wherein the synergistic value is ascertained by Bliss independence criterion in accordance with the formula:

$$Y_{AB,O} - Y_{AB,P}$$

wherein:

$Y_{AB,O}$ is observed percent growth inhibition of the cancer cells by the application of (a) and (b) comprising (a) at dose A and (b) at dose B;

$Y_{AB,P}$ is predicted percent growth inhibition of the cancer cells by the application of (a) and (b) comprising (a) at dose A and (b) at dose B, wherein $Y_{AB,P} = Y_A + Y_B - Y_AY_B$;

Y_A is observed percent growth inhibition of the cancer cells by (a) alone at dose A;

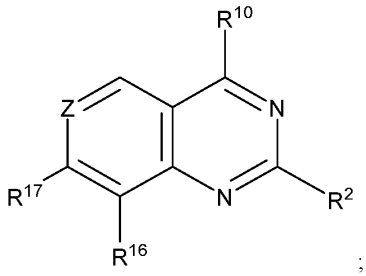
Y_B is observed percent growth inhibition of the cancer cells by (b) alone at dose B; and

Y_AY_B is the product of Y_A and Y_B.

Embodiment 10. A pharmaceutical composition comprising (i) a SOS1 inhibitor, or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

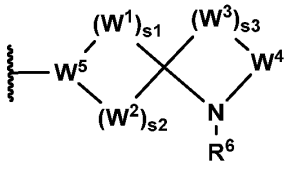
Embodiment 11. The method or pharmaceutical composition of any preceding embodiment, wherein

(i) the KRAS inhibitor has the formula:



;

Wherein Z is N or C(R^8); R^{10} is -L^7-R^7; L^7 is a bond; R^8 is halogen; R^{16} is halogen;

R^7 is 

;

W^1, W^2, and W^3 are independently selected from C(R^1)(R^1), C(R^1)(R^4), C(R^4)(R^4), and O; W^4 is selected from C(R^1)(R^1), C(R^1)(R^4), and C(R^4)(R^4); W^5 is selected from N and CH;

R^2 is -$OR^{12'}$; each $R^{12'}$ is independently selected from -C(R^{12c})$_2$-C_{3-10}cycloalkyl and -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl, wherein -C(R^{12c})$_2$-C_{3-10}cycloalkyl and -C(R^{12c})$_2$-C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20d};

s1 is 1 and s2 is 0, 2, or 3; s1 is 2 and s2 is 0, 1, or 3; s1 is 3 and s2 is 0 to 3; s1 is 4 and s2 is 0 to 3; s1 is 5 and s2 is 0 to 3; or s1 is 6 and s2 is 0 to 3; s3 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, -CH_2-C_{3-12}cycloalkyl, C_{1-11}heterocycloalkyl, -CH_2-C_{1-11}heterocycloalkyl, C_{6-12}aryl, -CH_2-C_{6-12}aryl, -CH_2-C_{1-11}heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl,

C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, =$C(R^{21b})_2$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{12}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{12}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$C(O)N(R^{12})(R^{13})$, -($C_{1-6}$alkyl)-$N(R^{14})C(O)R^{12}$, -($C_{1-6}$alkyl)-$S(O)_2R^{15}$, -($C_{1-6}$alkyl)-$N(R^{12})(R^{13})$, and -($C_{1-6}$alkyl)-$S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is -L^2-R^5 and wherein R^6 is optionally capable of forming a covalent bond with a Ras amino acid; L^2 is -C(O)-; R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N ring atom of R^5;

R^{17} is -L^1-R^{19}; L^1 is a bond; R^{19} is selected from a C_{6-12}aryl and C_{2-12}heteroaryl, wherein the C_{6-12}aryl and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i}; each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -OR^{12}, -$N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted with one, two, or three R^{20i};

each R^{12} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, =$C(R^{21b})_2$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{21}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{21}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

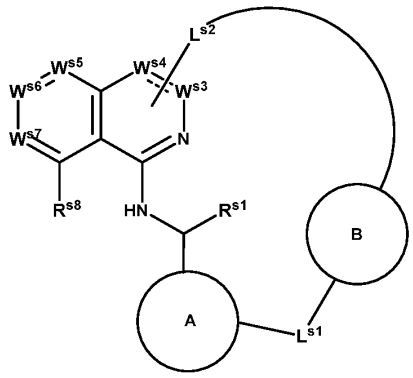
each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

------ indicates a single or double bond such that all valences are satisfied; and

(ii) the SOS1 inhibitor has the formula:



(SI-1),

wherein:

is selected from C_{5-7} carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R^{s11};

is absent or selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

W^{s3} is selected from N(R^{s3b}), N, C(R^{s3}), and C(O);

W^{s4} is selected from N(R^{s4b}), N, C(R^{s4}), and C(O);

W^{s5} is selected from N(R^{s5b}), N, and C(R^{s5});

W^{s6} is selected from C(R^{s6}) and C(O);

W^{s7} is C(R^{s7});

R^{s1} is C_{1-3} alkyl optionally substituted with one or more R^{s11c};

R^{s8} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, -OR^{s12}, -SR^{s12}, -N(R^{s12})(R^{s13}), -C(O)OR^{s12}, -OC(O)N(R^{s12})(R^{s13}), -N(R^{s14})C(O)N(R^{s12})(R^{s13}), -

$N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, and R^{s5b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s11} and R^{s11a} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11c} is independently selected at each occurrence from halogen, $-OR^{s12}$, and $-N(R^{s12})(R^{s13})$;

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3-

to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, $-CH_2-$(3- to 10-membered heterocycle), $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, $-OCH_2C(O)OR^{s22}$, and $-OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10}$ carbocycle), 3- to 10-membered heterocycle, and $-CH_2-$(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{s21}$, $-SR^{s21}$, $-N(R^{s22})(R^{s23})$, $-C(O)OR^{s22}$, $-C(O)N(R^{s22})(R^{s23})$, $-C(O)C(O)N(R^{s22})(R^{s23})$, $-OC(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)N(R^{s22})(R^{s23})$, $-N(R^{s24})C(O)OR^{s25}$, $-N(R^{s24})C(O)R^{s25}$, $-N(R^{s24})S(O)_2R^{s25}$, $-C(O)R^{s25}$, $-S(O)_2R^{s25}$, $-S(O)_2N(R^{s22})(R^{s23})$, and $-OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

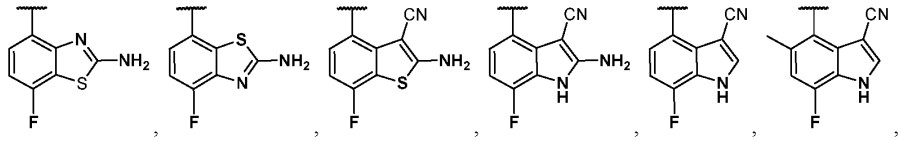
R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

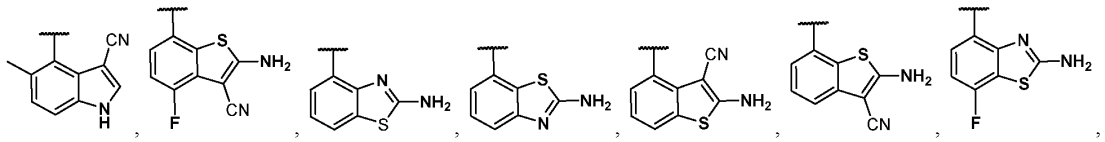
R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle.

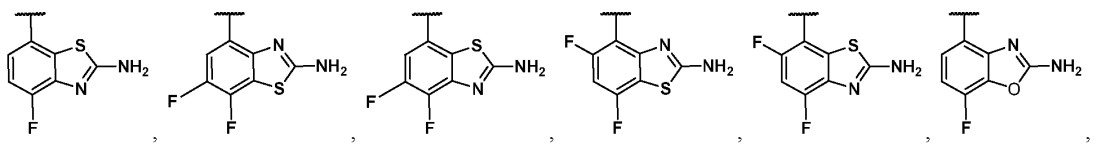
Embodiment 12. The method or pharmaceutical composition of embodiment 11, wherein Z is $C(R^8)$.

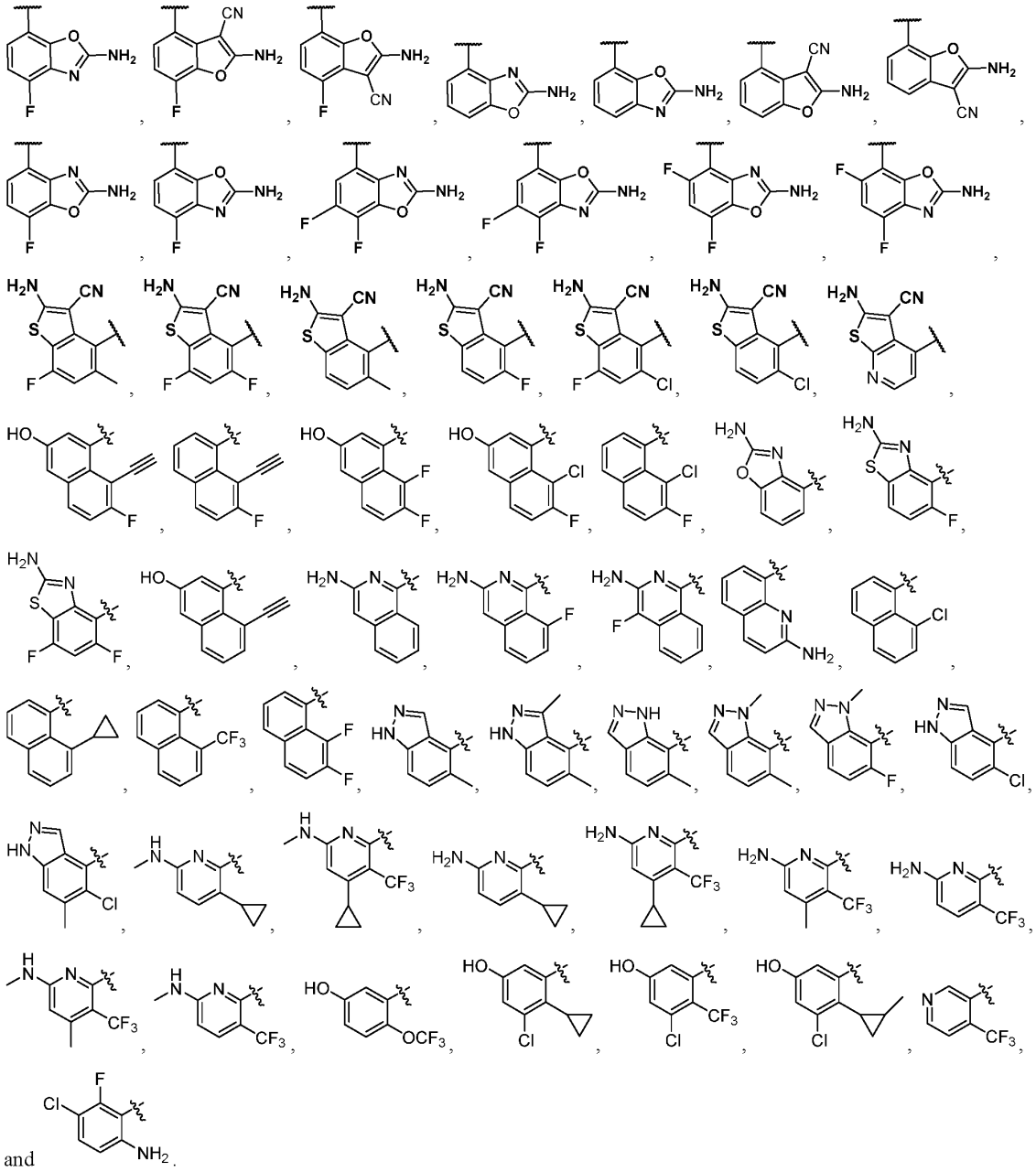
Embodiment 13. The method or pharmaceutical composition of embodiment 11, wherein Z is N.

Embodiment 14. The method or pharmaceutical composition of any one of embodiments 11 to 13, wherein R^{19} is selected from



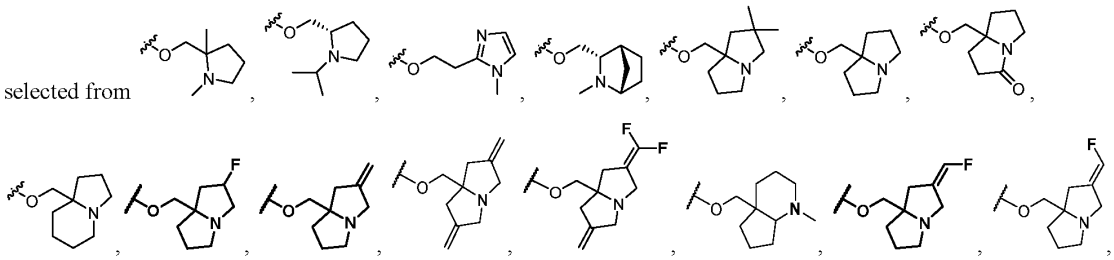


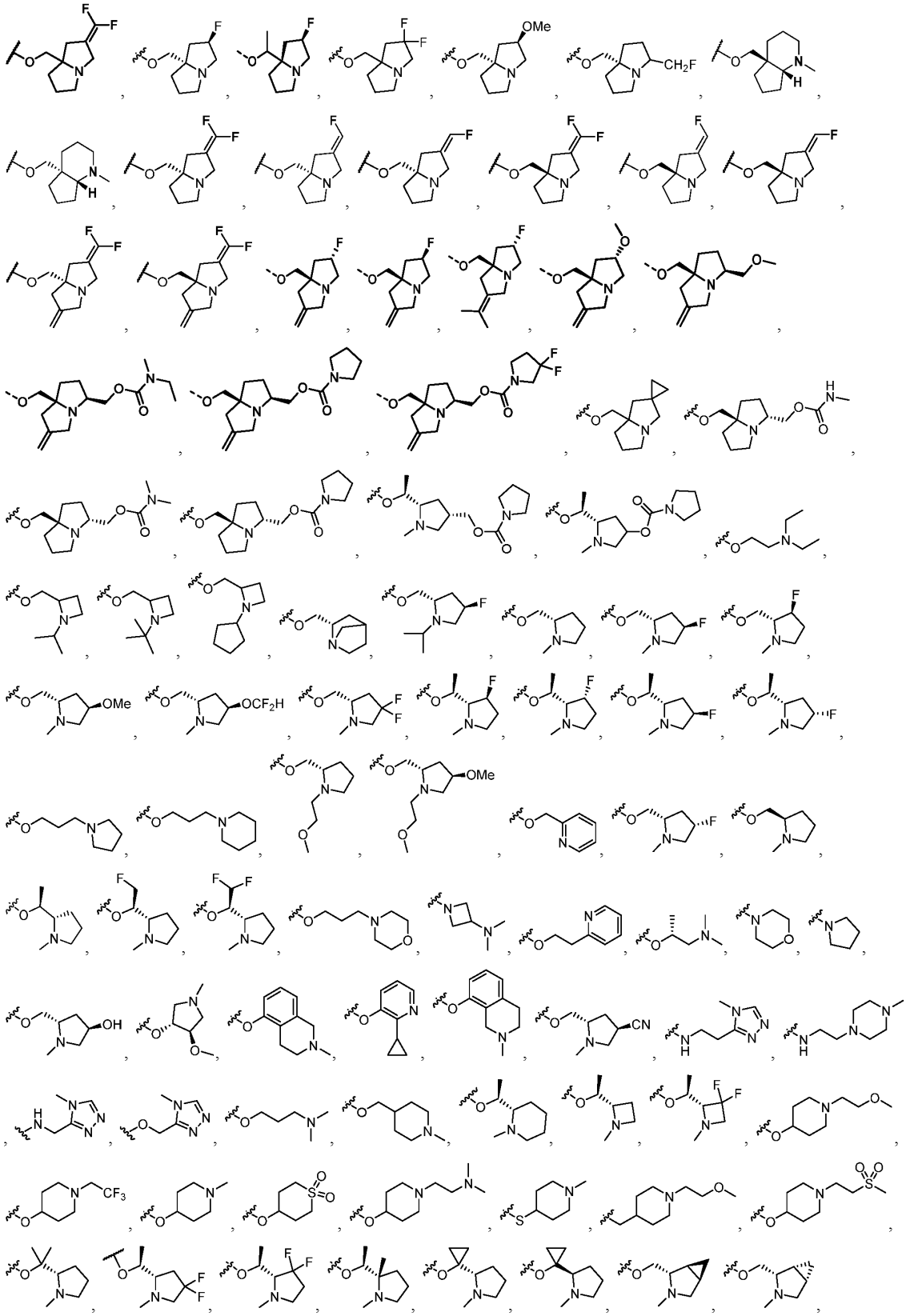


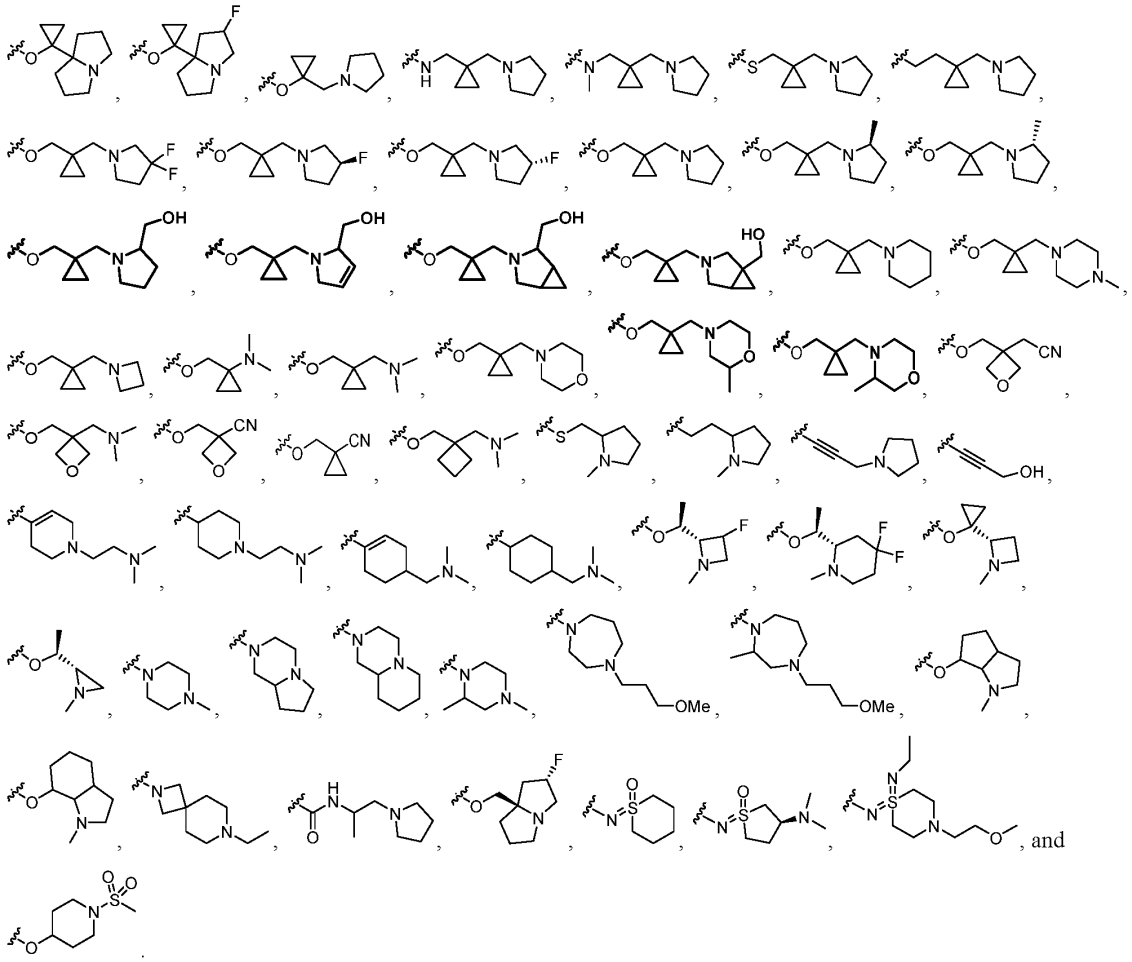


and

Embodiment 15. The method or pharmaceutical composition of any one of embodiments 11 to 14, wherein R^2 is selected from

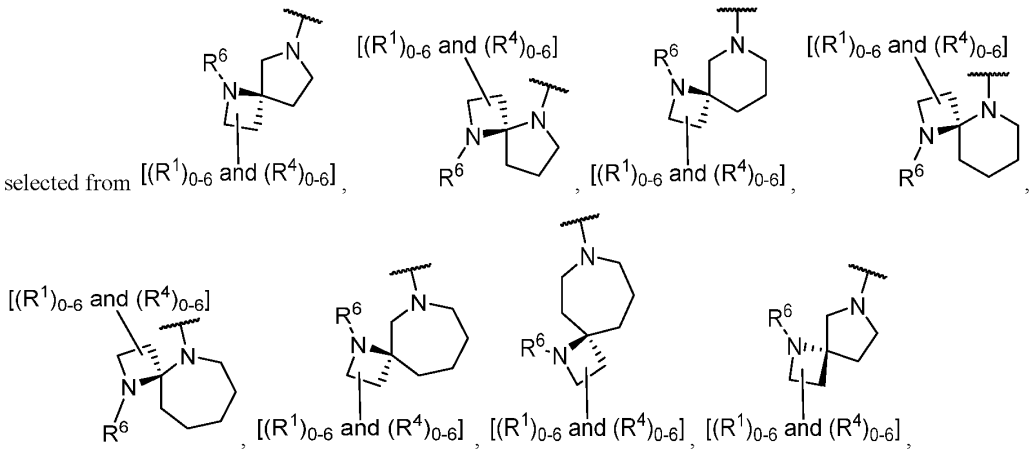


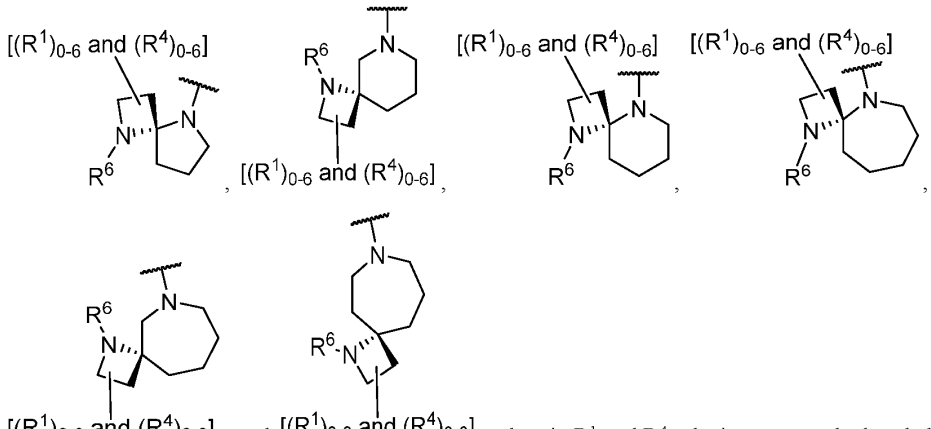




Embodiment 16. The method or pharmaceutical composition of any one of embodiments 11 to 15, wherein s1 is 2 and s2 is 0, 1, or 3.

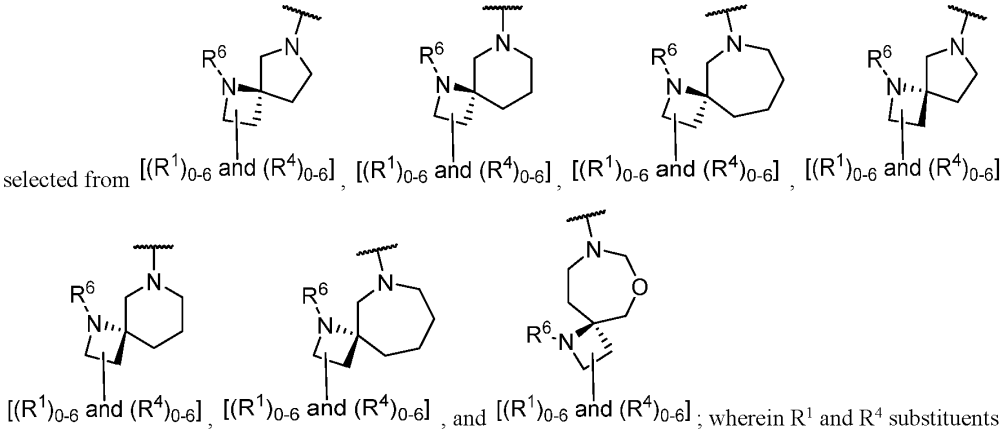
Embodiment 17. The method or pharmaceutical composition of any one of embodiments 11 to 16, wherein R^7 is selected from





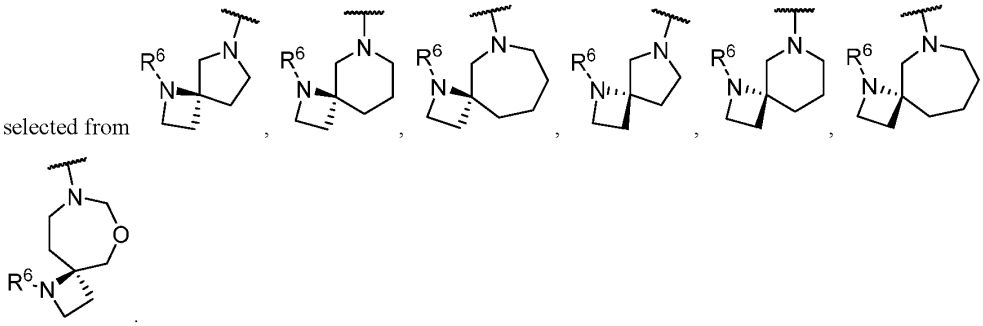
; wherein R^1 and R^4 substituents may be bonded to either spirocyclic ring.

Embodiment 18. The method or pharmaceutical composition of any one of embodiments 11 to 17, wherein R^7 is selected from

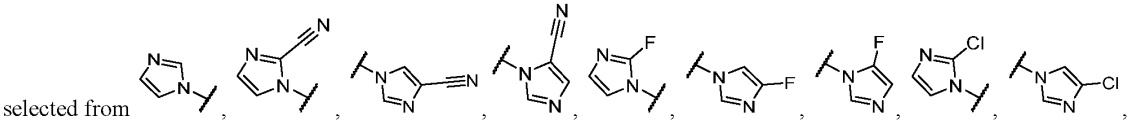


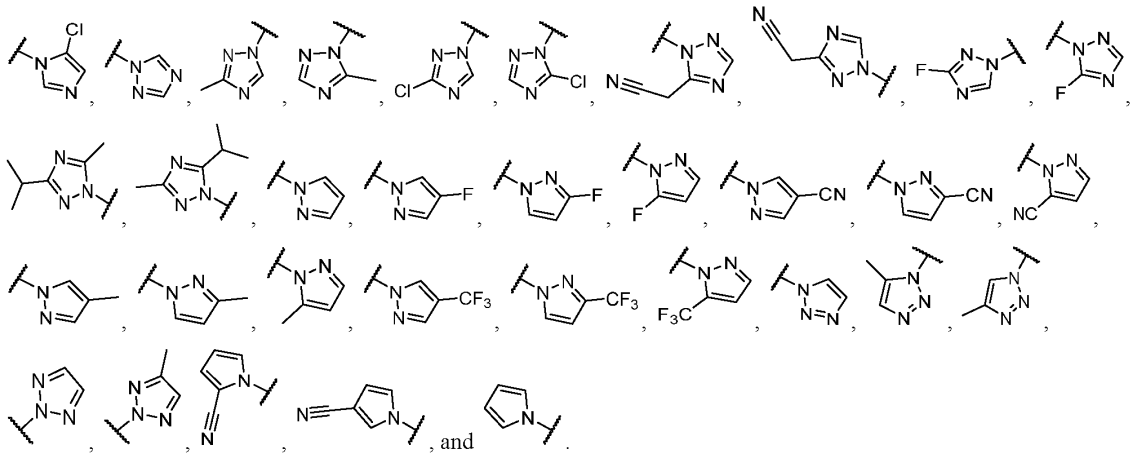
; wherein R^1 and R^4 substituents may be bonded to either spirocyclic ring.

Embodiment 19. The method or pharmaceutical composition of any one of embodiments 11 to 17, wherein R^7 is selected from

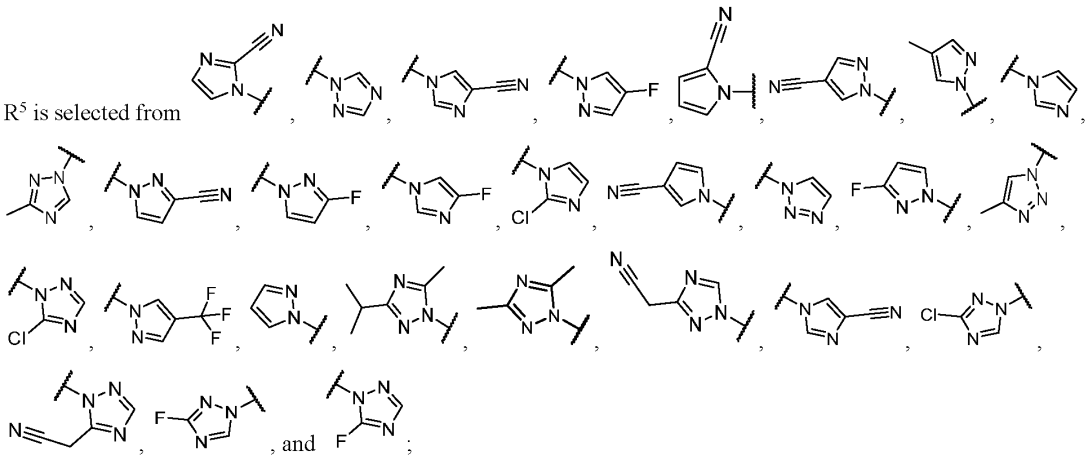


Embodiment 20. The method or pharmaceutical composition of any one of embodiments 11 to 19, wherein R^5 is selected from

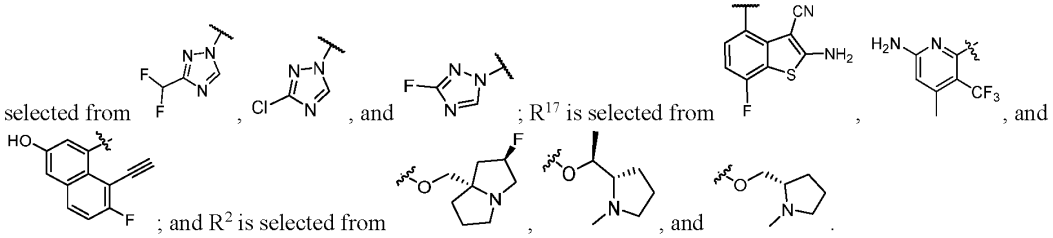




Embodiment 21. The method or pharmaceutical composition of any one of embodiments 11 to 19, wherein R^5 is selected from

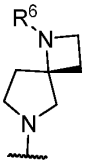


Embodiment 22. The method or pharmaceutical composition of any one of embodiments 11 to 21, wherein R^5 is selected from

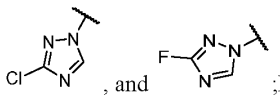


; and R^2 is selected from

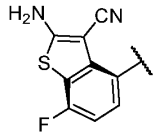
Embodiment 23. The method or pharmaceutical composition of any one of embodiments 11 to 21, wherein L^7 is a bond;R^7 is



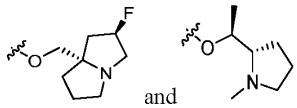
; L^2 is -C(O)-; R^5 is a selected from



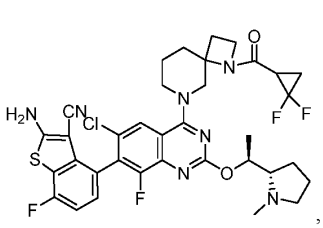
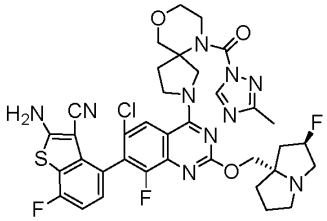
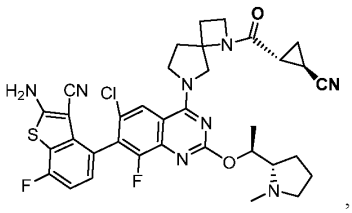
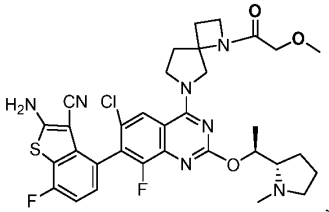
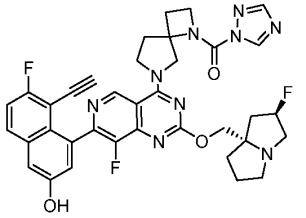
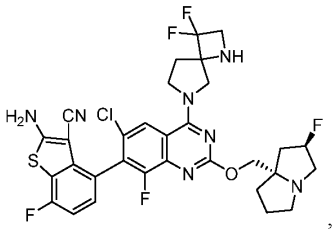
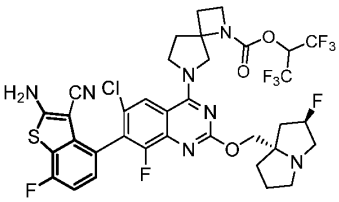
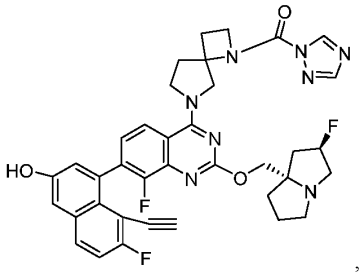
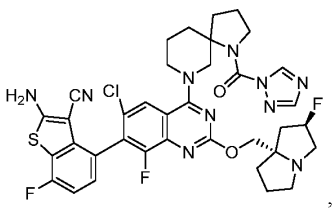
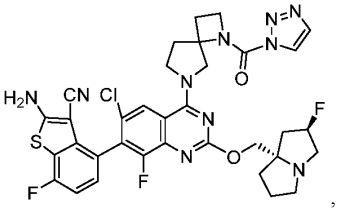
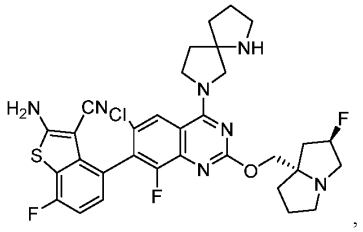
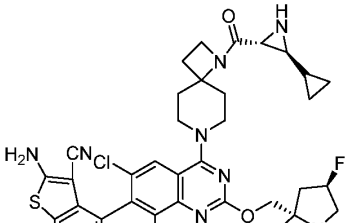
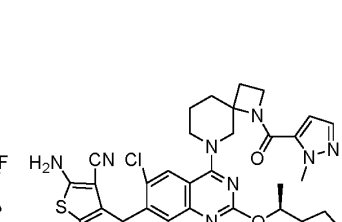
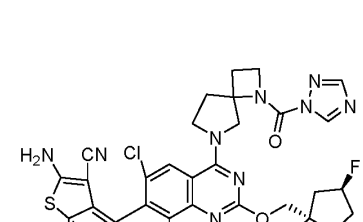
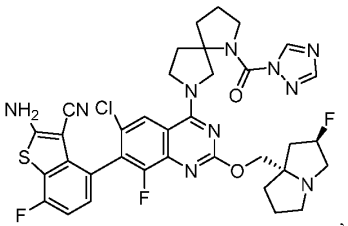
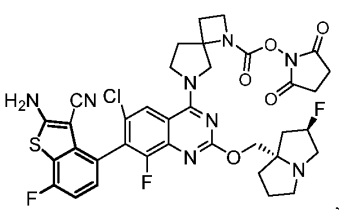
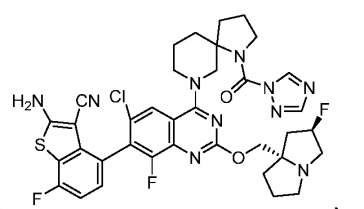
;R^8 is independently -Cl; R^{17} is

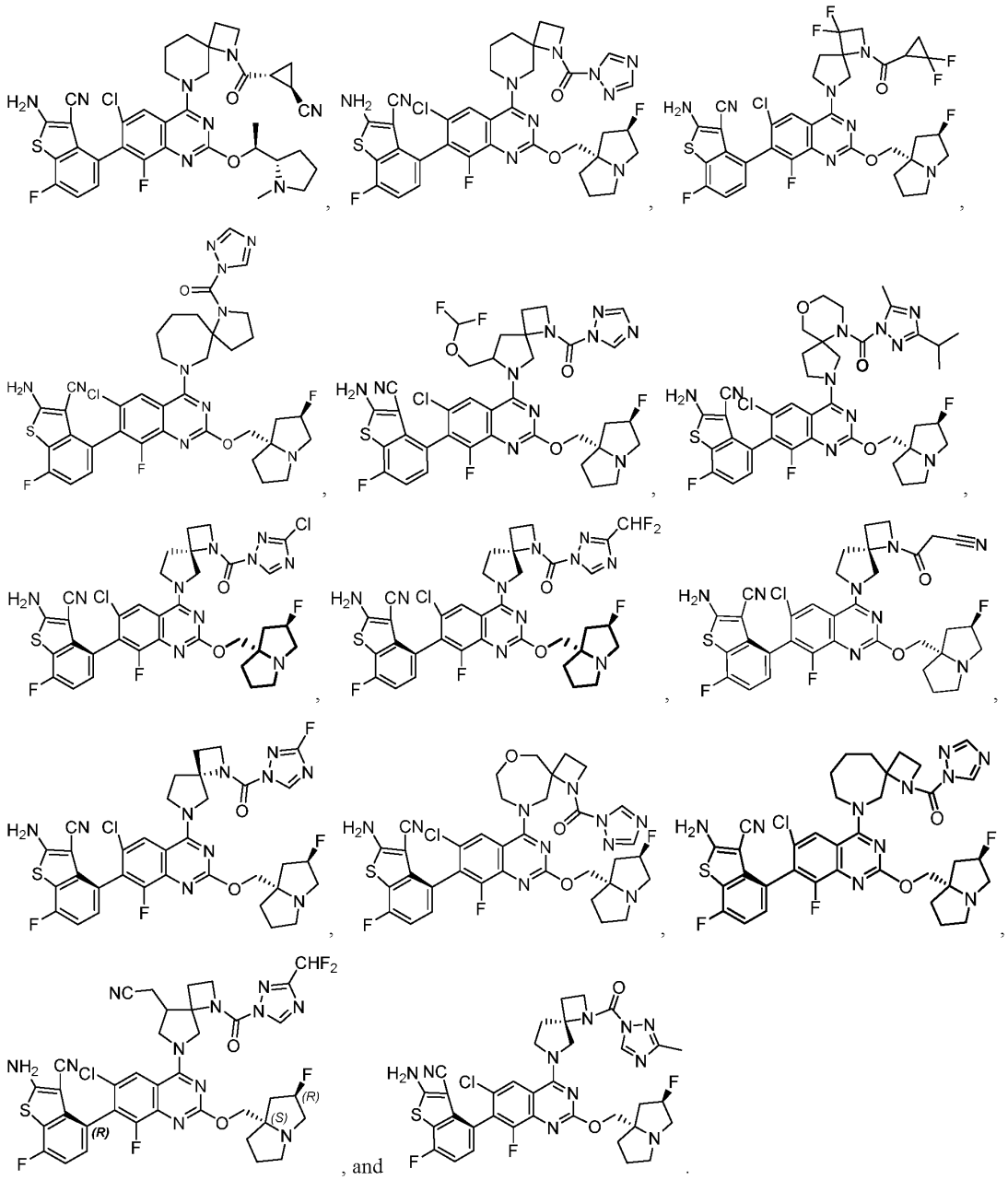


; R^{16} is -F; and R^2 is selected from

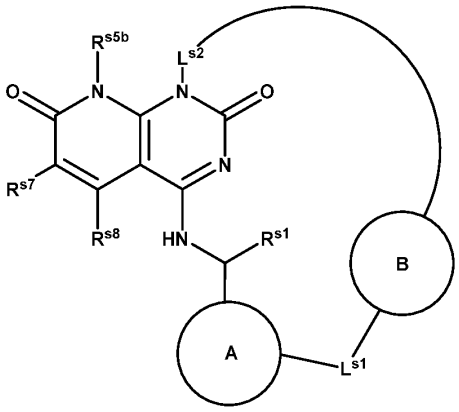


Embodiment 24. The method or pharmaceutical composition of any preceding embodiment, wherein the KRAS

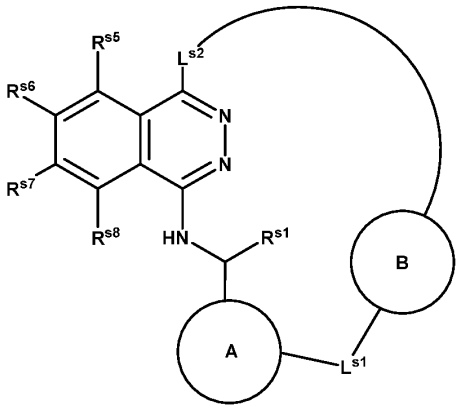
inhibitor is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , ,  ,  ,  .



Embodiment 25. The method or pharmaceutical composition of any preceding embodiment, wherein the SOS1 inhibitor has the structure of Formula (SI-B1) or (SI-B2):

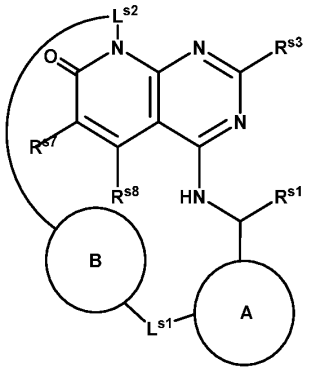


(SI-B1), or

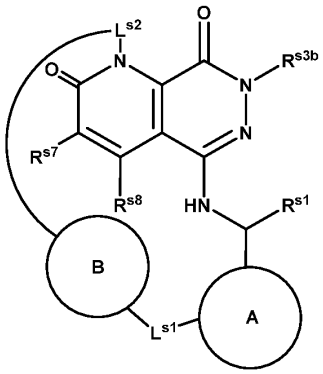


(SI-B2).

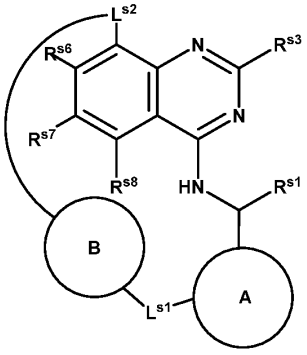
Embodiment 26. The method or pharmaceutical composition of any preceding embodiment, wherein the SOS1 inhibitor has the structure of Formula (SI-C1), (SI-C2), or (SI-C3):



(SI-C1),



(SI-C2), or



(SI-C3).

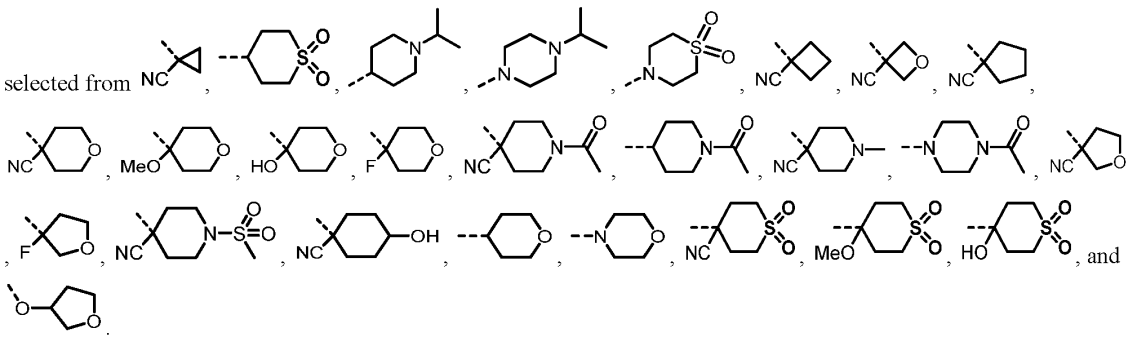
Embodiment 27. The method or pharmaceutical composition of any one of embodiments 1 to 26, wherein R^{s1} is -CH_3.

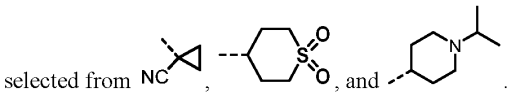
Embodiment 28. The method or pharmaceutical composition of any one of embodiments 1 to 27, wherein R^{s3} is selected from hydrogen, -CN, -OR^{s12}, and -CH_3.

Embodiment 29. The method or pharmaceutical composition of any one of embodiments 1 to 28, wherein R^{s6} is selected from hydrogen, -OR^{s12}, and C_{1-6} alkyl optionally substituted with one, two, or three R^{s20}, and wherein R^{s12} is

selected from C_{1-6} alkyl.

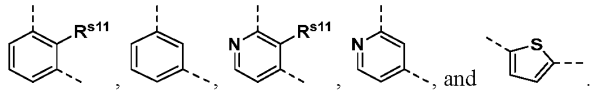
Embodiment 30. The method or pharmaceutical composition of any one of embodiments 1 to 29, wherein R^{s7} is selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $-N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl are optionally substituted with one, two, or three R^{s20}.

Embodiment 31. The method or pharmaceutical composition of any one of embodiments 1 to 29, wherein R^{s7} is selected from  .

Embodiment 32. The method or pharmaceutical composition of any one of embodiments 1 to 29, wherein R^{s7} is selected from  .

Embodiment 33. The method or pharmaceutical composition of any one of embodiments 1 to 32, wherein R^{s8} is hydrogen.

Embodiment 34. The method or pharmaceutical composition of any one of embodiments 1 to 33, wherein is selected from phenyl and 5- to 7-membered heteroaryl, each of which is optionally substituted with one or more R^{s11}.

Embodiment 35. The method or pharmaceutical composition of any one of embodiments 1 to 33, wherein is selected from  .

Embodiment 36. The method or pharmaceutical composition of any one of embodiments 1 to 35, wherein R^{s11} is independently selected from fluorine and $-CH_3$.

Embodiment 37. The method or pharmaceutical composition of any one of embodiments 1 to 36, wherein L^{s1} is C_{1-3} haloalkylene.

Embodiment 38. The method or pharmaceutical composition of any one of embodiments 1 to 36, wherein L^{s1} is selected from $-CF_2-$, $-CF_2CH_2-$, and $-CF_2CH_2CH_2-$.

Embodiment 39. The method or pharmaceutical composition of any one of embodiments 1 to 38, wherein

is selected from absent, phenyl, and 4- to 8-membered heterocycle, wherein the phenyl and 4- to 8-membered heterocycle are optionally substituted with one or more R^{s11a}.

Embodiment 40. The method or pharmaceutical composition of any one of embodiments 1 to 38, wherein

is selected from azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more $-CH_3$.

Embodiment 41. The method or pharmaceutical composition of any one of embodiments 1 to 40, wherein L^{s2} is selected from C_{6-15} alkylene, C_{6-15} alkenylene, C_{6-15} alkynylene, 6- to 15-membered heteroalkylene, and 6- to 15-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}.

Embodiment 42. The method or pharmaceutical composition of any one of embodiments 1 to 40, wherein L^{s2} is selected from C_{5-10} alkylene, C_{5-10} alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}.

Embodiment 43. The method or pharmaceutical composition of any one of embodiments 1 to 42, wherein the alkenylene and heteroalkenylene contain one carbon-carbon double bond.

Embodiment 44. The method or pharmaceutical composition of any one of embodiments 1 to 43, wherein the heteroalkylene and heteroalkenylene comprise at least one oxygen or nitrogen atom.

Embodiment 45. The method or pharmaceutical composition of any one of embodiments 1 to 44, wherein:

R^{s5} is hydrogen;

R^{s5b} is $-CH_3$;

R^{s6} is selected from hydrogen and $-OCH_3$;

R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}; and

R^{s8} is hydrogen.

Embodiment 46. The method or pharmaceutical composition of any one of embodiments 1 to 45, wherein:

R^{s3} is hydrogen or $-CH_3$;

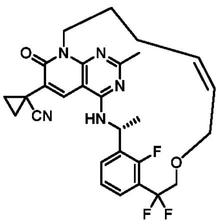
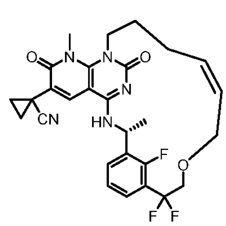
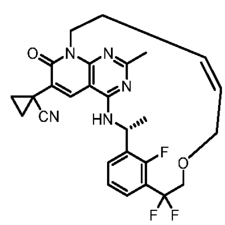
R^{s3b} is $-CH_3$;

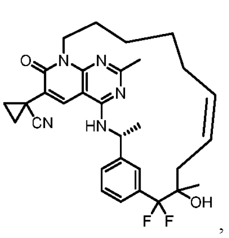
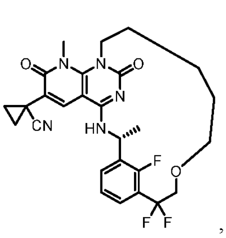
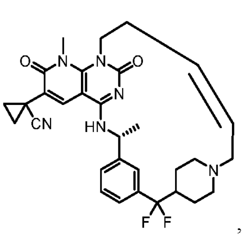
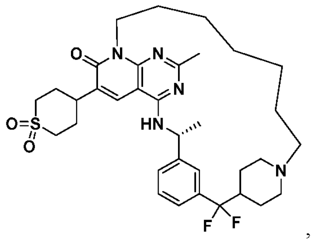
R^{s6} is selected from hydrogen and $-OCH_3$;

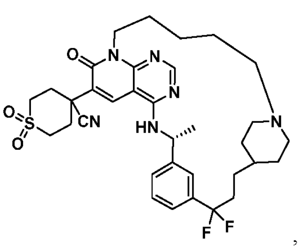
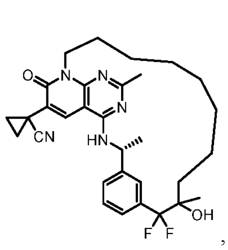
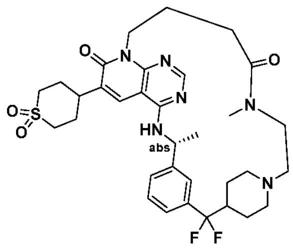
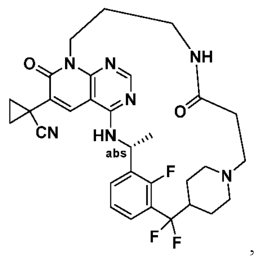
R^{s7} is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, and $-SO_2N(R^{s12})(R^{s13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20}; and

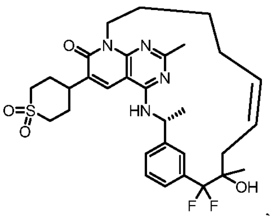
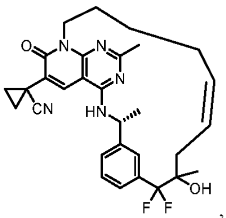
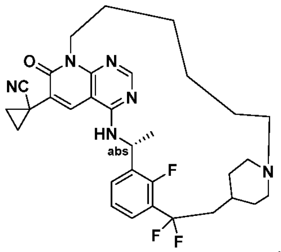
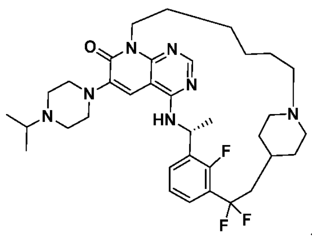
R^{s8} is hydrogen.

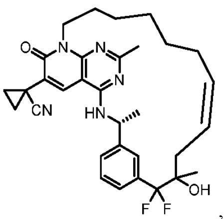
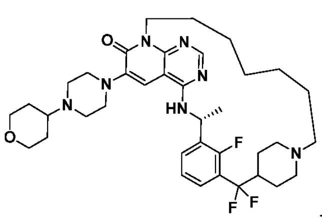
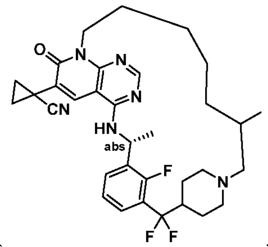
Embodiment 47. The method or pharmaceutical composition of any one of embodiments 1 to 24, wherein the

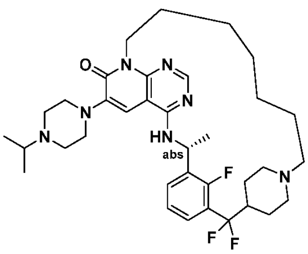
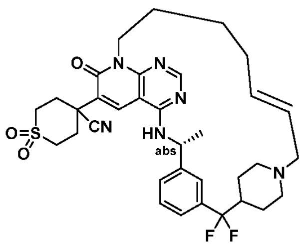
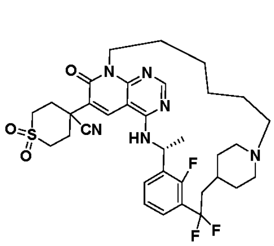
SOS1 inhibitor is selected from  ,  ,  ,

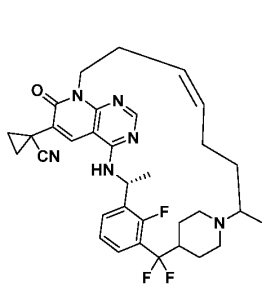
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,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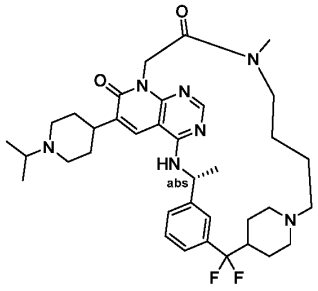
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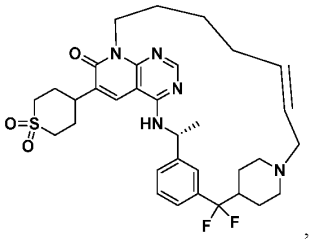
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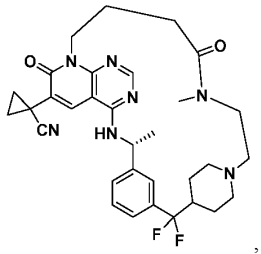
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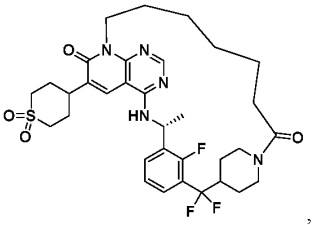
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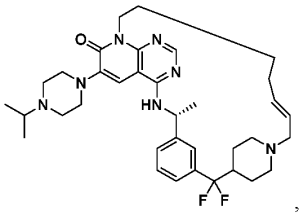
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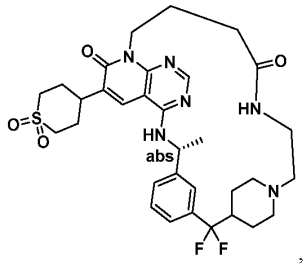
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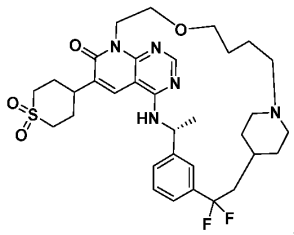
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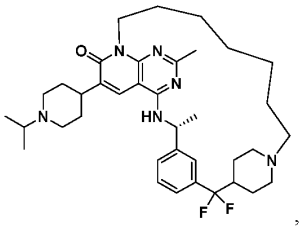
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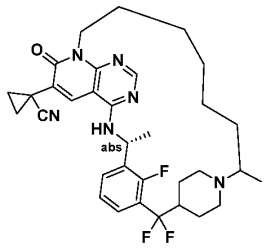
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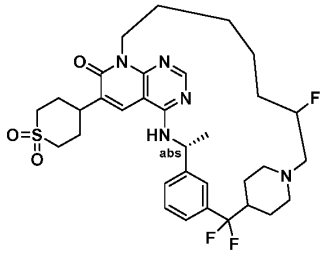
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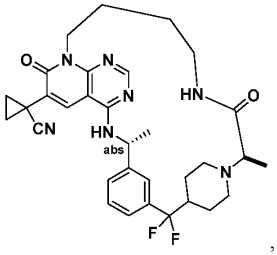
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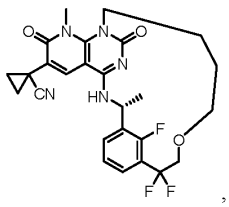
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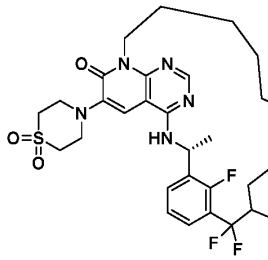
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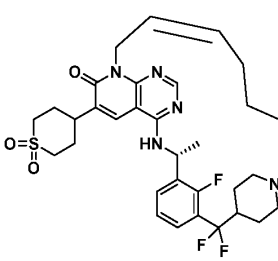
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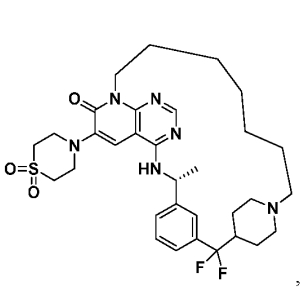
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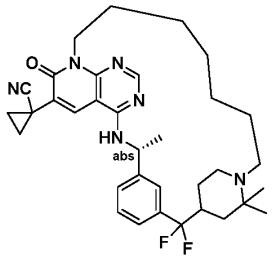
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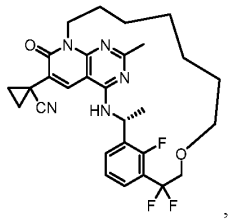
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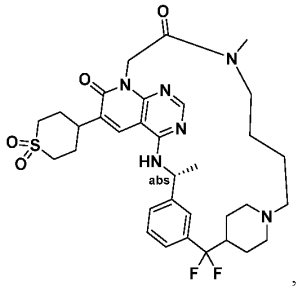
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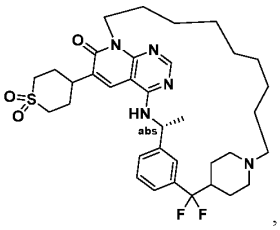
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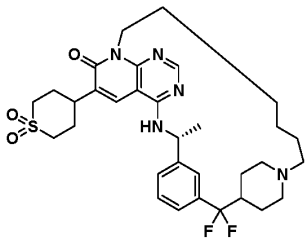
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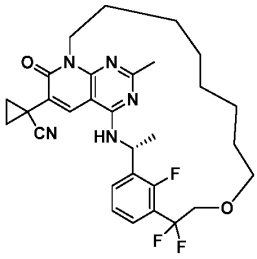
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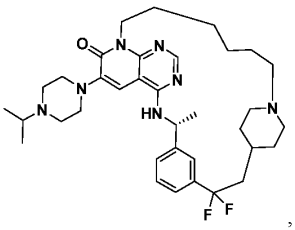
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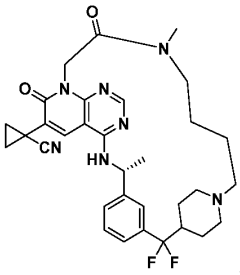
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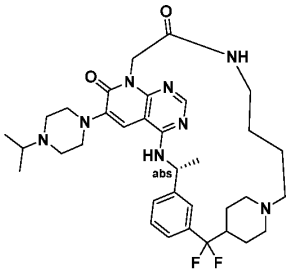
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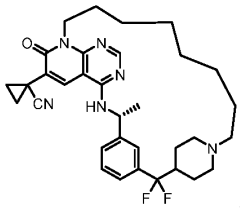
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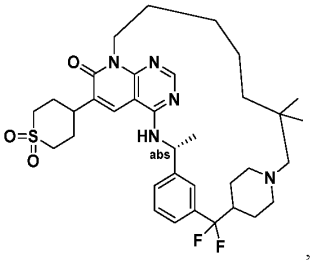
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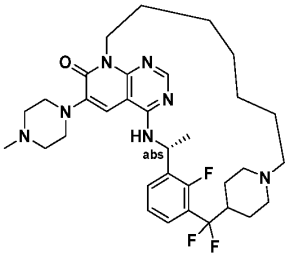
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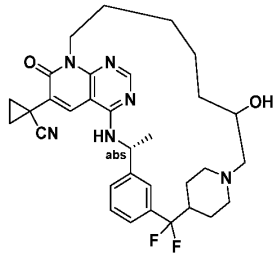
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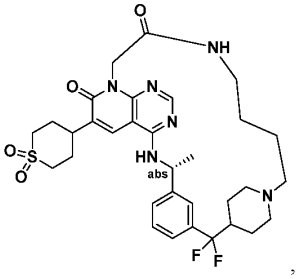
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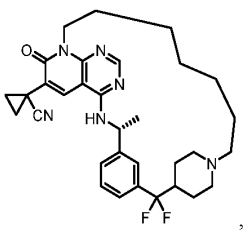
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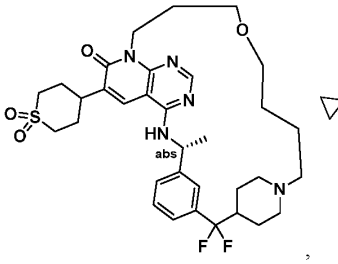
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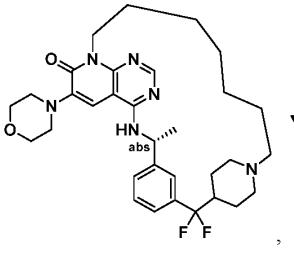
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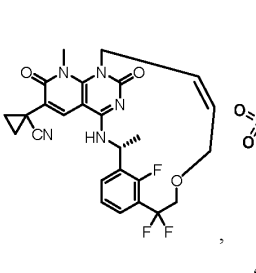
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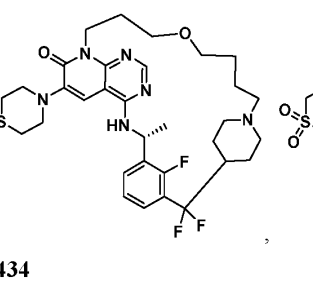
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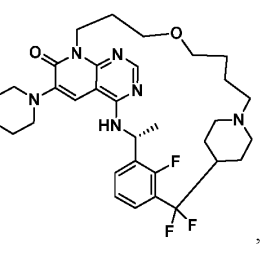
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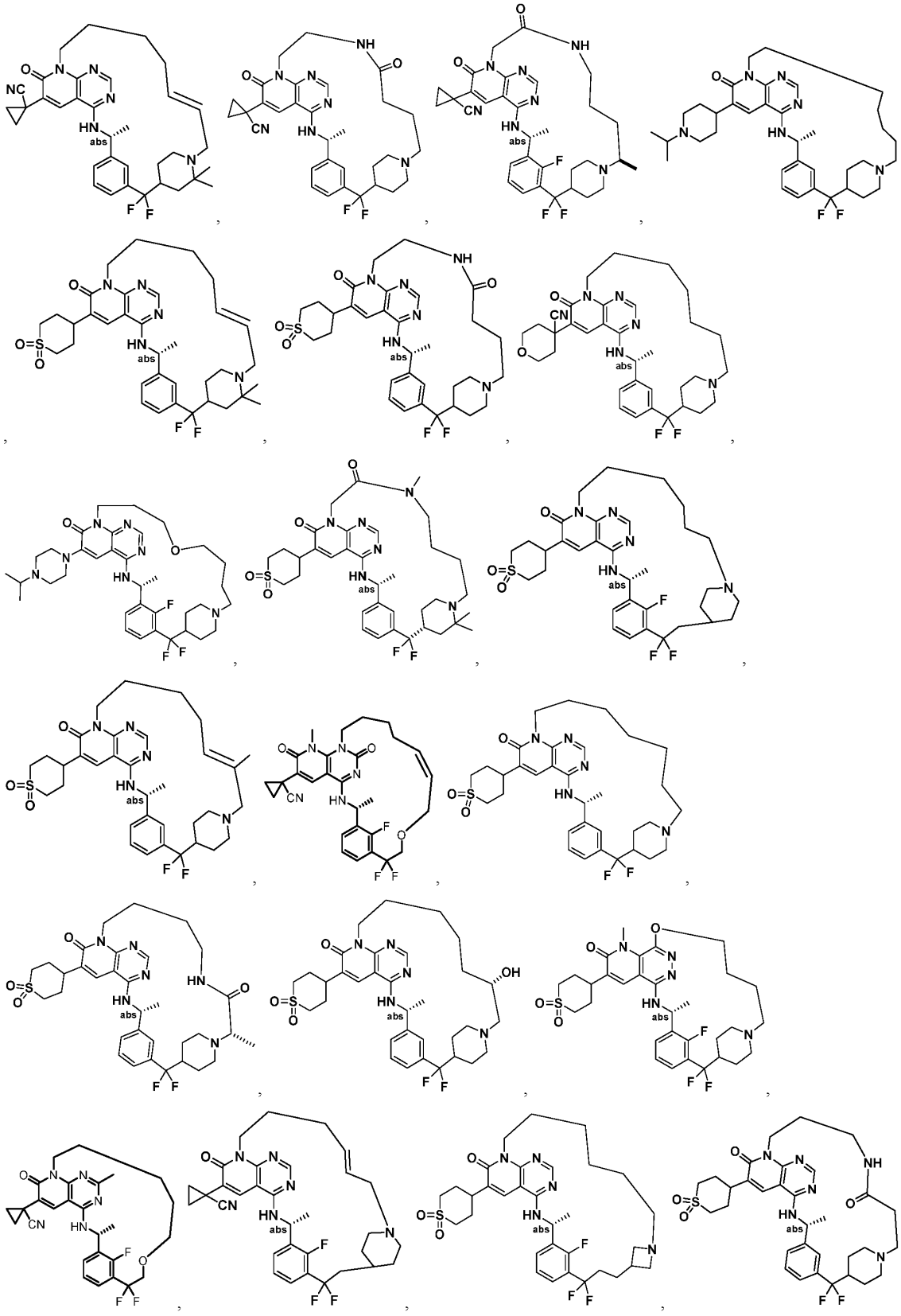

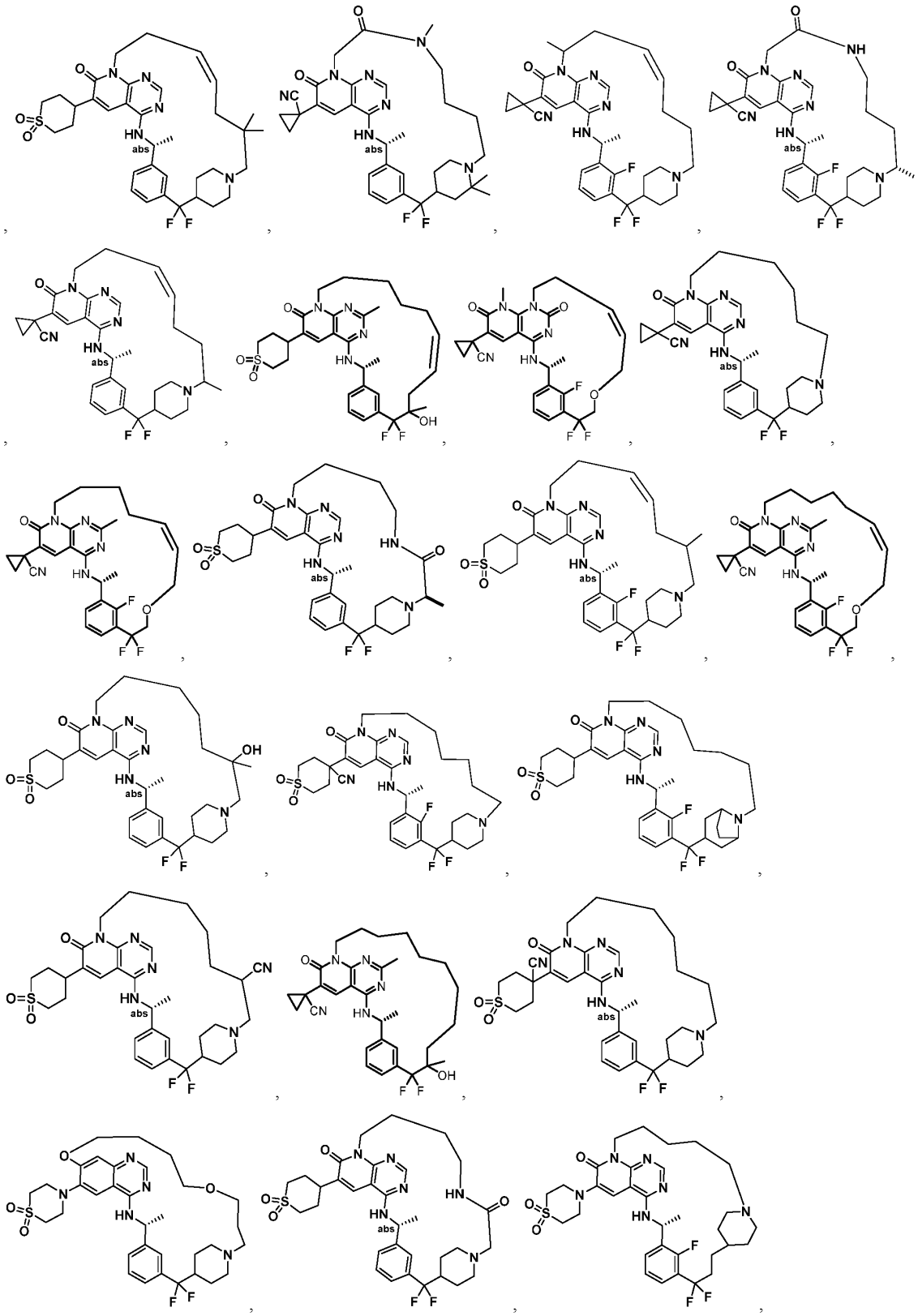

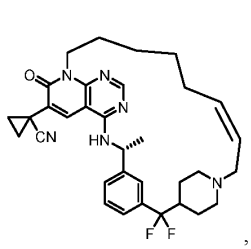
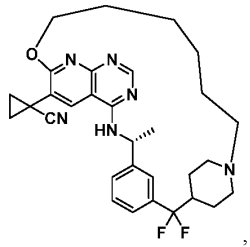
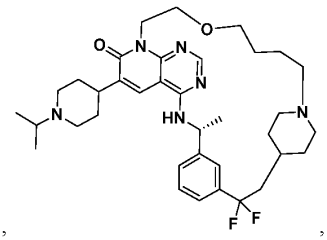
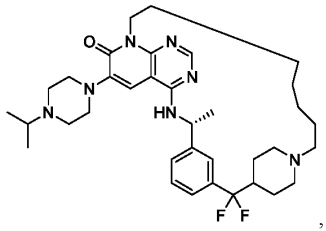
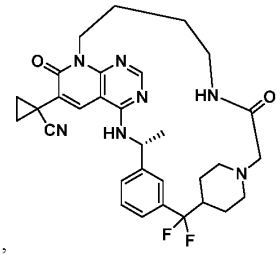
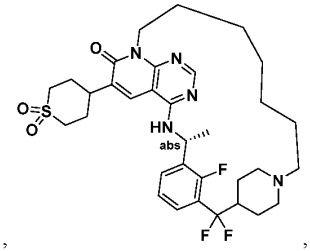
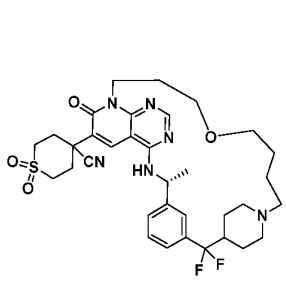
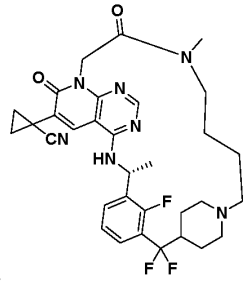
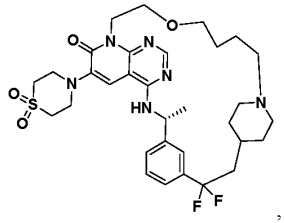
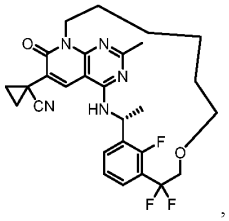
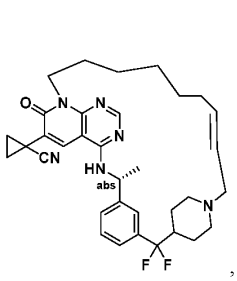
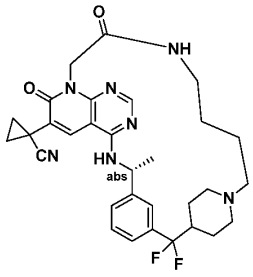
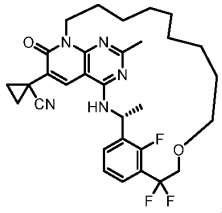
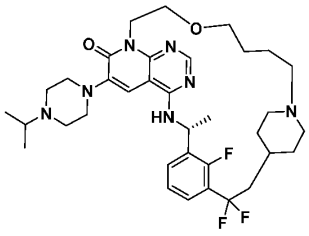
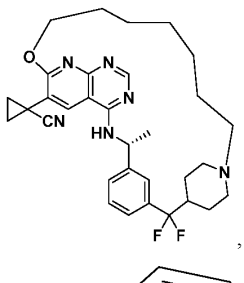
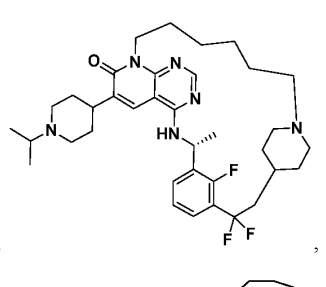
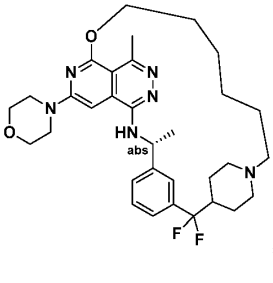

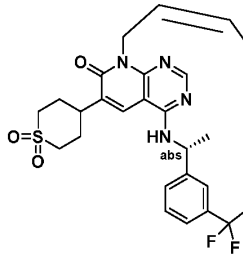
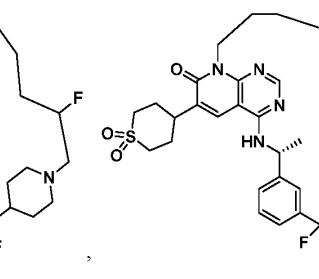
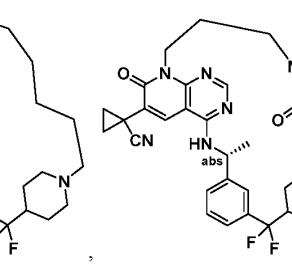

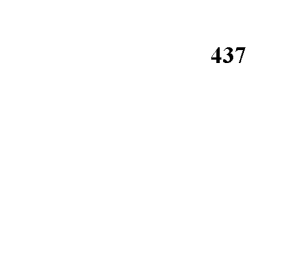

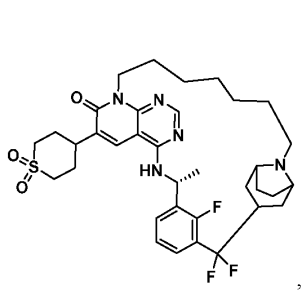
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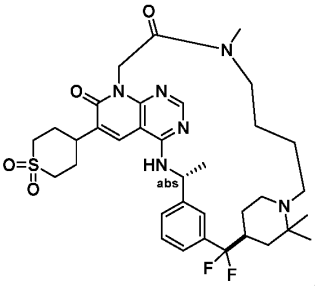
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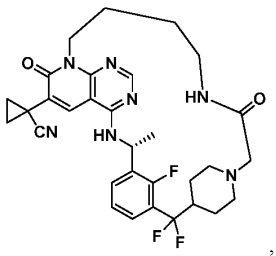
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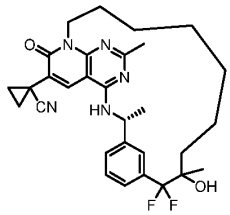
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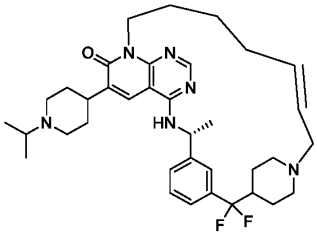
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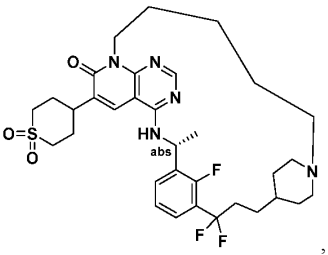
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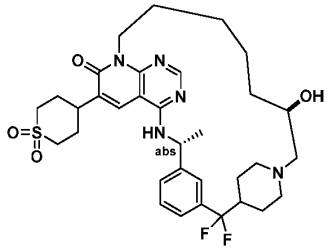
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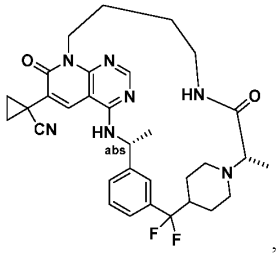
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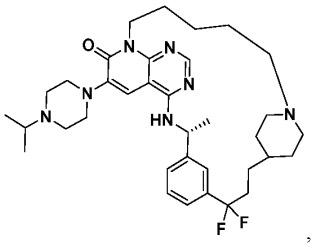
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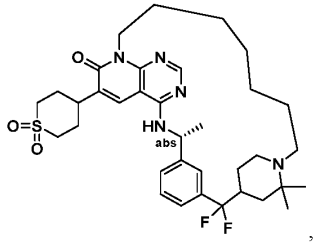
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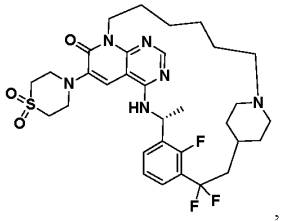
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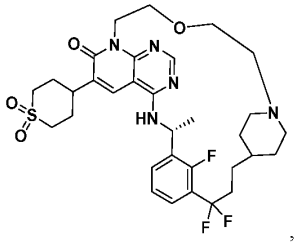
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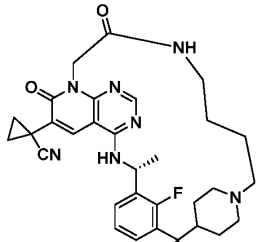
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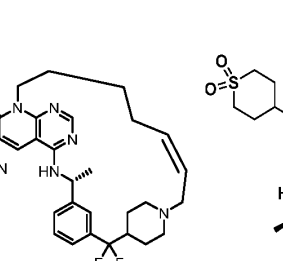
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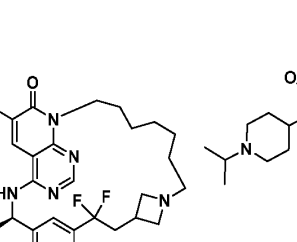
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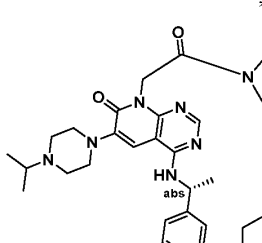
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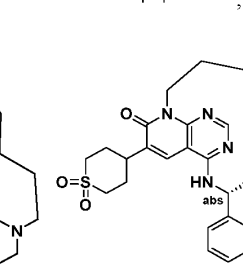
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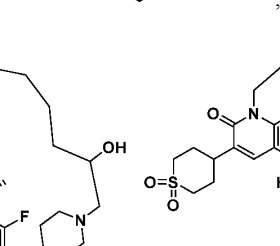
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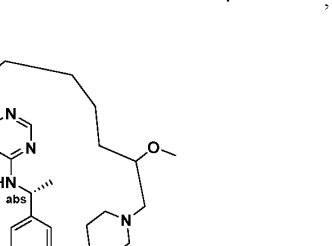
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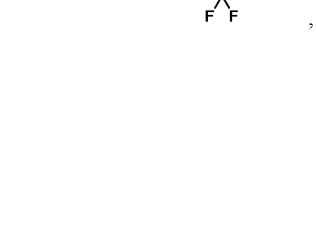
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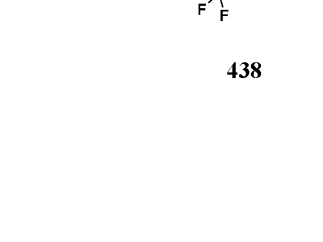
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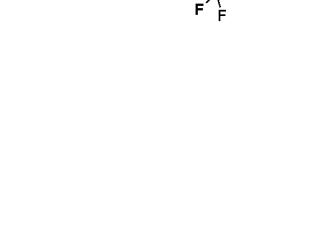
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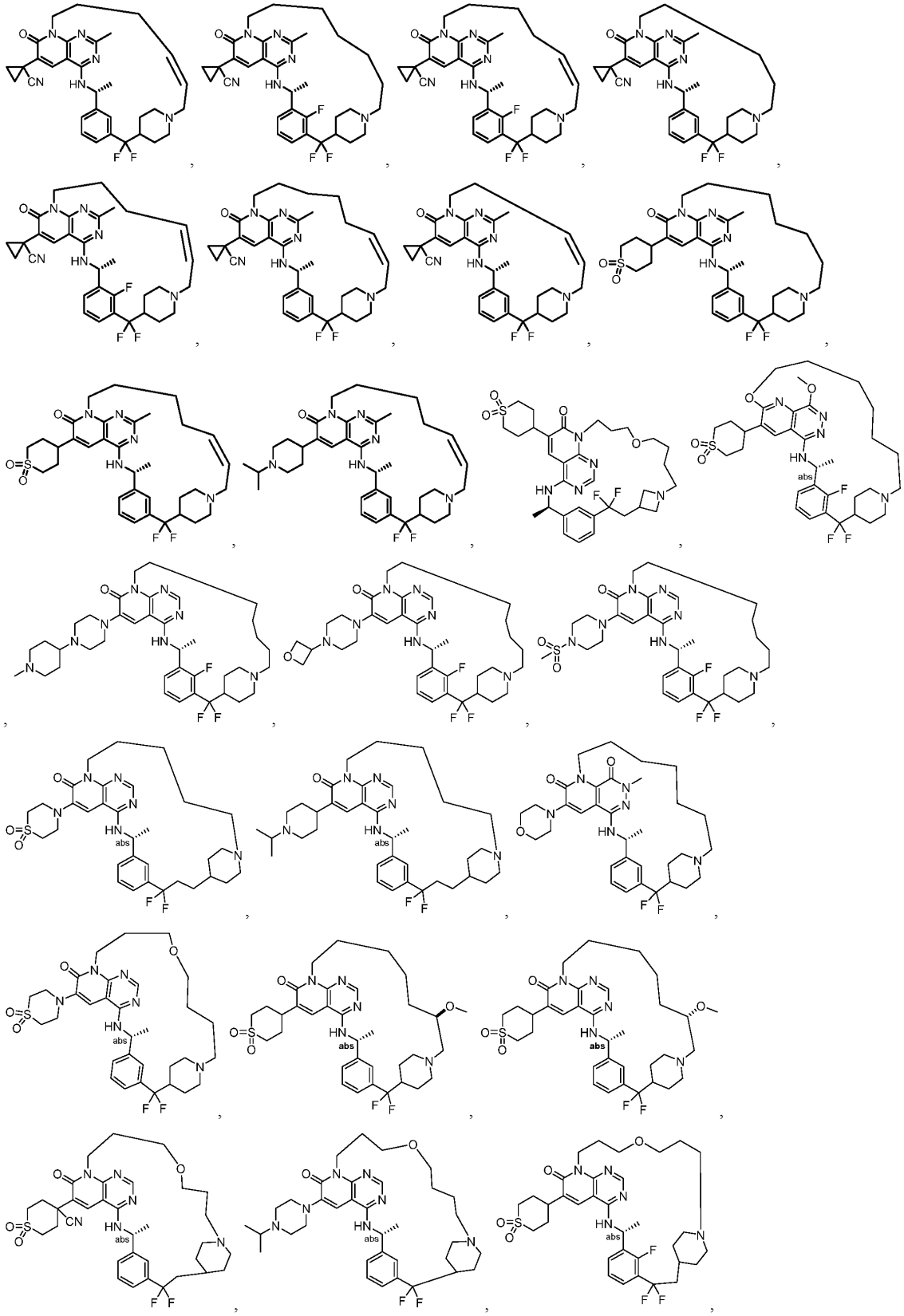

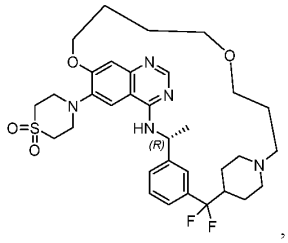
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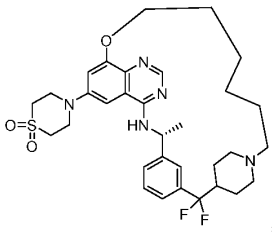
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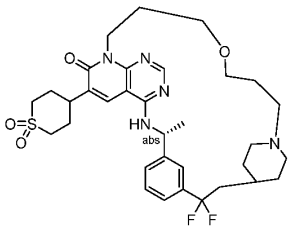
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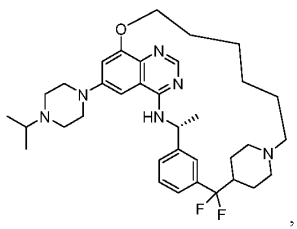
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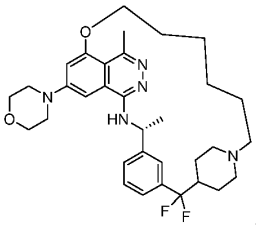
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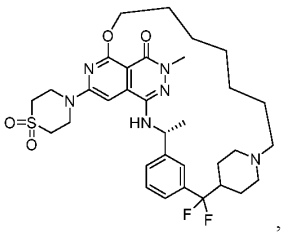
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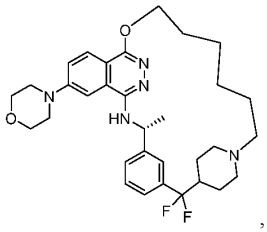
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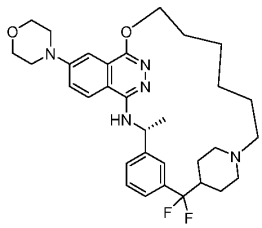
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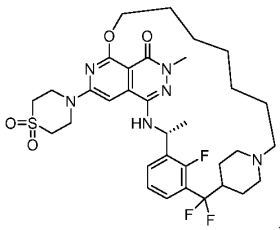
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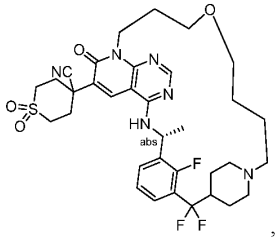
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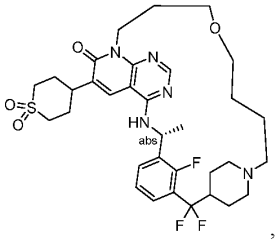
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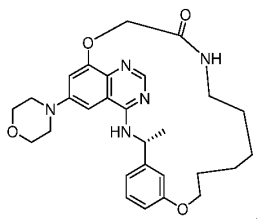
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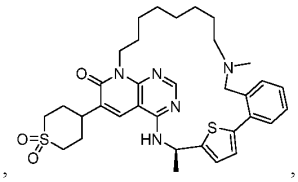
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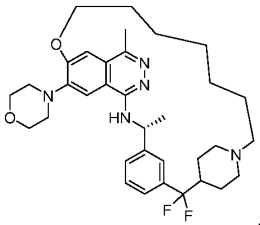
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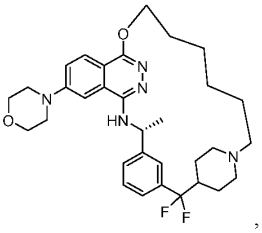
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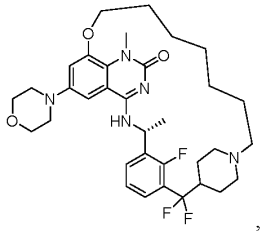
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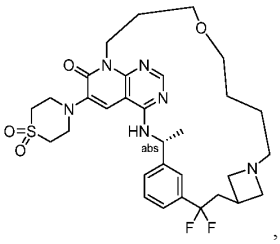
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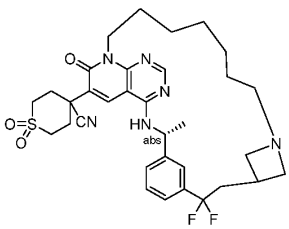
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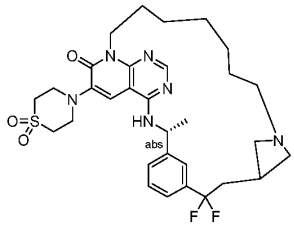
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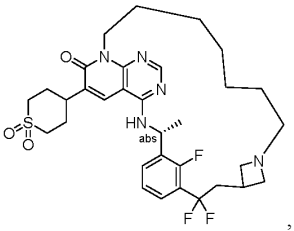
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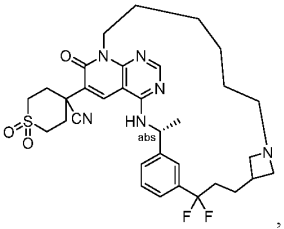
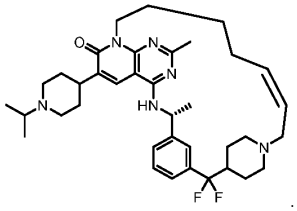
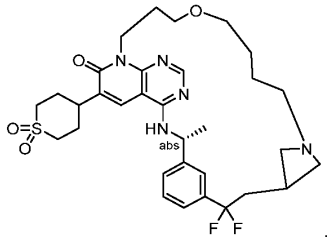

, or a pharmaceutically acceptable salt or solvate thereof.

Embodiment 48. The method or pharmaceutical composition of any one of embodiments 1 to 24, wherein the

SOS1 inhibitor has the structure  .

Embodiment 49. The method or pharmaceutical composition of any one of embodiments 1 to 24, wherein the SOS1 inhibitor has the structure  .

Embodiment 50. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 201 of Table 1a. Embodiment 51. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 202 of Table 1a. Embodiment 52. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 203 of Table 1a. Embodiment 53. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 204 of Table 1a. Embodiment 54. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 205 of Table 1a. Embodiment 55. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 206 of Table 1a. Embodiment 56. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 207 of Table 1a. Embodiment 57. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 208 of Table 1a. Embodiment 58. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 209 of Table 1a. Embodiment 59. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 210 of Table 1a. Embodiment 60. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 211 of Table 1a. Embodiment 61. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 212 of Table 1a. Embodiment 62. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 213 of Table 1a. Embodiment 63. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 214 of Table 1a. Embodiment 64. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 215 of Table 1a. Embodiment 65. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 216 of Table 1a. Embodiment 66. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 217 of Table 1a. Embodiment 67. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 218 of Table 1a. Embodiment 68. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 219 of Table 1a. Embodiment 69. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 220 of Table 1a. Embodiment 70. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 221 of Table

1a. Embodiment 71. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 222 of Table 1a. Embodiment 72. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 223 of Table 1a. Embodiment 73. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 224 of Table 1a. Embodiment 74. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 225 of Table 1a. Embodiment 75. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 226 of Table 1a. Embodiment 76. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 227 of Table 1a. Embodiment 77. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 228 of Table 1a. Embodiment 78. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 229 of Table 1a. Embodiment 79. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 230 of Table 1a. Embodiment 80. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 231 of Table 1a. Embodiment 81. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 232 of Table 1a. Embodiment 82. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 233 of Table 1a. Embodiment 83. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 234 of Table 1a. Embodiment 84. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 235 of Table 1a. Embodiment 85. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 236 of Table 1a. Embodiment 86. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 237 of Table 1a. Embodiment 87. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 238 of Table 1a. Embodiment 88. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 239 of Table 1a. Embodiment 89. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 240 of Table 1a. Embodiment 90. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 241 of Table 1a. Embodiment 91. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 242 of Table 1a. Embodiment 92. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 243 of Table 1a. Embodiment 93. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 244 of Table 1a. Embodiment 94. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 245 of Table 1a. Embodiment 95. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 246 of Table 1a. Embodiment 96. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 247 of Table 1a. Embodiment 97. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 248 of Table 1a. Embodiment 98. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 249 of Table 1a. Embodiment 99. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 250 of Table 1a. Embodiment 100. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 251 of Table 1a. Embodiment 101. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the

KRAS inhibitor is compound 252 of Table 1a. Embodiment 102. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 253 of Table 1a. Embodiment 103. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 254 of Table 1a. Embodiment 104. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 255 of Table 1a. Embodiment 105. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 256 of Table 1a. Embodiment 106. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 257 of Table 1a. Embodiment 107. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 258 of Table 1a. Embodiment 108. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 259 of Table 1a. Embodiment 109. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 260 of Table 1a. Embodiment 110. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 261 of Table 1a. Embodiment 111. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 262 of Table 1a. Embodiment 112. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 263 of Table 1a. Embodiment 113. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 264 of Table 1a. Embodiment 114. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 265 of Table 1a. Embodiment 115. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 266 of Table 1a. Embodiment 116. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 267 of Table 1a. Embodiment 117. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 268 of Table 1a. Embodiment 118. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 269 of Table 1a. Embodiment 119. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 270 of Table 1a. Embodiment 120. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 271 of Table 1a. Embodiment 121. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 272 of Table 1a. Embodiment 122. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 273 of Table 1a. Embodiment 123. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 274 of Table 1a. Embodiment 124. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 275 of Table 1a. Embodiment 125. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 276 of Table 1a. Embodiment 126. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 277 of Table 1a. Embodiment 127. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 278 of Table 1a. Embodiment 128. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 279 of Table 1a. Embodiment 129. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 280 of Table 1a. Embodiment 130. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 281 of Table 1a. Embodiment 131. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS

inhibitor is compound 282 of Table 1a. Embodiment 132. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 283 of Table 1a. Embodiment 133. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 284 of Table 1a. Embodiment 134. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 285 of Table 1a. Embodiment 135. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 286 of Table 1a. Embodiment 136. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 287 of Table 1a. Embodiment 137. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 288 of Table 1a. Embodiment 138. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 289 of Table 1a. Embodiment 139. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 290 of Table 1a. Embodiment 140. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 291 of Table 1a. Embodiment 141. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 292 of Table 1a. Embodiment 142. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 293 of Table 1a. Embodiment 143. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 294 of Table 1a. Embodiment 144. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 295 of Table 1a. Embodiment 145. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 296 of Table 1a. Embodiment 146. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 297 of Table 1a. Embodiment 147. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 298 of Table 1a. Embodiment 148. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 299 of Table 1a. Embodiment 149. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 300 of Table 1a. Embodiment 150. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 301 of Table 1a. Embodiment 151. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 302 of Table 1a. Embodiment 152. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 303 of Table 1a. Embodiment 153. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 304 of Table 1a. Embodiment 154. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 305 of Table 1a. Embodiment 155. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 306 of Table 1a. Embodiment 156. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 307 of Table 1a. Embodiment 157. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 308 of Table 1a. Embodiment 158. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 309 of Table 1a. Embodiment 159. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 310 of Table 1a. Embodiment 160. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 311 of Table 1a. Embodiment 161. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound

312 of Table 1a. Embodiment 162. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 313 of Table 1a. Embodiment 163. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 314 of Table 1a. Embodiment 164. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 315 of Table 1a. Embodiment 165. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 316 of Table 1a. Embodiment 166. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 317 of Table 1a. Embodiment 167. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 318 of Table 1a. Embodiment 168. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 319 of Table 1a. Embodiment 169. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 320 of Table 1a. Embodiment 170. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 321 of Table 1a. Embodiment 171. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 322 of Table 1a. Embodiment 172. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 323 of Table 1a. Embodiment 173. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 324 of Table 1a. Embodiment 174. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 325 of Table 1a. Embodiment 175. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 326 of Table 1a. Embodiment 176. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 327 of Table 1a. Embodiment 177. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 328 of Table 1a. Embodiment 178. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 329 of Table 1a. Embodiment 179. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 330 of Table 1a. Embodiment 180. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 331 of Table 1a. Embodiment 181. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 332 of Table 1a. Embodiment 182. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 333 of Table 1a. Embodiment 183. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 334 of Table 1a. Embodiment 184. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 335 of Table 1a. Embodiment 185. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 336 of Table 1a. Embodiment 186. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 337 of Table 1a. Embodiment 187. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 338 of Table 1a. Embodiment 188. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 339 of Table 1a. Embodiment 189. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 340 of Table 1a. Embodiment 190. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 341 of Table 1a. Embodiment 191. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 342 of

Table 1a. Embodiment 192. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 343 of Table 1a. Embodiment 193. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 344 of Table 1a. Embodiment 194. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 345 of Table 1a. Embodiment 195. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 346 of Table 1a. Embodiment 196. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 347 of Table 1a. Embodiment 197. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 348 of Table 1a. Embodiment 198. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 349 of Table 1a. Embodiment 199. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 350 of Table 1a. Embodiment 200. The method or pharmaceutical composition of any one of embodiments 1 to 49, wherein the KRAS inhibitor is compound 351 of Table 1a. Embodiment 201. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S1 of Table 2a. Embodiment 202. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S2 of Table 2a. Embodiment 203. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S3 of Table 2a. Embodiment 204. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S4 of Table 2a. Embodiment 205. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S5 of Table 2a. Embodiment 206. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S6 of Table 2a. Embodiment 207. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S7 of Table 2a. Embodiment 208. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S8 of Table 2a. Embodiment 209. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S9 of Table 2a. Embodiment 210. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S10 of Table 2a. Embodiment 211. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S11 of Table 2a. Embodiment 212. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S12 of Table 2a. Embodiment 213. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S13 of Table 2a. Embodiment 214. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S14 of Table 2a. Embodiment 215. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S15 of Table 2a. Embodiment 216. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S16 of Table 2a. Embodiment 217. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S17 of Table 2a. Embodiment 218. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S18 of Table 2a. Embodiment 219. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S19 of Table 2a. Embodiment 220. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S20 of Table 2a. Embodiment 221. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S21 of Table 2a.

Embodiment 222. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S22 of Table 2a. Embodiment 223. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S23 of Table 2a. Embodiment 224. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S24 of Table 2a. Embodiment 225. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S25 of Table 2a. Embodiment 226. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S26 of Table 2a. Embodiment 227. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S27 of Table 2a. Embodiment 228. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S28 of Table 2a. Embodiment 229. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S29 of Table 2a. Embodiment 230. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S30 of Table 2a. Embodiment 231. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S31 of Table 2a. Embodiment 232. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S32 of Table 2a. Embodiment 233. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S33 of Table 2a. Embodiment 234. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S34 of Table 2a. Embodiment 235. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S35 of Table 2a. Embodiment 236. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S36 of Table 2a. Embodiment 237. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S37 of Table 2a. Embodiment 238. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S38 of Table 2a. Embodiment 239. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S39 of Table 2a. Embodiment 240. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S40 of Table 2a. Embodiment 241. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S41 of Table 2a. Embodiment 242. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S42 of Table 2a. Embodiment 243. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S43 of Table 2a. Embodiment 244. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S44 of Table 2a. Embodiment 245. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S45 of Table 2a. Embodiment 246. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S46 of Table 2a. Embodiment 247. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S47 of Table 2a. Embodiment 248. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S48 of Table 2a. Embodiment 249. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S49 of Table 2a. Embodiment 250. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S50 of Table 2a. Embodiment 251. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound

S51 of Table 2a. Embodiment 252. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S52 of Table 2a. Embodiment 253. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S53 of Table 2a. Embodiment 254. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S54 of Table 2a. Embodiment 255. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S55 of Table 2a. Embodiment 256. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S56 of Table 2a. Embodiment 257. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S57 of Table 2a. Embodiment 258. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S58 of Table 2a. Embodiment 259. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S59 of Table 2a. Embodiment 260. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S60 of Table 2a. Embodiment 261. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S61 of Table 2a. Embodiment 262. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S62 of Table 2a. Embodiment 263. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S63 of Table 2a. Embodiment 264. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S64 of Table 2a. Embodiment 265. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S65 of Table 2a. Embodiment 266. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S66 of Table 2a. Embodiment 267. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S67 of Table 2a. Embodiment 268. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S68 of Table 2a. Embodiment 269. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S69 of Table 2a. Embodiment 270. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S70 of Table 2a. Embodiment 271. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S71 of Table 2a. Embodiment 272. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S72 of Table 2a. Embodiment 273. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S73 of Table 2a. Embodiment 274. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S74 of Table 2a. Embodiment 275. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S75 of Table 2a. Embodiment 276. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S76 of Table 2a. Embodiment 277. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S77 of Table 2a. Embodiment 278. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S78 of Table 2a. Embodiment 279. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S79 of Table 2a. Embodiment 280. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S80 of Table 2a. Embodiment 281. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein

the SOS1 inhibitor is compound S81 of Table 2a. Embodiment 282. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S82 of Table 2a. Embodiment 283. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S83 of Table 2a. Embodiment 284. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S84 of Table 2a. Embodiment 285. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S85 of Table 2a. Embodiment 286. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S86 of Table 2a. Embodiment 287. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S87 of Table 2a. Embodiment 288. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S88 of Table 2a. Embodiment 289. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S89 of Table 2a. Embodiment 290. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S90 of Table 2a. Embodiment 291. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S91 of Table 2a. Embodiment 292. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S92 of Table 2a. Embodiment 293. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S93 of Table 2a. Embodiment 294. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S94 of Table 2a. Embodiment 295. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S95 of Table 2a. Embodiment 296. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S96 of Table 2a. Embodiment 297. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S97 of Table 2a. Embodiment 298. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S98 of Table 2a. Embodiment 299. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S99 of Table 2a. Embodiment 300. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S100 of Table 2a. Embodiment 301. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S101 of Table 2a. Embodiment 302. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S102 of Table 2a. Embodiment 303. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S103 of Table 2a. Embodiment 304. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S104 of Table 2a. Embodiment 305. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S105 of Table 2a. Embodiment 306. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S106 of Table 2a. Embodiment 307. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S107 of Table 2a. Embodiment 308. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S108 of Table 2a. Embodiment 309. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S109 of Table 2a. Embodiment 310. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S110 of Table 2a. Embodiment 311. The method or pharmaceutical composition of any one of

embodiments 1 to 200, wherein the SOS1 inhibitor is compound S111 of Table 2a. Embodiment 312. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S112 of Table 2a. Embodiment 313. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S113 of Table 2a. Embodiment 314. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S114 of Table 2a. Embodiment 315. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S115 of Table 2a. Embodiment 316. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S116 of Table 2a. Embodiment 317. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S117 of Table 2a. Embodiment 318. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S118 of Table 2a. Embodiment 319. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S119 of Table 2a. Embodiment 320. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S120 of Table 2a. Embodiment 321. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S121 of Table 2a. Embodiment 322. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S122 of Table 2a. Embodiment 323. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S123 of Table 2a. Embodiment 324. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S124 of Table 2a. Embodiment 325. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S125 of Table 2a. Embodiment 326. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S126 of Table 2a. Embodiment 327. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S127 of Table 2a. Embodiment 328. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S128 of Table 2a. Embodiment 329. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S129 of Table 2a. Embodiment 330. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S130 of Table 2a. Embodiment 331. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S131 of Table 2a. Embodiment 332. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S132 of Table 2a. Embodiment 333. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S133 of Table 2a. Embodiment 334. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S134 of Table 2a. Embodiment 335. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S135 of Table 2a. Embodiment 336. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S136 of Table 2a. Embodiment 337. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S137 of Table 2a. Embodiment 338. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S138 of Table 2a. Embodiment 339. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S139 of Table 2a. Embodiment 340. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S140 of Table 2a. Embodiment 341. The method or pharmaceutical

composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S141 of Table 2a. Embodiment 342. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S142 of Table 2a. Embodiment 343. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S143 of Table 2a. Embodiment 344. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S144 of Table 2a. Embodiment 345. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S145 of Table 2a. Embodiment 346. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S146 of Table 2a. Embodiment 347. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S147 of Table 2a. Embodiment 348. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S148 of Table 2a. Embodiment 349. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S149 of Table 2a. Embodiment 350. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S150 of Table 2a. Embodiment 351. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S151 of Table 2a. Embodiment 352. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S152 of Table 2a. Embodiment 353. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S153 of Table 2a. Embodiment 354. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S154 of Table 2a. Embodiment 355. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S155 of Table 2a. Embodiment 356. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S156 of Table 2a. Embodiment 357. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S157 of Table 2a. Embodiment 358. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S158 of Table 2a. Embodiment 359. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S159 of Table 2a. Embodiment 360. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S160 of Table 2a. Embodiment 361. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S161 of Table 2a. Embodiment 362. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S162 of Table 2a. Embodiment 363. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S163 of Table 2a. Embodiment 364. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S164 of Table 2a. Embodiment 365. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S165 of Table 2a. Embodiment 366. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S166 of Table 2a. Embodiment 367. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S167 of Table 2a. Embodiment 368. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S168 of Table 2a. Embodiment 369. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S169 of Table 2a. Embodiment 370. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S170 of Table 2a. Embodiment 371. The

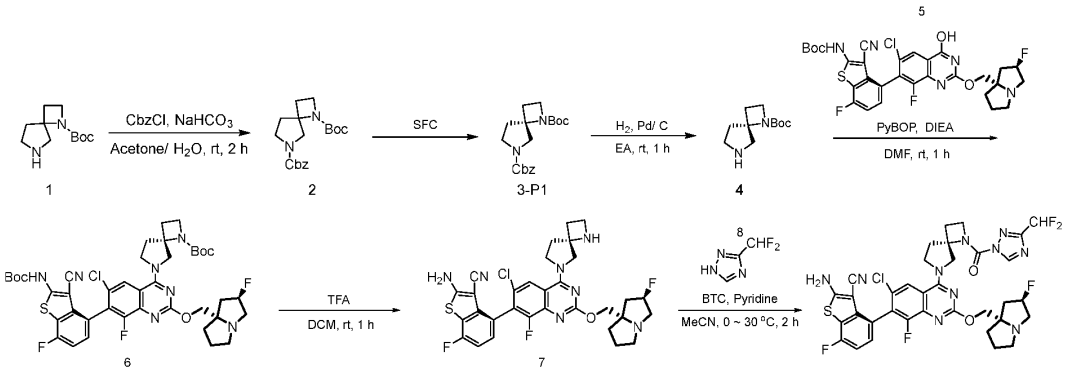
method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S171 of Table 2a. Embodiment 372. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S172 of Table 2a. Embodiment 373. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S173 of Table 2a. Embodiment 374. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S174 of Table 2a. Embodiment 375. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S175 of Table 2a. Embodiment 376. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S176 of Table 2a. Embodiment 377. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S177 of Table 2a. Embodiment 378. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S178 of Table 2a. Embodiment 379. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S179 of Table 2a. Embodiment 380. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S180 of Table 2a. Embodiment 381. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S181 of Table 2a. Embodiment 382. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S182 of Table 2a. Embodiment 383. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S183 of Table 2a. Embodiment 384. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S184 of Table 2a. Embodiment 385. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S185 of Table 2a. Embodiment 386. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S186 of Table 2a. Embodiment 387. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S187 of Table 2a. Embodiment 388. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S188 of Table 2a. Embodiment 389. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S189 of Table 2a. Embodiment 390. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S190 of Table 2a. Embodiment 391. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S191 of Table 2a. Embodiment 392. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S192 of Table 2a. Embodiment 393. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S193 of Table 2a. Embodiment 394. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S194 of Table 2a. Embodiment 395. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S195 of Table 2a. Embodiment 396. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S196 of Table 2a. Embodiment 397. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S197 of Table 2a. Embodiment 398. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S198 of Table 2a. Embodiment 399. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S199 of Table 2a. Embodiment 400. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S200 of

Table 2a. Embodiment 401. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S201 of Table 2a. Embodiment 402. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S202 of Table 2a. Embodiment 403. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S203 of Table 2a. Embodiment 404. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S204 of Table 2a. Embodiment 405. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S205 of Table 2a. Embodiment 406. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S206 of Table 2a. Embodiment 407. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S207 of Table 2a. Embodiment 408. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S208 of Table 2a. Embodiment 409. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S209 of Table 2a. Embodiment 410. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S210 of Table 2a. Embodiment 411. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S211 of Table 2a. Embodiment 412. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S212 of Table 2a. Embodiment 413. The method or pharmaceutical composition of any one of embodiments 1 to 200, wherein the SOS1 inhibitor is compound S213 of Table 2a. The method of any preceding embodiment, wherein the KRAS inhibitor and/or the SOS1 inhibitor are included in one pharmaceutical composition or in separate pharmaceutical compositions, wherein the single or multiple pharmaceutical compositions each further comprises an independently selected pharmaceutically acceptable excipient.

EXAMPLES

[636] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example A: Synthesis of 2-amino-4-((R)-6-chloro-4-((R)-1-(3-(difluoromethyl)-1H-1,2,4-triazole-1-carbonyl)-1,6-diazaspiro[3.4]octan-6-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (278)



[637] To a solution of compound 1 (2 g, 7.78 mmol) and $NaHCO_3$ (1.31 g, 15.56 mmol) in acetone (20 ml) and H_2O (10 ml) was added CbzCl (1.33 g, 7.78 mmol). The reaction mixture was stirred at 25 °C for 1 h. The solution was extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine (100 mL), dried over anhydrous

sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by silica gel column (PE/EA=2/1) to give compound 2 (2.2 g, Yield: 81 %) as colorless oily liquid.

[638] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 5.20 – 5.05 (m, 2H), 4.00 – 3.30 (m, 6H), 2.70 – 2.30 (m, 1H), 2.25 – 2.04 (m, 2H), 1.96 (s, 1H), 1.55 – 1.23 (m, 9H).

[639] Compound 2 (4 g, 11.55 mmol) was separated by SFC (solvent: EtOH) to give compound 3-P1 (1.8 g) as colorless oily liquid and compound 3-P2 (1.6 g) as colorless oily liquid.

[640] To a solution of compound 3-P1 (1.5 g, 4.33 mmol) in ethyl acetate (50 ml) was added Pd/C (750 mg). The reaction mixture was stirred at 25 °C under H_2 atmosphere for 1 h. The reaction mixture was diluted with ethyl acetate (50 ml) and methanol (100 ml). The organic layer was filtered, and concentrated to afford compound 4 (780 mg, 85 %) as colorless oily liquid.

[641] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 – 3.65 (m, 2H), 3.54 – 3.05 (m, 2H), 2.95 – 2.62 (m, 2H), 2.42 – 2.17 (m, 4H), 1.91 (m, 1H), 1.65 – 1.35 (m, 9H).

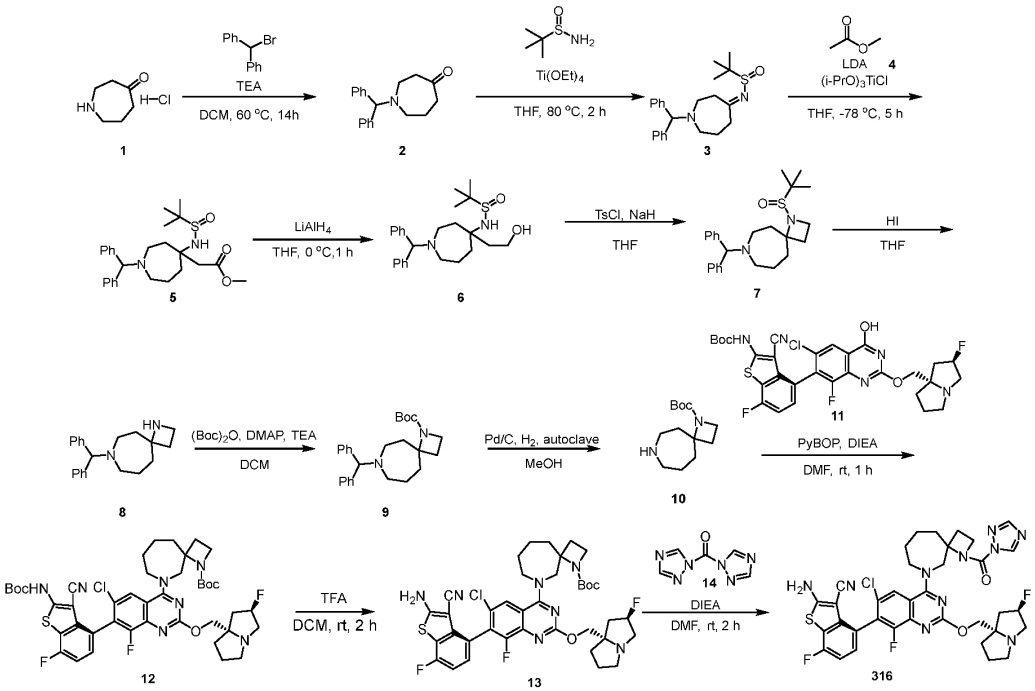
[642] To a solution of compound 4 (299 mg, 1.41 mmol), compound 5 (700 mg, 1.09 mmol), and PyBop (847 mg, 1.63 mmol) in DMF (5 mL) was added DIEA (210 mg, 1.63 mmol). The mixture was stirred at 25 °C for 1 h. The solution was extracted with ethyl acetate (100 mL x 3). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by silica gel column (DCM/ MeOH =15/1) to give compound 6 (700 mg, Yield: 77 %) as a yellow solid. MS m/z (ESI): 840.3 [M+H].

[643] To a solution of compound 6 (1.3 g, 1.55 mmol) in DCM (15 ml) was added TFA (15 ml). The reaction mixture was stirred at 20 °C for 30 min. The solvent was removed under reduced pressure. The reaction mixture was diluted with a.q. $NaHCO_3$ (200 mL) and DCM/ MeOH=10/ 1(300 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to give compound 7 (830 mg, Yield: 84 %) as a yellow solid. MS m/z (ESI): 640.6 [M+H].

[644] To a solution of compound 8 (274 mg, 2.30 mmol) and pyridine (0.74 mL, 9.21 mmol) in 9 mL MeCN, was added BTC (615 mg, 2.07 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was then stirred at 0 °C for 2 h. To a solution of compound 7 (90 mg, 0.14 mmol) in DME (1 mL) was added pyridine (0.37 ml, 4.6 mmol) and above reaction mixture (0.7 mL) at 30 °C under N_2 atmosphere. LCMS showed the reaction was completed. The mixture was poured into water (15 mL), and the solution was extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The crude was purified by prep-HPLC (FA) to give final product (27.10 mg, Yield: 24.6 %). MS m/z (ESI): 785.2 [M+H].

[645] 1H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.17 - 8.11 (m, 3H), 7.39 – 7.02 (m, 3H), 5.27 (d, J = 54.0 Hz, 1H), 4.74 – 4.49 (m, 3H), 4.27 – 3.96 (m, 5H), 3.11 – 3.00 (m, 3H), 2.95 - 2.75 (m, 2H), 2.67 – 2.57 (m, 1H), 2.46 – 2.32 (m, 2H), 2.14 – 1.71 (m, 6H).

Example B: Synthesis of 4-((7R)-4-(1-(1H-1,2,4-triazole-1-carbonyl)-1,6-diazaspiro[3.6]decan-6-yl)-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-2-amino-7-fluorobenzo[b]thiophene-3-carbonitrile (316)



[646] To a solution of 1 (1 g, 6.7 mmol) and TEA (1.35 mg, 13.4 mmol) in dry THF (10 mL) was added 1a (1.65 mg, 6.7 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (100 mL X 3). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by column on silica gel to give compound 2 as colorless oil. (1 g, Yield: 53%).

[647] A mixture of compound 2 (1 g, 3.582 mmol), compound 2a (650 mg, 5.37 mmol) and $Ti(OEt)_4$ (1.6 g, 7.1 mmol) in THF (10 ml) was stirred at 80 °C for 2 h. The mixture was added $Na_2SO_4 \cdot 10H_2O$ (100 mg) in ice bath, and the solution was extracted with ethyl acetate (100 mL x 3). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by silica gel column (PE/EA=9/20) to give compound 3 (670 mg, Yield: 48.9 %) as a white solid.

[648] N-butyllithium (2.5 M in hexanes, 9.4 mL, 23.55 mmol) was added dropwise at 0 °C to a solution of Diisopropylamine (1.99 g, 19.63 mmol) in dry THF (30 mL) and the solution was stirred at 0°C for 0.5 h. The reaction mixture was then cooled to -78 °C followed by dropwise addition of a solution of 4 (1.16 g, 15.7 mmol). The resulting reaction mixture was stirred at -78 °C for 1.5 h. After this time, a solution of $(i\text{-PrO})_3TiCl$ (24 mL, 23.56 mmol) was added dropwise and the reaction stirred for 1 h. A solution of sulfonamide 3 (3 g, 7.85 mmol) in THF (10 mL) was then added dropwise and the reaction stirred for an additional 1 h. The reaction mixture was diluted with NH_4Cl (aq) (50 mL) and extracted with EA (50 mL X 3). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by column on silica gel to give compound 5 as colorless oil. (1.9 g, Yield: 53%). MS m/z (ESI):457.3$[M+H]^+$.

[649] To a solution of 5 (2.3 g, 5.04 mmol) in dry THF (30 mL) was added $LiAlH_4$ (7.6 mL, 7.6 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. Water (0.3 mL), 2 mmol/L NaOH solution (0.3 mL) and water (0.6 mL) were added. The reaction solution was filtered, and the solution was extracted with ethyl acetate (100 mL x 3). Dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure The residue was purified by reversed phase column to give compound 6 (1.6 g, Yield: 81%) as colorless oil. MS m/z (ESI):

429.2[M+H]$^+$.

[650] To a solution of 6 (800 mg, 1.869 mmol) and TsCl (535 mg, 2.804 mmol) in dry THF (10 mL) was added NaH (300 mg, 7.48 mmol) at 0 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with NH_4Cl (aq) (20 mL) and extracted with EA (20 mL X 3). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by column on silica gel to give compound 7 as colorless oil. (510 mg, Yield: 65%). MS m/z (ESI): 411.2(M+H)+.

[651] To a solution of 7 (300 mg, 0.732 mmol) in THF (2 mL) was added HI (937 mg, 7.32 mmol) at 0 °C. The mixture was stirred at 25 °C for 2 h. The solvent was removed under reduced pressure. The reaction mixture was diluted with $NaHCO_3$ (aq) (20 mL) and DCM (50 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to afford compound 8 (400 mg, crude) as a colorless oil. MS m/z (ESI): 307.2 [M+H]$^+$.

[652] To a solution of 8 (400 mg, crude), TEA (303 mg, 3 mmol) and DMAP (24 mg, 0.2 mmol) in DCM (4 mL) was added $(Boc)_2O$ (327 mg, 1.5 mmol) at 0 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EA (10 mL X 3). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by column on silica gel to give compound 9 as colorless oil. (250 mg, Yield: 15%). MS m/z (ESI): 407.3

[653] To a solution of compound 9 (70 mg, 0.172 mmol) dissolved in EA (15 mL) in autoclave was added $Pd(OH)_2$ (70 mg) stirred at 50 °C under 2 Mpa H_2 for 1.5 h. The TLC (PE: EA=6/ 1) show the reaction was completed. The reaction mixture was diluted with methanol, filtered through diatomaceous earth and concentrated in vacuo to give compound 10 (70 mg, crude) as a colorless oily liquid.

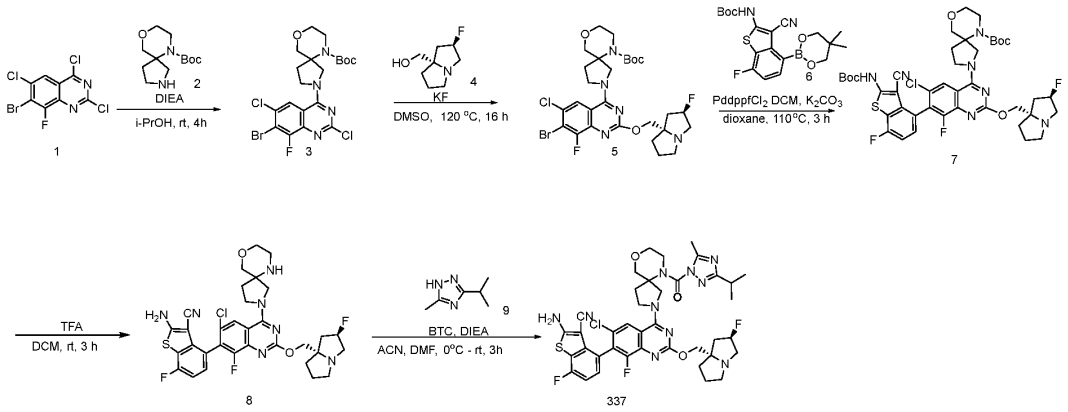
[654] To a solution of compound 11 (70 mg, 0.109 mmol), compound 10 (39 mg, 0.164 mmol) and PyBop (85 mg, 0.164 mmol) in DMF (2 ml) was added DIEA (21 mg, 0.164 mmol). The reaction mixture was stirred at 25 °C for 1 h. The mixture was poured into ice water (50 mL), and the solution was extracted with ethyl acetate (50 mL x 3). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by prep-TLC (DCM/ MeOH=15/ 1) to give compound 12 (50 mg, Yield: 53 %) as a yellow solid. MS m/z (ESI): 868.2 [M+H]

[655] To a solution of compound 12 (50 mg, 0.058 mmol) in DCM (1 ml) was added TFA (1 ml). The reaction mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure. The reaction mixture was diluted with a.q. $NaHCO_3$ (20 mL) and DCM (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was compound 13 (30 mg, Yield: 77 %) as a yellow solid. MS m/z (ESI): 668.3 [M+H].

[656] To a solution of compound 13 (30 mg, 0.045 mmol) and DIEA (17 mg, 0.135 mmol) in 0.8 mL DMF, was added compound 14 (22 mg, 0.135 mmol). The reaction mixture was then stirred at rt for 1 h. LCMS showed the reaction was completed. The crude was purified by prep-HPLC to give 316 (10.66 mg, Yield: 31 %). MS m/z (ESI): 763.2 [M+H].

[657] 1H NMR (400 MHz, DMSO-d_6) δ 9.06 (d, J = 16.4 Hz, 1H), 8.24 (d, J = 5.2 Hz, 1H), 8.12 (d, J = 14.8 Hz, 2H), 7.97 (d, J = 23.4 Hz, 1H), 7.31 – 7.20 (m, 1H), 7.15 (t, J = 8.4 Hz, 1H), 5.26 (d, J = 47.2 Hz, 1H), 4.86 (m, 1H), 4.60 – 3.73 (m, 7H), 3.09 – 2.58 (m, 4H), 2.43 – 1.52 (m, 14H).

Example C: Synthesis of 2-Amino-4-(6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro -1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(6-(3-isopropyl-5-methyl-1H-1,2,4-triazole-1-carbonyl)-9-oxa-2,6-diazaspiro[4.5]decan-2-yl)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (337)



[658] To a solution of compound 1 (680 mg, 2.06 mmol) and compound 2 (499 mg, 2.06 mmol) in i-PrOH (8 ml) was added DIEA (799 mg, 6.18 mmol). The reaction mixture was stirred at 25 °C for 4 h. The mixture was poured into ice water (100 mL). and the solution was extracted with ethyl acetate (100 mL X 3). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate. The organic solution was concentrated to dryness under reduced pressure to give compound 3 (1.0 g, Yield: 90.9%) as a yellow solid.

[659] MS m/z (ESI): 535.1 [M+H].

[660] To a solution of compound 3 (950 mg, 1.77 mmol) and compound 4 (1.41 g, 8.86 mmol) in DMSO (10 ml) was added KF (514 mg, 8.86 mmol). The reaction mixture was stirred at 120 °C for 16 h. The mixture was poured into ice water (100 mL), and the solution was extracted with ethyl acetate (100 mL x 3). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by silica gel column (PE/EA=1/1) to give compound 5 (400 mg, Yield: 34.4 %) as a yellow solid.

[661] MS m/z (ESI): 658.2 [M+H].

[662] To a solution of compound 5 (400 mg, 0.61 mmol), compound 6 (410 mg, 1.22 mmol), and K_2CO_3 (506 mg, 3.66 mmol) in 1,4-dioxane (15 mL) was added $PddppfCl_2$ with DCM (49 mg, 0.06 mmol). The mixture was stirred at 110 °C under nitrogen for 3 hours. The mixture was poured into water (100 mL), and the solution was extracted with ethyl acetate (100 mL X 3). The organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by silica gel column (PE/EA=1/1) to give compound 7 (430 mg, Yield: 81.13 %) as a white solid. MS m/z (ESI): 870.3 [M+H].

[663] To a solution of compound 7 (170 mg, 0.20 mmol) in DCM (10 ml) was added TFA (5 ml). The reaction mixture was stirred at rt for 3 h. The reaction mixture was concentrated to dryness under reduced pressure. The reaction mixture was diluted with a.q. $NaHCO_3$ (20 mL) and EA (50 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure to give compound 8 (130 mg, Yield: 99.3 %) as a yellow solid.

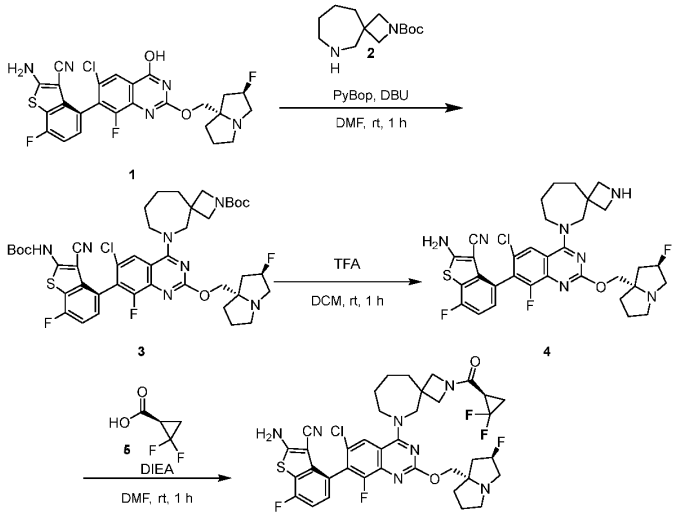
[664] MS m/z (ESI): 670.2 [M+H].

[665] To a solution of compound 9 (93 mg, 0.75 mmol) and DIEA (0.5 ml, 3.025 mmol) in MeCN (4.5 ml) was added triphosgene (200 mg, 0.675 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was then stirred at 20 °C for 2 h, then was added to the solution of compound 8 (50 mg, 0.07 mmol) in DMF (1 mL) at 20 °C under N_2 atmosphere. The crude was purified by prep-HPLC (FA) to give 337 as a white solid (4.96 mg, Yield: 8.1%). MS m/z (ESI): 821.4 [M+H].

[666] ^{1}H NMR (400 MHz, DMSO) δ 8.15 (s, 1H), 8.11 (s, 2H), 7.27 – 7.20 (m, 1H), 7.15 (t, J = 8.6 Hz, 1H), 5.27 (d,

J = 54.0 Hz, 1H), 4.48 – 4.31 (m, 1H), 4.32 – 4.05 (m, 4H), 4.04 – 3.97 (m, 1H), 3.86 – 3.54 (m, 7H), 3.14 – 3.05 (m, 2H), 3.03 – 2.89 (m, 2H), 2.85 – 2.76 (m, 1H), 2.28 (s, 1H), 2.19 – 1.95 (m, 3H), 1.89 – 1.71 (m, 3H), 1.23 (d, *J* = 64.0 Hz, 6H).

[667] Example D: Synthesis of (R)-2-amino-4-(6-chloro-4-(2-((R)-2,2-difluorocyclopropane-1-carbonyl)-2,6-diazaspiro[3.6]decan-6-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-7-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile



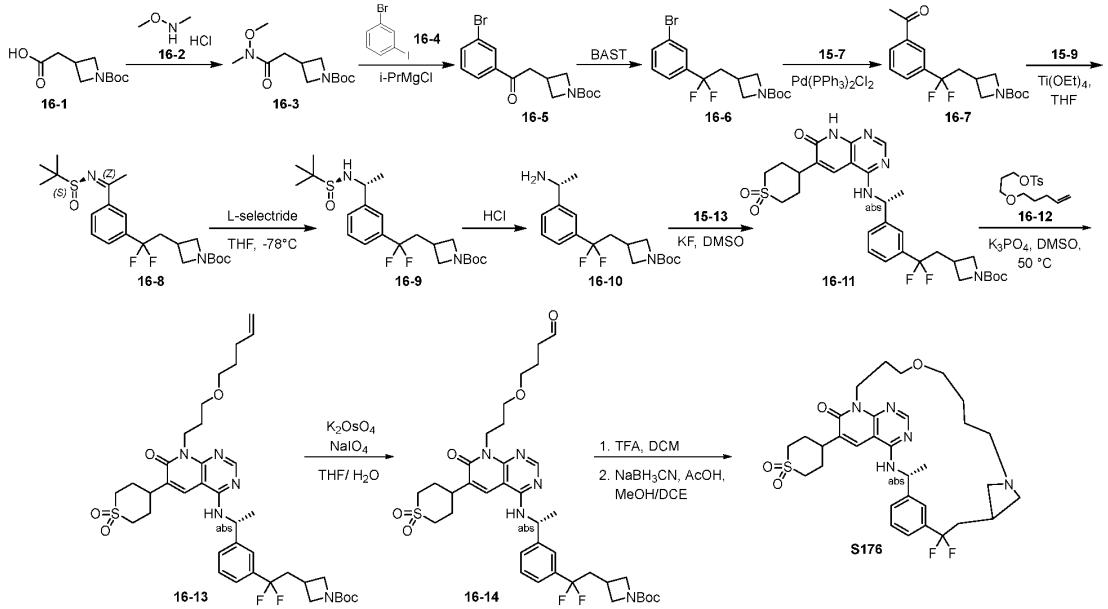
[668] To a solution of compound 6 (280 mg, 0.434 mmol), compound 2 (125 mg, 0.521 mmol) and PyBop (339 mg, 0.651 mmol) in DMF (20 mL) was added DBU (132 mg, 0.868 mmol) . The mixture was stirred at room temperature for 1h. The mixture was extracted with ethyl acetate (50 mL), adn washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by prep-TLC (MeOH:DCM=15:1) to get a yellow solid (290 mg, Yield: 77 %). MS m/z (ESI): 868.5 [M+H].

[669] To a solution of compound 3 (300 mg, 0.346 mmol) in DCM (10 ml) was added TFA (5 ml). The reaction mixture was stirred at 20 °C for 2 h. The solvent was removed under reduced pressure. The reaction mixture was diluted with a.q. $NaHCO_3$ (20 mL) and DCM (50 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to afford compound 4 (220 mg, 95.3%) as a yellow solid. MS m/z (ESI): 668.2 [M+H].

[670] To a solution of compound 5 (183 mg, 1.499 mmol) and DIEA (387 mg, 2.99 mmol) in DMF (10 mL) was added HATU (684 mg, 1.799 mmol), the mixture was stirred at 25 °C for 1 h. To a solution of compound 4 (100 mg, 0.1499 mmol) in DMF (1 mL) was added above reaction mixture (1 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated and purified by prep-HPLC (FA) to give A118 (20.21 mg, Yield: 17%) as a white solid. MS m/z (ESI):772.5 [M+H].

[671] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 2H), 8.00 (d, *J* = 2.8 Hz, 1H), 7.28 - 7.22 (m, 1H), 7.18 - 7.12 (m, 1H), 5.27 (d, *J* = 55.2 Hz, 1H), 4.38 - 4.28 (m, 1H), 4.26 - 4.15 (m, 1H), 4.14 - 3.88 (m, 7H), 3.65 (d, *J* = 9.7 Hz, 1H), 3.15 - 3.00 (m, 3H), 2.82 (d, *J* = 7.2 Hz, 1H), 2.70 - 2.62 (m, 1H), 2.19 - 2.08 (m, 1H), 2.07 - 1.97 (m, 2H), 1.93 - 1.76 (m, 9H), 1.64 (s, 2H).

[672] Example E: Synthesis of (3R)-1^6-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-5,5-difluoro-3-methyl-1^7,1^8-dihydro-12-oxa-2-aza-1(4,8)-pyrido[2,3-d]pyrimidina-7(3,1)-azetidina-4(1,3)-benzenacyclopentadecaphan-1^7-one (S176).



[673] Step A: Preparation of *tert*-butyl 3-(2-(methoxy(methyl)amino)-2-oxoethyl)azetidine-1-carboxylate (**16-3**). To a solution of 2-(1-(tert-butoxycarbonyl)azetidin-3-yl)acetic acid (**16-1**) (10 g, 1.0 eq., 46.5 mmol), *N,O*-dimethylhydroxylamine hydrochloride (**16-2**) (5.47 g, 1.2 eq., 55.8 mmol) and DIEA (18.0 g, 3.0 eq., 139.5 mmol) in DCM (100 mL) was added drop-wise T_3P (35.5 g, 1.2 eq., 55.8 mmol, 50% in ethyl acetate) at 0 °C, and the resulting solution was stirred at room temperature for 12 hours. The reaction mixture was quenched by addition water, the organic phase was separated, and the aqueous phase was extracted with DCM (2 x 200 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography (petroleum ether/ethyl acetate = 3/1) to provide the desired product as a colorless oil. ^{1}H NMR (400 MHz, DMSO) δ 3.92 (s, 2H), 3.66 (s, 3H), 3.50 (s, 2H), 3.07 (s, 3H), 2.81 – 2.66 (m, 3H), 1.37 (s, 9H).

[674] Step B: Preparation of *tert*-butyl 3-(2-(3-bromophenyl)-2-oxoethyl)azetidine-1-carboxylate (**16-5**). To a solution of 1-bromo-3-iodobenzene (**16-4**) (11.52 g, 1.05 eq., 40.7 mmol) in dry THF (120 mL) was added drop-wise i-PrMgCl (40.7 mL, 1.05 eq., 40.7 mmol, 2M) at -78 °C under nitrogen atmosphere. The reaction mixture was allowed warm to 0 °C and stirred for 2 hours, then cooled to -78 °C and **16-3** (10 g, 1.0 eq., 38.76 mmol) in dry THF (50 mL) at -78 °C added drop-wise while maintaining the reaction temperature below -55 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 hours. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 x 80 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to give the desired product as a yellow oil. ESI-MS m/z: $(M+Na)^+$ = 376.0. ^{1}H NMR (400 MHz, DMSO) δ 8.09 (t, J = 1.7 Hz, 1H), 8.03 – 7.90 (m, 1H), 7.89 – 7.78 (m, 1H), 7.58 – 7.43 (m, 1H), 4.08 – 3.91 (m, 2H), 3.61 – 3.50 (m, 2H), 3.45 (d, J = 7.4 Hz, 2H), 2.97 – 2.85 (m, 1H), 1.37 (s, 9H).

[675] Step C: Preparation of *tert*-butyl 3-(2-(3-bromophenyl)-2,2-difluoroethyl)azetidine-1-carboxylate (**16-6**). A solution of **16-5** (3.8 g, 1.0 eq., 10.76 mmol) in bis(2-methoxyethyl)aminosulfurtrifluoride) (11.89 g, 5.0 eq., 53.8 mmol) was stirred at 50 °C for 56 hours under nitrogen atmosphere, then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (80 mL) at 0 °C. The mixture was extracted with ethyl acetate (3 x 50 mL) and the

combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to give the desired product as a yellow oil. ESI-MS m/z: $(M+H-tBu)^+$ = 320.0. ^1H NMR (400 MHz, DMSO) δ 7.88 – 7.66 (m, 2H), 7.59 – 7.39 (m, 2H), 3.84 (s, 2H), 3.51 (s, 2H), 2.80 – 2.64 (m, 1H), 2.64 – 2.53 (m, 2H), 1.36 (s, 9H).

[676] Step D: Preparation of *tert*-butyl 3-(2-(3-acetylphenyl)-2,2-difluoroethyl)azetidine-1-carboxylate (**16-7**). A solution of **16-6** (2.6 g, 1.0 eq., 6.93 mmol), **15-7** (3.8 g, 1.5 eq., 10.4 mmol) and $Pd(PPh_3)_2Cl_2$ (487 mg, 0.1 eq., 0.693 mmol) in 1,4-dioxane (30 mL) was stirred at 100 °C for 12 hours under nitrogen atmosphere. The mixture was cooled to room temperature and quenched with saturated aqueous KF (80 mL). The resulting solution was stirred for 1 hour, then filtered and the filter cake washed with ethyl acetate. The filtrate was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was concentrated to afford a residue, which was dissolved in THF (50 mL) and HCl (1M). The resulting mixture was stirred at room temperature for 1 hour, then treated with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a residue, which was purified by flash silica gel column chromatography (0%~20% ethyl acetate in petroleum ether) to afford the desired product as a light-yellow oil. ESI-MS m/z: $(M+Na)^+$ = 362.2. 1H NMR (400 MHz, DMSO) δ 8.10 (d, J = 7.7 Hz, 1H), 8.02 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 3.84 (s, 2H), 3.52 (s, 2H), 2.82 – 2.67 (m, 1H), 2.64 (s, 3H), 2.62 – 2.52 (m, 2H), 1.35 (s, 9H).

[677] Step E: Preparation of *tert*-butyl (S,Z)-3-(2-(3-(1-((tert-butylsulfinyl)imino)ethyl)phenyl)-2,2-difluoroethyl)azetidine-1-carboxylate (**16-8**). A solution of **16-7** (2.2 g, 1.0 eq., 6.49 mmol), **15-9** (1.02 g, 1.3 eq., 8.44 mmol) and tetraethyl titanate (4.44 g, 3.0 eq. 19.47 mmol) in THF (20 mL) was stirred at 80 °C for 16 hours under nitrogen. The resulting mixture was cooled to room temperature and diluted with ethyl acetate (50 mL) and water (100 mL). The resulting solution was stirred at room temperature for 1 hour and filtered through celite. The filter cake was washed with ethyl acetate and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by com-flash column (0%~40% ethyl acetate in petroleum ether) to give the desired product as a yellow oil. ESI-MS m/z: $(M+H)^+$ = 443.3. ^1H NMR (400 MHz, DMSO) δ 8.03 (d, J = 7.7 Hz, 1H), 7.97 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 3.84 (s, 2H), 3.51 (s, 2H), 2.77 (s, 3H), 2.75 – 2.67 (m, 1H), 2.58 (td, J = 16.8, 7.3 Hz, 2H), 1.35 (s, 9H), 1.23 (s, 9H).

[678] Step F: Preparation of *tert*-butyl 3-(2-(3-((R)-1-(((S)-tert-butylsulfinyl)amino)ethyl)phenyl)-2,2-difluoroethyl)azetidine-1-carboxylate (**16-9**). To a solution of **16-8** (2.28 g, 1.0 eq., 5.16 mmol) in dry THF (20 mL) was added dropwise L-selectride (10.32 mL, 2.0 eq., 10.32 mmol, 1M) at -78 °C under nitrogen atmosphere. The resulting solution was stirred for 1 hour, then quenched by addition of saturated aqueous NH_4Cl and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash silica gel column chromatography (0~50% ethyl acetate in petroleum ether) to give the desired product as a light-yellow oil. ESI-MS m/z: $(M+H)^+$ = 445.4. ^1H NMR (400 MHz, DMSO) δ 7.59 – 7.40 (m, 3H), 7.36 (d, J = 7.3 Hz, 1H), 5.43 (d, J = 5.1 Hz, 1H), 4.57 – 4.37 (m, 1H), 3.79 (s, 2H), 3.44 (s, 2H), 2.72 – 2.60 (m, 1H), 2.58 – 2.51 (m, 2H), 1.46 (d, J = 6.7 Hz, 3H), 1.34 (s, 9H), 1.11 (s, 9H).

[679] Step G: Preparation of *tert*-butyl (R)-3-(2-(3-(1-aminoethyl)phenyl)-2,2-difluoroethyl)azetidine-1-carboxylate (**16-10**). To a stirred solution of **16-9** (1.88 g, 4.23 mmol) in MeOH (32 mL) was added HCl/dioxane (8 mL, 1.9 eq., 8.037 mmol, 1M) at 0 °C. The resulting mixture was stirred for 2 hours, then treated with sat. aqueous $NaHCO_3$ and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired product as a yellow oil, which was used in the next step

without further purification. ESI-MS m/z: $(M+H)^+$ = 341.3.

[680] Step H: Preparation of *tert*-butyl (R)-3-(2-(3-(1-((6-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)amino)ethyl)phenyl)-2,2-difluoroethyl)azetidine-1-carboxylate (**16-11**). To a solution of **15-13** (300 mg, 1 eq., 0.95 mmol) in DMSO (10 mL) at 25 °C were added **16-10** (358 mg, 1.1 eq., 1.05 mmol) and KF (444.6 mg, 6.0 eq., 5.70 mmol). The mixture was stirred at 100 °C for 2 hours, then cooled to room temperature, poured into water and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography to afford the desired product. ESI-MS m/z: $(M+H)^+$ = 618.3.

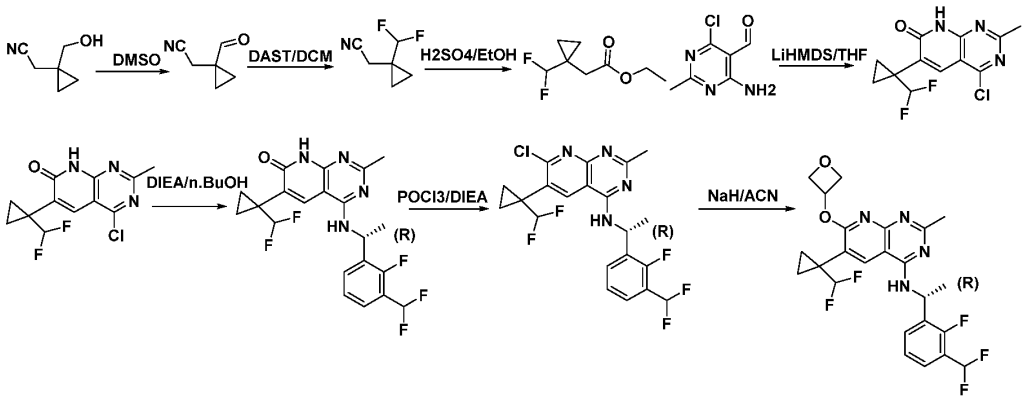
[681] Step I: Preparation of *tert*-butyl (R)-3-(2-(3-(1-((6-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-7-oxo-8-(3-(pent-4-en-1-yloxy)propyl)-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)amino)ethyl)phenyl)-2,2-difluoroethyl)azetidine-1-carboxylate (**16-13**). To a stirring solution of **16-11** (450 mg, 0.73 mmol) in DMSO (20 mL) were added 3-(pent-4-en-1-yloxy)propyl 4-methylbenzenesulfonate (**16-12**) (260 mg, 0.87 mmol) and K_3PO_4 (462 mg, 2.18 mmol). The resulting mixture was stirred at 30 °C for 2 hours, then cooled to room temperature, quenched with water, and extracted with ethyl acetate (20 mL × 3). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by com-flash chromatography on a silica gel column to give the desired product. ESI-MS m/z: $(M+H)^+$ = 744.8.

[682] Step J: Preparation of *tert*-butyl (R)-3-(2-(3-(1-((6-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-7-oxo-8-(3-(4-oxobutoxy)propyl)-7,8-dihydropyrido[2,3-d]pyrimidin-4-yl)amino)ethyl)phenyl)-2,2-difluoroethyl)azetidine-1-carboxylate (**16-14**). To a stirred solution of **16-13** (310 mg, 0.42 mmol) in THF and H_2O (40 mL) was added K_2OsO_4 (3.07 mg, 0.0083 mmol) at 0 °C. The resulting mixture was stirred for 5 minutes, then $NaIO_4$ (451 mg, 2.09 mmol) was added and the reaction stirred at 25 °C for 2 hours. The reaction mixture was treated with $Na_2S_2O_3$ solution and extracted with ethyl acetate (20 mL × 3). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by com-flash chromatography on a silica gel column to give the desired product. ESI-MS m/z: $(M+H)^+$ = 746.8.

[683] Step K: Preparation of (3R)-1^6-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-5,5-difluoro-3-methyl-1^7,1^8-dihydro-12-oxa-2-aza-1(4,8)-pyrido[2,3-d]pyrimidina-7(3,1)-azetidina-4(1,3)-benzenacyclopentadecaphan-1^7-one (**S176**). To a stirred solution of **16-14** (240 mg, 0.32 mmol) in DCM (20 mL) was added TFA (5 mL). The resulting mixture was stirred at 25 °C for 2 hours, then concentrated *in vacuo* to give the free amine, which was used in next step directly without further purification. ESI-MS m/z: $(M+H)^+$ = 646.8.

[684] To a stirred solution of (R)-4-(3-(4-((1-(3-(2-(azetidin-3-yl)-1,1-difluoroethyl)phenyl)ethyl)amino)-6-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)propoxy)butanal (165 mg, 0.26 mmol) in methanol and dichloroethane (150 mL) was added AcOH (2 drops) and $NaBH_3CN$ (48.4 mg, 0.77 mmol). The resulting mixture was stirred at 25 °C for 2 hours, then treated with water and extracted with DCM (150 mL × 3). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by com-flash chromatography on a silica gel column to give the desired product. ESI-MS m/z: $(M+H)^+$ = 630.4. ^1H NMR (400 MHz, DMSO) δ 8.36 (s, 1H), 8.17 (s, 1H), 7.58 (d, J = 6.7 Hz, 2H), 7.45 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 5.49 (q, J = 6.9 Hz, 1H), 4.71 (dd, J = 12.8, 6.7 Hz, 1H), 4.28 – 4.09 (m, 1H), 3.37 (m, 3H), 3.30 – 3.23 (m, 1H), 3.22 – 3.11 (m, 3H), 2.97 (t, J = 6.0 Hz, 2H), 2.89 (brs, 1H), 2.80 (brs, 1H), 2.46 – 2.30 (m, 3H), 2.28 – 2.09 (m, 6H), 2.03 (t, J = 10.9 Hz, 2H), 1.93 (m, 2H), 1.61 (d, J = 7.1 Hz, 3H), 1.23 (s, 1H), 1.13 – 0.93 (m, 2H), 0.74 – 0.67 (m, 2H).

[685] Example F: Synthesis of (R)-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-(1-(difluoromethyl)cyclopropyl)-2-methyl-7-(oxetan-3-yloxy)pyrido[2,3-d]pyrimidin-4-amine (S1186)



[686] 2-(1-formylcyclopropyl)acetonitrile. To a solution of oxalyl dichloride (2.75 g, 21.63 mmol) was added dry DCM (15 mL) at -78 °C under argon. DMSO (1.45 g, 19.82 mmol in dry DCM 5 mL) was added dropwise and the resulting mixture was stirred for 15 min at 78 °C. 2-(1-(hydroxymethyl)cyclopropyl)acetonitrile (2.0 g, 18.02 mmol, in 5 mL DCM 5) was added dropwise and the resulting mixture was stirred for 25 min at -78 °C, followed by the addition of triethylamine (9.1 g, 90.10 mmol) The resulting mixture was stirred -78 °C to 0 °C under argon for 2 hours. The reaction mixture was quenched water (30 mL) and extracted with DCM (30 mL x 2). Organic extracts were combined, washed with brine, and dried over Na_2SO_4. It was filtered and solvent was removed under reduced pressure to give a crude. The crude was purified by flash chromatography on silica gel (petroleum : ethyl acetate = 10 : 1) to give the desired product as an oil. ESI-MS m/z: 110[M+H]+.

[687] 2-(1-(difluoromethyl)cyclopropyl)acetonitrile. To a solution of 2-(1-formylcyclopropyl)acetonitrile (1.3 g, 11.82 mmol) in DCM (15 mL) was added DAST (2.3 g, 14.19 mmol) dropwise at 0 °C under argon. Then the resulting mixture was stirred for 5 hours. The reaction mixture was quenched with water (30 mL) and extracted with DCM (30 mL x 2). Organic extracts were combined, washed with brine, and dried over Na_2SO_4. It was filtered and solvent was removed under reduced pressure to give a crude. The crude was purified by flash chromatography on silica gel (petroleum : ethyl acetate = 10 : 1) to give the desired product as an oil. ESI-MS m/z: 132[M-H]$^+$.

[688] Ethyl 2-(1-(difluoromethyl)cyclopropyl)acetate. To a solution of 2-(1-(difluoromethyl)cyclopropyl)acetonitrile(1.0 g, 7.64 mmol) in EtOH (15 mL) was added H_2SO_4 (3 mL) dropwise. Then the resulting mixture was stirred at 95°C under argon for 16.0 hours. It was quenched saturated $NaHCO_3$ (30 mL) and extracted with ethyl acetate (30 mL x 2). Organic extracts were combined, washed with brine, and dried over Na_2SO_4. It was filtered and solvent was removed under reduced pressure to give a crude. The crude was purified by flash chromatography on silica gel (petroleum : ethyl acetate = 10 : 1) to give the desired product as an oil. ESI-MS m/z: 179[M+H]$^+$.

[689] 4-chloro-6-(1-(difluoromethyl)cyclopropyl)-2-methylpyrido[2,3-d]pyrimidin-7(8H)-one. A solution of ethyl 2-(1-(difluoromethyl)cyclopropyl)acetate (477 mg, 2.67 mmol) in THF (10 mL) and 4-amino-6-chloro-2-methylpyrimidine-5-carbaldehyde(350 mg, 2.05 mmol) was cooled to -78 °C under argon. LiHMDS (6.1 mL, 1 M in THF, 6.1 mmol) was added dropwise and the resulting mixture was stirred for 5 hours at -78 °C and allowed to warm room temperature. The reaction mixture was quenched saturated NH_4Cl (20 mL) and extracted with ethyl acetate (30 mL x 2). Organic extracts were combined, washed with brine, and dried over Na_2SO_4. It was filtered and solvent was

removed under reduced pressure to give a crude. The crude was purified by flash chromatography on silica gel (dichloromethane : methyl alcohol = 96: 4) to give the desired product as a solid.. ESI-MS m/z: 286[M-H]$^+$.

[690] (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-6-(1-(difluoromethyl)cyclopropyl)-2-methylpteridin-7(8H)-one. To a solution of 4-chloro-6-(1-(difluoromethyl)cyclopropyl)-2-methylpyrido[2,3-d]pyrimidin-7(8H)-one (260 mg, 0.92 mmol) and (R)-1-(3-(difluoromethyl)-2-fluorophenyl)ethan-1-amine hydrochloride(206 mg, 0.92 mmol) in *n*-BuOH (15 mL) was added DIEA (1.2 g, 9.2 mmol).The resulting mixture was heated at 120°C under argon and stirred for 5 h. It was cooled to room temperature and ethyl acetate (60 mL) was added. The organics were washed with brine, dried over Na_2SO_4. It was filtered and solvent was removed under reduced pressure to give a crude. The crude was purified by flash chromatography on silica gel (dichloromethane : methyl alcohol = 95 : 5) to afford the desired product as a solid. ESI-MS m/z: 440[M+H]$^+$;

[691] (R)-7-chloro-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-(1-(difluoromethyl)cyclopropyl)-2-methylpyrido[2,3-d]pyrimidin-4-amine. To a solution of (R)-4-((1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)amino)-6-(1-(difluoromethyl)cyclopropyl)-2-methylpteridin-7(8H)-one (150 mg, 0.35 mmol) in $POCl_3$ (6 mL) was added DIEA (cat) at room temperature. The resulting mixture was heated at 105°C under argon and stirred for 5 h. Then it was cooled to room temperature and concentrated to remove most $POCl_3$. The resulted residue was partitioned between saturated $NaHCO_3$ (5 mL) and dichloromethane (20 mL). The aqueous layer was extracted with dichloromethane (20 mL x 2). The organics were combined, washed with brine, and dried over Na_2SO_4. It was filtered and solvent was removed under reduced pressure to give a crude. The crude was purified by flash chromatography on silica gel (dichloromethane : methyl alcohol = 95 : 5) to afford the desired product as a solid. ESI-MS m/z: 457[M+H]$^+$;

[692] N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-(1-(difluoromethyl)cyclopropyl)-2-methyl-7-(oxetan-3-yloxy)pyrido[2,3-d]pyrimidin-4-amine. To a solution of oxetan-3-ol (30 mg, 0.40 mmol) in ACN (10 mL) at 0°C was added NaH (60%, 16 mg, 0.40 mmol), and the resulting mixture was stirred for 30 min at 0°C under argon. (R)-7-chloro-N-(1-(3-(difluoromethyl)-2-fluorophenyl)ethyl)-6-(1-(difluoromethyl)cyclopropyl)-2-methylpyrido[2,3-d]pyrimidin-4-amine (120 mg, 0.27 mmol) was added. Then the resulting mixture was heated at 65°C under argon and stirred for 2 hours. Then it was cooled to room temperature. The mixture was extracted with ethyl acetate (20 mL x 2). Organic extracts were combined, washed with brine, and dried over Na_2SO_4. It was filtered and solvent was removed under reduced pressure to give a crude. The crude was purified by prep-TLC (dichloromethane : methyl alcohol = 25 : 1)to afford the desired product as a solid. ESI-MS m/z: 495[M+H]$^+$. ^{1}HNMR(MeOD, 400 MHz): δ 8.61 (s, 1 H), 7.49-7.46 (t, J = 6.8 Hz, 1H), 7.37-7.34 (m, 1H), 7.13-7.10 (t, J = 7.6 Hz, 1H), 7.03-6.76 (t, J = 54.8 Hz, 1H), 5.94 (t, J = 58 Hz, 1H), 5.73-5.71 (m, 2H), 4.99 (m, 2H), 4.64 (m, 2H), 2.30 (s, 3H), 1.57-1.55 (d, J = 6.8 Hz, 3H), 1.22 (m, 2H), 0.99 (m, 2H).

[693] **Example 1: Ras sequence**

[694] Human K-Ras4b (SEQ ID NO. 1):

1 MTEYKLVVVG AGGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHHYREQI
101 KRVKDSEDVP MVLVGNKCDL PSRTVDTKQA QDLARSYGIP FIETSAKTRQ
151 GVDDAFYTLV REIRKHKEKM SKDGKKKKKK SKTKCVIM

[695] Human SOS1 (SEQ ID NO. 2):

1 MQAQQLPYEF FSEENAPKWR GLLVPALKKV QGQVHPTLES NDDALQYVEE
51 LILQLLNMLC QAQPRSASDV EERVQKSFPH PIDKWAIADA QSAIEKRKRR
101 NPLSLPVEKI HPLLKEVLGY KIDHQVSVYI VAVLEYISAD ILKLVGNYVR

151 NIRHYEITKQ DIKVAMCADK VLMDMFHQDV EDINILSLTD EEPSTSGEQT
201 YYDLVKAFMA EIRQYIRELN LIIKVFREPF VSNSKLFSAN DVENIFSRIV
251 DIHELSVKLL GHIEDTVEMT DEGSPHPLVG SCFEDLAEEL AFDPYESYAR
301 DILRPGFHDR FLSQLSKPGA ALYLQSIGEG FKEAVQYVLP RLLLAPVYHC
351 LHYFELLKQL EEKSEDQEDK ECLKQAITAL LNVQSGMEKI CSKSLAKRRL
401 SESACRFYSQ QMKGKQLAIK KMNEIQKNID GWEGKDIGQC CNEFIMEGTL
451 TRVGAKHERH IFLFDGLMIC CKSNHGQPRL PGASNAEYRL KEKFFMRKVQ
501 INDKDDTNEY KHAFEIILKD ENSVIFSAKS AEEKNNWMAA LISLQYRSTL
551 ERMLDVTMLQ EEKEEQMRLP SADVYRFAEP DSEENIIFEE NMQPKAGIPI
601 IKAGTVIKLI ERLTYHMYAD PNFVRTFLTT YRSFCKPQEL LSLIIERFEI
651 PEPEPTEADR IAIENGDQPL SAELKRFRKE YIQPVQLRVL NVCRHWVEHH
701 FYDFERDAYL LQRMEEFIGT VRGKAMKKWV ESITKIIQRK KIARDNGPGH
751 NITFQSSPPT VEWHISRPGH IETFDLLTLH PIEIARQLTL LESDLYRAVQ
801 PSELVGSVWT KEDKEINSPN LLKMIRHTTN LTLWFEKCIV ETENLEERVA
851 VVSRIIEILQ VFQELNNFNG VLEVVSAMNS SPVYRLDHTF EQIPSRQKKI
901 LEEAHELSED HYKKYLAKLR SINPPCVPFF GIYLTNILKT EEGNPEVLKR
951 HGKELINFSK RRKVAEITGE IQQYQNQPYC LRVESDIKRF FENLNPMGNS
1001 MEKEFTDYLF NKSLEIEPRN PKPLPRFPKK YSYPLKSPGV RPSNPRPGTM
1051 RHPTPLQQEP RKISYSRIPE SETESTASAP NSPRTPLTPP PASGASSTTD
1101 VCSVFDSDHS SPFHSSNDTV FIQVTLPHGP RSASVSSISL TKGTDEVPVP
1151 PPVPPRRRPE SAPAESSPSK IMSKHLDSPP AIPPRQPTSK AYSPRYSISD
1201 RTSISDPPES PPLLPPREPV RTPDVFSSSP LHLQPPPLGK KSDHGNAFFP
1251 NSPSPFTPPP PQTPSPHGTR RHLPSPPLTQ EVDLHSIAGP PVPPRQSTSQ
1301 HIPKLPPKTY KREHTHPSMH RDGPPLLENA HSS

[696] Example 2: SOS purification

[697] A SOS construct or a variant thereof is His-tagged. E. coli cultures are induced in a fermenter, harvested, and lysed in lysis buffer, for example, in 25 mM Tris HCl 7.5, 500 mM NaCl, 20 mM Imidazol, Complete EDTA-free (Roche)). For immobilized metal ion affinity chromatography (IMAC), the centrifuged lysate (50,000 x g, 45 min, 40) is incubated with 30 mL Ni-NTA (Macherey-Nagel; #745400.100) in a spinner flask (16 h, 40) and subsequently transferred to a chromatography column connected to a chromatography system, e.g., an Akta chromatography system. The column is rinsed with wash buffer, e.g., in 25 mM Tris HCl 7.5, 500 mM NaCl, 20 mM Imidazol and the bound protein is eluted with a linear gradient (0-100%) of elution buffer (25 mM Tris HCl 7.5, 500 mM NaCl, 300 mM Imidazol). The main fractions of the elution peak (monitored by OD280) containing homogenous His10-hSOS is pooled.

EXAMPLE 3: Protein expression

[698] DNA expression constructs encoding one or more protein sequences of interest (e.g., Kras fragments thereof, mutant variants thereof, etc.) and its corresponding DNA sequences are optimized for expression in E. coli and synthesized by, for example, the GeneArt Technology at Life Technologies. In some cases, the protein sequences of interest are fused with a tag (e.g., glutathione S-transferase (GST), histidine (His), or any other affinity tags) to facilitate recombinant expression and purification of the protein of interest. Such tag can be cleaved subsequent to purification. Alternatively, such tag may remain intact to the protein of interest and may not interfere with activities (e.g., target

binding and/or phosphorylation) of the protein of interest

[699] A resulting expression construct is additionally encoded with (i) att-site sequences at the 5'and 3' ends for subcloning into various destination vectors using, for example, the Gateway Technology, as well as (ii) a Tobacco Etch Virus (TEV) protease site for proteolytic cleavage of one or more tag sequences. The applied destination vectors can be a pET vector series from Novagen (e.g., with ampicillin resistance gene), which provides an N-terminal fusion of a GST-tag to the integrated gene of interest and/or a pET vector series (e.g., with ampicillin resistance gene), which provides a N-terminal fusion of a HIS-tag to the integrated gene. To generate the final expression vectors, the expression construct of the protein of interest is cloned into any of the applied destination ventors. The expression vectors are transformed into E. coli strain, e.g., BL21 (DE3). Cultivation of the transformed strains for expression is performed in 10 L and 1 L fermenter. The cultures are grown, for example, in Terrific Broth media (MP Biomedicals, Kat. #1 13045032) with 200 ug/mL ampicillin at a temperature of 37 °C to a density of 0.6 (OD600), shifted to a temperature of ~27 °C (for K-Ras expression vectors) induced for expression with 100 mM IPTG, and further cultivated for 24 hours. After cultivation, the transformed E. coli cells are harvested by centrifugation and the resulting pellet is suspended in a lysis buffer, as provided below, and lysed by passing three-times through a high pressure device. The lysate is centrifuged (49000g, 45 min, 4 °C) and the supernatant is used for further purification.

EXAMPLE 4: Ras protein purification

[700] A Ras (e.g., K-Ras wildtype or a mutant such as K-Ras G12S, K-Ras G12D, K-Ras G12V, K-Ras G12C, K-Ras G13D, K-Ras G13C, or K-Ras G13V construct or a variant thereof is tagged with GST. E. coli culture from a 10L fermenter is lysed in lysis buffer (50mM Tris HCI 7.5, 500mM NaCI,1 mM DTT, 0,5% CHAPS, Complete Protease Inhibitor Cocktail-(Roche)). As a first chromatography step, the centrifuged lysate is incubated with 50mL Glutathione Agarose 4B (Macherey-Nagel; 745500.100) in a spinner flask (16 h, 10O). The Glutathione Agarose 4B loaded with protein is transferred to a chromatography column connected to a chromatography system, e.g., an Akta chromatography system. The column is washed with wash buffer (50mM Tris HCI 7.5, 500mM NaCI, 1 mM DTT) and the bound protein is eluted with elution buffer (50mM Tris HCI 7.5, 500mM NaCI, 1 mM DTT, 15mM Glutathione). The main fractions of the elution peak (monitored by OD280) is pooled. For further purification by size-exclusion chromatography, the above eluate volume is applied to a column Superdex 200 HR prep grade (GE Healthcare) and the resulting peak fractions of the eluted fusion protein is collected. Native mass spectrometry analyses of the final purified protein construct can be performed to assess its homogeneous load with GDP.

EXAMPLE 5: HTRF (homogenous time-resolved fluorescence resonance energy transfer assay

[701] The ability of a compound of the present disclosure to reduce a Ras signaling output can be demonstrated by an HTRF assay. This assay can be also used to assess a selective inhibition or reduction of signaling output of a mutant Ras protein relative to a wildtype, or relative to a different mutant Ras protein. For example, the equilibrium interaction of wildtype Kras or K-Ras mutant (e.g., wildtype or a mutant thereof including those mentioned in Example 4) with SOS1 (e.g., hSOS1) can be assessed as a proxy or an indication for a subject compound's ability to bind and inhibit Ras protein. HTRF assay detects from (i) a fluorescence resonance energy transfer (FRET) donor (e.g., antiGST-Europium) that is bound to GST-tagged K-Ras mutant to (ii) a FRET acceptor (e.g., anti-6His-XL665) bound to a His-tagged hSOS1.

[702] The assay buffer can contain ~5 mM HEPES pH 7.4, ~150 mM NaCI, ~ 1 mM DTT, 0.05% BSA and 0.0025% (v/v) Igepal. A Ras working solution is prepared in an assay buffer containing typically a suitable amount of the protein construct (e.g., GST-tagged K-Ras mutant) and the FRET donor (e.g., antiGST-Eu(K) from Cisbio, France). A SOS1 working solution is prepared in an assay buffer containing suitable amount of the protein construct (e.g., His-hSOS1)

and the FRET acceptor (e.g., anti-6His-XL665 from Cisbio, France). A suitable amount of the protein construct will depend on the range of activity or range of IC50 values being detected or under investigation. For detecting IC50 within a range of 500 nM, the protein constructs of the same range of molarity can be utilized. An inhibitor control solution is prepared in an assay buffer containing comparable amount of the FRET acceptor without the SOS1 protein. A fixed volume of DMSO with or without test compound is transferred into a 384-well plate. Ras working solution is added to all wells of the test plate. SOS1 working solution is added to all wells except for those that are subsequently filled the inhibitor control solution. Upon incubation for about 10 minutes or longer, the fluorescence is measured with a M1000Pro plate reader (Tecan) using HTRF detection (excitation 337nm, emission 1 : 620nm, emission 2: 665nm). Compounds are tested in duplicates at different concentrations (for example, 10 μM, 2.5 μM, 0.63 μM, 0.16 μM, 0.04 μM, 0.01 μM test compound). The ratiometric data (i.e., emission 2 divided by emission 1) is used to calculate IC50 values against Ras using GraphPad Prism (GraphPad software). Following this general procedure, samples were tested with or without a subject compound disclosed herein including compounds exemplified in Table 1a and 1b to assess their abilities to inhibit a mutant K-Ras relative to another mutant K-Ras or wildtype K-Ras. Signaling output measured in terms of IC50 values can be obtained, a ratio of IC50 against one mutant relative to another mutant can be calculated. For instance, a selective reduction of K-Ras G12D signaling output can be evidenced by a ratio greater than one. In particular, a selective reduction of K-Ras G12D signaling relative to K-Ras WT signaling is evidenced as the ratio of IC50 (against K-Ras WT) to IC50 (against K-Ras G12D) is greater than 1.

[703] **Table 3a** HTRF assay results using an assay as generally described above.

Compound No.	KRAS G12S	KRAS G12D	KRAS WT	Compound No.	KRAS G12S	KRAS G12D	KRAS WT
201	+++	+++	+++	277	+++	+++	+++
202	+++	+++	+++	278	+++	+++	+++
203	+++	++	+++	279	++	++	++
204	+++	+++	+++	280	+++	+++	+++
205	+++	+++	+++	281	+++	+++	+++
206	+++	+++	+++	282	+++	+++	+++
207	+++	+++	+++	283	+++	+++	+++
208	+++	+++	+++	284	+++	+++	+++
209	+++	+++	+++	285	+++	+++	+++
210	+++	+++	+++	286	+++	+++	+++
211	+++	+++	+++	287	+++	+++	+++
212	+++	+++	+++	288	+++	+++	+++
213	+++	+++	+++	289	+++	+++	+++
214	+++	+++	+++	290	+++	+++	+++
215	+++	+++	+++	291	+++	+++	+++
216	+++	+++	+++	292	+++	+++	+++
217	+++	+++	+++	293	+++	+++	+++
218	+++	+++	+++	294	+++	+++	+++
219	+++	+++	+++	295	+++	+++	+++
220	ND	+++	+++	296	+++	+++	+++
221	+++	+++	+++	297	+++	+++	+++
222	+++	+++	+++	298	+++	+++	+++
223	+++	+++	+++	299	+++	+++	+++
224	+++	+++	+++	300	+++	+++	+++
225	+++	+++	+++	301	+++	+++	+++
226	+++	+++	+++	302	+++	+++	+++
227	+++	+++	+++	303	+++	+++	+++
228	+++	+++	+++	304	+++	+++	+++
229	+++	+++	+++	305	+++	+++	+++
230	+++	+++	+++	306	+++	+++	+++
231	+++	+++	+++	307	+++	+++	+++

232	+++	+++	+++	308	+++	+++	+++
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234	+++	+++	+++	310	+++	+++	+++
235	+++	+++	+++	311	+++	+++	+++
236	+++	+++	+++	312	+++	+++	+++
237	+++	++	+++	313	+++	+++	+++
238	+++	+++	+++	314	+++	+++	+++
239	+++	++	+++	315	+++	+++	+++
240	+++	+++	+++	316	+++	+++	+++
241	+++	+++	+++	317	+++	+++	+++
242	+++	+++	+++	318	+++	+++	+++
243	+++	+++	+++	319	+++	+++	+++
244	+++	+++	+++	320	+++	+++	+++
245	++	++	++	321	+++	+++	+++
246	+++	+++	+++	322	+++	+++	+++
247	+++	+++	+++	323	+++	++	++
248	+++	+++	+++	324	+++	+++	+++
249	+++	+++	+++	325	+++	+++	+++
250	+++	+++	+++	326	+++	+++	+++
251	++	+++	+++	327	+++	+++	+++
252	+++	+++	+++	328	+++	+++	+++
253	++	++	+++	329	+++	+++	+++
254	+++	+++	+++	330	+++	+++	+++
255	+++	+++	+++	331	+++	+++	+++
256	+++	++	++	332	+++	+++	+++
257	+++	+++	+++	333	+++	+++	+++
258	+++	+++	+++	334	+++	+++	+++
259	+++	+++	+++	335	+++	+++	+++
260	+++	+++	+++	336	+++	+++	+++
261	+++	+++	+++	337	+++	+++	+++
262	+++	+++	+++	338	+++	+++	+++
263	+++	+++	+++	339	+++	+++	+++
264	+++	+++	+++	340	+++	+++	+++
265	++	+++	+++	341	+++	+++	+++
266	+++	+++	+++	342	+++	+++	+++
267	+++	+++	+++	343	+++	+++	+++
268	+++	+++	+++	344	+++	+++	+++
269	+++	+++	+++	345	+++	+++	+++
270	+++	+++	+++	346	+++	+++	+++
271	+++	+++	+++	347	+++	+++	+++
272	+++	+++	+++	348	+++	+++	+++
273	+++	+++	+++	349	+++	+++	+++
274	+++	+++	+++	350	+++	+++	+++
275	+++	+++	+++	351	+++	+++	+++
276	+++	+++	+++				

++ IC50 greater than 5 μM; +++ IC50 less than or equal to 5 μM

Table 3b

CMPD	KRASG12D IC50	KRASwt IC50	CMPD	KRASG12D IC50	KRASwt IC50	CMPD	KRASG12D IC50	KRASwt IC50
A101	+++	+++	A184	+++	+++	A267	+++	+++
A102	ND	ND	A185	+++	+++	A268	+++	+++
A103	ND	ND	A186	ND	ND	A269	+++	+++
A104	+++	+++	A187	+++	+++	A270	+++	+++
A105	+++	+++	A188	+++	+++	A271	+++	+++
A106	ND	ND	A189	+++	+++	A272	+++	+++
A107	+++	+++	A190	+++	+++	A273	+++	+++
A108	++	++	A191	++	+++	A274	+++	+++
A109	ND	ND	A192	+++	+++	A275	+++	+++

A110	+++	+++	A193	+++	+++	A276	+++	+++
A111	+++	+++	A194	+++	+++	A277	+++	+++
A112	++	++	A195	+++	+++	A278	+++	+++
A113	+++	+++	A196	+++	+++	A279	+++	+++
A114	+++	+++	A197	+++	+++	A280	+++	+++
A115	ND	ND	A198	+++	+++	A281	+++	+++
A116	+++	+++	A199	+++	+++	A282	+++	+++
A117	ND	ND	A200	+++	+++	A283	+++	+++
A118	+++	+++	A201	+++	+++	A284	+++	+++
A119	+++	+++	A202	+++	+++	A285	+++	+++
A120	+++	+++	A203	+++	+++	A286	+++	+++
A121	+++	+++	A204	+++	+++	A287	+++	+++
A122	+++	+++	A205	+++	+++	A288	+++	+++
A123	+++	+++	A206	+++	+++	A289	+++	+++
A124	+++	+++	A207	+++	+++	A290	+++	+++
A125	+++	+++	A208	+++	+++	A291	+++	+++
A126	+++	+++	A209	+++	+++	A292	+++	+++
A127	+++	+++	A210	+++	+++	A293	+++	+++
A128	++	+++	A211	+++	+++	A294	+++	+++
A129	+++	+++	A212	+++	+++	A295	+++	+++
A130	+++	+++	A213	+++	+++	A296	+++	+++
A131	+++	+++	A214	+++	+++	A297	+++	+++
A132	ND	ND	A215	+++	+++	A298	+++	+++
A133	ND	ND	A216	+++	+++	A299	+++	+++
A134	+++	+++	A217	+++	+++	A300	+++	+++
A135	ND	ND	A218	+++	+++	A301	+++	+++
A136	ND	ND	A219	+++	+++	A302	+++	+++
A137	ND	ND	A220	+++	+++	A303	+++	+++
A138	+++	+++	A221	+++	+++	A304	+++	+++
A139	+++	+++	A222	+++	+++	A305	+++	+++
A140	ND	ND	A223	+++	+++	A306	+++	+++
A142	ND	ND	A224	+++	+++	A307	+++	+++
A143	+++	+++	A225	+++	+++	A308	+++	+++
A144	+++	+++	A226	++	++	A309	+++	+++
A145	ND	ND	A227	+++	+++	A310	+++	+++
A146	ND	ND	A228	+++	+++	A311	+++	+++
A147	+++	+++	A229	+++	+++	A312	+++	+++
A148	+++	+++	A230	+++	+++	A313	+++	+++
A149	+++	+++	A231	+++	+++	A314	+++	+++
A150	+++	+++	A232	+++	+++	A315	+++	+++
A151	+++	+++	A233	+++	+++	A316	+++	+++
A152	++	+++	A234	+++	+++	A317	+++	+++
A153	+++	+++	A235	+++	+++	A318	+++	+++
A154	+++	+++	A236	++	++	A319	+++	+++
A155	ND	ND	A237	+++	+++	A320	+++	+++
A156	ND	ND	A238	+++	+++	A321	+++	+++
A157	+++	+++	A239	+++	+++	A322	+++	+++
A158	+++	+++	A240	+++	+++	A323	+++	+++
A159	+++	+++	A241	+++	+++	A324	+++	+++
A160	+++	+++	A242	+++	+++	A325	+++	+++
A161	+++	+++	A243	+++	+++	A326	+++	+++
A162	ND	ND	A244	+++	+++	A327	+++	+++
A163	+++	+++	A245	+++	+++	A328	+++	+++
A164	+++	+++	A246	+++	+++	A329	+++	+++
A165	+++	+++	A247	+++	+++	A330	+++	+++
A166	+++	+++	A248	+++	+++	A331	+++	+++
A167	+++	+++	A249	+++	+++	A332	+++	+++
A168	++	+++	A250	+++	+++	A333	+++	+++
A169	+++	+++	A251	+++	+++	A334	+++	+++

A170	++	++	A252	+++	+++	A335	+++	+++
A171	+++	+++	A253	+++	+++	A336	+++	+++
A172	+++	+++	A254	+++	+++	A337	+++	+++
A173	+++	+++	A255	+++	+++	A338	+++	+++
A174	ND	ND	A256	+++	+++	A339	+++	+++
A175	+++	+++	A257	+++	+++	A340	+++	+++
A176	+++	+++	A258	+++	+++	A341	+++	+++
A177	+++	+++	A259	+++	+++	A342	+++	+++
A178	+++	+++	A260	+++	+++	A343	+++	+++
A179	++	+++	A261	+++	+++	A344	+++	+++
A180	++	+++	A262	+++	+++	A345	+++	+++
A181	+++	+++	A263	+++	+++	A346	+++	+++
A182	+++	+++	A264	+++	+++	A347	+++	+++
A183	+++	+++	A265	+++	+++	A348	+++	+++
			A266	+++	+++	A349	+++	+++

++ IC50 greater than or equal to 5 μM; +++ IC50 less than 5 μM

[704] **Example 6**: Ras-SOS interaction assay

[705] The ability of any compound of the present disclosure to reduce a Ras protein signaling output by, e.g., interfering or disrupting interaction (or binding) between SOS1 and a Ras protein can be assessed in vitro. For example, the equilibrium interaction of human SOS1 (hSOS1) with human wildtype Kras or K-Ras mutant (e.g., hK-Ras G12C mutant, or hK-Ras G12C) can be assessed as a proxy or an indication for a subject compound's ability to inhibit SOS. Detection of such interaction is achieved by measuring homogenous time-resolved fluorescence resonance energy transfer (HTRF) from (i) a fluorescence resonance energy transfer (FRET) donor (e.g., antiGST-Europium) that is bound to GST-tagged K-Ras G12C to (ii) a FRET acceptor (e.g., anti-6His-XL665) bound to a His-tagged hSOS1.

[706] The assay buffer can contain 5 mM HEPES pH 7.4, 150 mM NaCl, 10 mM EDTA, 1 mM DTT, 0.05% BSA, 0.0025% (v/v) Igepal and 100 mM KF. A Ras working solution is prepared in assay buffer containing typically 10 nM of the protein construct (e.g., GST-tagged hK-Ras G12C) and 2 nM of the FRET donor (e.g., antiGST-Eu(K) from Cisbio, France). A SOS1 working solution is prepared in assay buffer containing typically 10 nM of the protein construct (e.g., His-hSOS1) and 10 nM of the FRET acceptor (e.g., anti-6His-XL665 from Cisbio, France). An inhibitor control solution is prepared in assay buffer containing 10 nM of the FRET acceptor without the SOS1 protein.

[707] A fixed reaction mixture with or without test compound is transferred into a 384-well plate. Ras working solution is added to all wells of the test plate. SOS1 working solution is added to all wells except for those that are subsequently filled with the inhibitor control solution. After approximately 60 min incubation, the fluorescence is measured with a M1000Pro plate reader (Tecan) using HTRF detection (excitation 337 nm, emission 1: 620nm, emission 2: 665nm). Compounds are tested in duplicate at different concentrations (for example, 10 μM, 2.5 μM, 0.63 μM, 0.16 μM, 0.04 μM, 0.01 μM test compound). The ratiometric data (i.e., emission 2 divided by emission 1) is used to calculate IC50 values against SOS1 using GraphPad Prism (GraphPad software).

[708] **Table 4a** below shows the resulting IC50 values of the compounds exemplified in Table 2a against SOS1 using the Ras-SOS interaction assay as described above, wherein K-Ras G13D is utilized. The results demonstrate that compounds disclosed herein are capable of reducing Ras protein signaling by inhibiting SOS1-mediated signaling. Many of the exemplified compounds are potent SOS1 inhibitors, exhibiting an IC50 value against SOS1 less than about 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 80nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, or even less than 10 nM. For example, compounds S54, S61, S101, S120, S138, S159, S166, S167, S168, S170, S171, S173, S174, S175, S176, S209, S210, S211, S212, and S213 exhibit IC50 values less than 50 nM, 40 nM, 30 nM, 20 nM, or 10 nM.

[709] **Table 4a** shows the resulting IC50 values of selected compounds against SOS1 using the Ras-SOS interaction assay described herein. Compound numbers correspond to the numbers and structures provided in **Table 2a**. IC50

values were not determined for compounds of **Table 2a** that are not listed in **Table 4a**.

Table 4a

	< 100 nM (++)	100 nM to 5 μM (+)
SOS1 IC_{50}	S6, S8, S10, S11, S15, S16, S19, S20, S21, S22, S23, S24, S25, S26, S27, S28, S29, S30, S31, S32, S34, S35, S36, S38, S39, S40, S41, S42, S43, S45, S46, S47, S48, S49, S50, S51, S52, S53, S54, S55, S57, S58, S60, S61, S62, S63, S64, S65, S67, S69, S70, S71, S72, S73, S74, S75, S76, S77, S78, S79, S80, S83, S85, S86, S89, S90, S91, S92, S93, S94, S95, S97, S98, S100, S101, S104, S105, S106, S107, S108, S109, S110, S112, S113, S114, S116, S118, S119, S120, S121, S122, S123, S124, S125, S126, S127, S128, S129, S131, S132, S135, S137, S138, S140, S141, S142, S143, S144, S145, S146, S147, S149, S151, S152, S153, S154, S155, S156, S157, S158, S159, S160, S161, S162, S163, S164, S165, S166, S167, S168, S169, S170, S171, S173, S174, S175, S176, S177, S178, S179, S180, S181, S182, S186, S187, S188, S189, S190, S191, S192, S193, S194, S195, S196, S202, S203, S209, S210, S211, S212, S213	S1, S2, S3, S4, S5, S7, S9, S12, S13, S14, S18, S37, S44, S56, S66, S82, S87, S88, S99, S102, S115, S130, S133, S136, S148, S150, S172

[710] Table 4b below shows the resulting IC50 values of the compounds exemplified in Table 2b against SOS1 using the Ras-SOS interaction assay as described above, wherein K-RasG13D is utilized. The results demonstrate that compounds disclosed herein are capable of reducing Ras protein signaling by inhibiting SOS1-mediated signaling. Many of the exemplified compounds are potent SOS1 inhibitors, exhibiting an IC50 value against SOS1 less than about 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 80nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, or even less than 10 nM. For example, compounds No. S1102, S1103, S1104, S1105, S1109, S1112, S1113, S1114, S1115, S1116, S1117, S1118, S1119, S1120, S1121, S1122, S1123, S1124, S1125, S1126, S1127, S1128, S1129, S1130, S1131, S1132, S1133, S1134, S1135, S1136, S1137, S1138, S1139, S1141, S1142, S1143, S1145, S1146, S1147, S1148, S1149, S1150, S1151, S1152, S1153, S1154, S1155, S1156, S1157, S1159, S1160, S1161, S1162, S1163, S1164, S1165, S1166, S1167, S1169, S1171, S1172, S1173, S1174, S1175, S1176, S1177, S1178, S1179, S1180, S1181, S1182, S1183, S1187, S1188, S1190, S1191, S1192, S1193, S1194, S1195, S1196, S1197, S1198, S1199, S1200, S1201, S1202, S1203, S1204, S1205, S1206, S1207, S1209, S1210, S1211, S1212, S1214, S1215, S1216, S1217, S1218, S1219, S1220, S1221, S1222, S1223, S1224, S1227, S1229, S1231, S1232, S1233, S1234, S1235, S1236, S1238, S1239, S1242, S1243, S1244, S1245, S1246, S1247, S1248, S1249, S1250, S1251, S1252, S1253, S1254, S1255, S1256, S1257, S1258, S1259, S1260, S1261, S1262, S1263, S1264, S1265, S1266, S1267, S1268, S1269, S1270, S1271, S1272, S1273, S1277, S1285, S1287, S1288, S1289, S1290, S1291, S1292, S1293, S1294, S1295, S1297, S1299, S1301, S1302, S1303, S1304, S1305, S1307, S1308, S1309, S1312, S1313, S1314, S1316, S1317, S1318, S1320, S1321, S1322, S1323, S1324, S1325, S1326, S1327, S1328, S1329, S1330, S1331, S1332, S1333, S1334, S1336, S1337, S1338, S1339, S1340, S1341, S1342, S1343, S1344, S1345, S1346, S1347, S1348, S1349, S1350, S1351, S1352, S1353, S1355, S1356, S1357, S1358, S1359, S1360, S1361, S1362, S1363, S1365, S1366, S1367, S1368, S1369, S1370, S1371, S1373, S1374, S1375, S1376, S1378, S1379, S1380, S1381, S1382, S1383, S1384, S1385, S1386, S1387, S1388, S1389, S1390, S1391, S1392, S1393, S1394, S1395, S1396, S1397, S1399, S1401, S1404, S1405, S1406, S1407, S1410, S1411, S1412, S1413, S1414, S1415, S1416, S1417, S1418, S1419, S1420, S1421, S1424, S1425, S1426, and S1427 exhibit IC50 values less than 50 nM, 40 nM, 30 nM, 20 nM, or 10 nM.

[711] **Table 4b** below shows the resulting IC50 values of the compounds exemplified in Table 2b against SOS1 using the Ras-SOS interaction assay described herein.

Table 4b

Compound	IC50 inhibition of SOS	Compound	IC50 inhibition of SOS	Compound	IC50 inhibition of SOS
S1101	A	S1210	A	S1319	B
S1102	A	S1211	A	S1320	A
S1103	A	S1212	A	S1321	A
S1104	A	S1213	A	S1322	A
S1105	A	S1214	A	S1323	A
S1106	A	S1215	A	S1324	A
S1107	A	S1216	A	S1325	A
S1108	A	S1217	A	S1326	A
S1109	A	S1218	A	S1327	A
S1110	A	S1219	A	S1328	A
S1111	B	S1220	A	S1329	A
S1112	A	S1221	A	S1330	A
S1113	A	S1222	A	S1331	A
S1114	A	S1223	A	S1332	A
S1115	A	S1224	A	S1333	A
S1116	A	S1225	B	S1334	A
S1117	A	S1226	A	S1335	A
S1118	A	S1227	A	S1336	A
S1119	A	S1228	B	S1337	A
S1120	A	S1229	A	S1338	A
S1121	A	S1230	B	S1339	A
S1122	A	S1231	A	S1340	A
S1123	A	S1232	A	S1341	A
S1124	A	S1233	A	S1342	A
S1125	A	S1234	A	S1343	A
S1126	A	S1235	A	S1344	A
S1127	A	S1236	A	S1345	A
S1128	A	S1237	B	S1346	A
S1129	A	S1238	A	S1347	A
S1130	A	S1239	A	S1348	A
S1131	A	S1240	B	S1349	A
S1132	A	S1241	A	S1350	A
S1133	A	S1242	A	S1351	A
S1134	A	S1243	A	S1352	A
S1135	A	S1244	A	S1353	A
S1136	A	S1245	A	S1354	A
S1137	A	S1246	A	S1355	A
S1138	A	S1247	A	S1356	A
S1139	A	S1248	A	S1357	A
S1140	B	S1249	A	S1358	A
S1141	A	S1250	A	S1359	A
S1142	A	S1251	A	S1360	A

S1143	A	S1252	A	S1361	A
S1144	B	S1253	A	S1362	A
S1145	A	S1254	A	S1363	A
S1146	A	S1255	A	S1364	B
S1147	A	S1256	A	S1365	A
S1148	A	S1257	A	S1366	A
S1149	A	S1258	A	S1367	A
S1150	A	S1259	A	S1368	A
S1151	A	S1260	A	S1369	A
S1152	A	S1261	A	S1370	A
S1153	A	S1262	A	S1371	A
S1154	A	S1263	A	S1372	A
S1155	A	S1264	A	S1373	A
S1156	A	S1265	A	S1374	A
S1157	A	S1266	A	S1375	A
S1158	A	S1267	A	S1376	A
S1159	A	S1268	A	S1377	A
S1160	A	S1269	A	S1378	A
S1161	A	S1270	A	S1379	A
S1162	A	S1271	A	S1380	A
S1163	A	S1272	A	S1381	A
S1164	A	S1273	A	S1382	A
S1165	A	S1274	B	S1383	A
S1166	A	S1275	B	S1384	A
S1167	A	S1276	A	S1385	A
S1168	B	S1277	A	S1386	A
S1169	A	S1278	A	S1387	A
S1170	A	S1279	B	S1388	A
S1171	A	S1280	B	S1389	A
S1172	A	S1281	B	S1390	A
S1173	A	S1282	B	S1391	A
S1174	A	S1283	A	S1392	A
S1175	A	S1284	A	S1393	A
S1176	A	S1285	A	S1394	A
S1177	A	S1286	B	S1395	A
S1178	A	S1287	A	S1396	A
S1179	A	S1288	A	S1397	A
S1180	A	S1289	A	S1398	B
S1181	A	S1290	A	S1399	A
S1182	A	S1291	A	S1400	B
S1183	A	S1292	A	S1401	A
S1184	A	S1293	A	S1402	A
S1185	B	S1294	A	S1403	B
S1186	A	S1295	A	S1404	A
S1187	A	S1296	A	S1405	A
S1188	A	S1297	A	S1406	A

S1189	A	S1298	B	S1407	A
S1190	A	S1299	A	S1408	B
S1191	A	S1300	A	S1409	B
S1192	A	S1301	A	S1410	A
S1193	A	S1302	A	S1411	A
S1194	A	S1303	A	S1412	A
S1195	A	S1304	A	S1413	A
S1196	A	S1305	A	S1414	A
S1197	A	S1306	B	S1415	A
S1198	A	S1307	A	S1416	A
S1199	A	S1308	A	S1417	A
S1200	A	S1309	A	S1418	A
S1201	A	S1310	A	S1419	A
S1202	A	S1311	B	S1420	A
S1203	A	S1312	A	S1421	A
S1204	A	S1313	A	S1422	A
S1205	A	S1314	A	S1423	B
S1206	A	S1315	A	S1424	A
S1207	A	S1316	A	S1425	A
S1208	B	S1317	A	S1426	A
S1209	A	S1318	A	S1427	A

where 'A' means IC50< 100 nM, and 'B' means IC50> 100 nM but less than 1uM.

[712] Example 7: Testing for modification of Ras protein via covalent binding

[713] Test compounds are prepared as 10 mM stock solutions in DMSO (Fisher cat#BP231-100). KRAS protein (His-tagged GDP-loaded wildtype 1-169, His-tagged GDP-loaded G12S 1-169 or His-tagged GDP-loaded G12D 1-169) is diluted to ~2 μM in appropriate buffer (e.g., a Hepes buffer at physiological conditions). For testing KRAS modification, compounds are diluted to 50X final test concentration in DMSO in 96-well storage plates. 2 μL of the diluted 50X compounds are added to appropriate wells in the PCR plate (Fisher cat#AB-0800). ~49 μL of the stock protein solution is added to each well of the 96-well PCR plate. Reactions are mixed carefully. The plate is sealed well with aluminum plate seal and stored in a drawer at room temperature for 24 hrs. 5 μL of 2% formic acid (Fisher cat#A117-50) in MilliQ H_2O is then added to each well followed by mixing with a pipette. The plate is then resealed with aluminum seal and stored until mass spectrometry analysis.

[714] The extent of covalent modification of KRAS proteins can be determined by liquid chromatography electrospray mass spectrometry analysis of the intact proteins on a Thermo Q-Exactive Plus mass spectrometer. 20 μL of sample is injected onto a bioZen 3.6 μm Intact C4 column (Phenomenex cat#00B-4767-AN) placed in a column oven set to 40 °C and separated using a suitable LC gradient from ~20% to ~60% solvent B. Solvent A is 0.1% formic acid and solvent B is 0.1% formic acid in acetonitrile. HESI source settings are set to 40, 5 and 1 for the sheath, auxiliary and sweep gas flow, respectively. The spray voltage is 4 kV, and the capillary temperature is 320 °C. S-lens RF level is 50 and auxiliary gas heater temperature is set to 200 °C. The mass spectrometry is acquired using a scan range from 650 to 1750 m/z using positive polarity at a mass resolution of 70,000, AGC target of 1e6 ions and maximum injection time of 250 ms. The recorded protein mass spectrum is deconvoluted from the raw data file using Protein Deconvolution v4.0 (Thermo). The protein mass and adduct masses are exported with their peak intensities. The peak intensities for the unmodified and modified protein are used to calculate the percent covalent modification of the KRAS protein based on

the following equation: %KRAS protein modification = ((KRAS-compound) / (KRAS) + (KRAS-Compound)) *100.

[715] **Example 8**: Ras cellular assay

[716] The ability of a compound of the present disclosure to inhibit Ras protein signaling can be demonstrated by inhibiting growth of a given KRAS mutant cell line. For example, this assay can be also used to assess selective growth inhibition of a mutant Ras protein relative to a wildtype or different mutant Ras protein. In embodiments, a compound described herein (e.g., a compound of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), or any embodiment of the preceding formulae), may inhibit growth of cells including a KRAS G12C mutation, KRAS G12D mutation, or KRAS G12S mutation, with an IC50 of less than 5 μM, 1 μM, or 500 nM.

a. Growth of cells with K-Ras G12C mutation

[717] Cell lines comprising a KRas G12C mutant protein, such as MIA PaCa-2 (ATCC CRL-1420) and NCI-H1792 (ATCC CRL-5895), can be used to assess Ras cellular signaling in vitro, e.g., in response to an inhibitor compound of the present disclosure. This cellular assay can also be used to discern selective inhibition of a subject compound against certain types of KRAS mutants, e.g., more potent inhibition against KRAS G12C relative to KRAS G12D mutant, by comparing inhibition of MIA PaCa-2 (G12C driven tumor cell line) to inhibition of GP2d (G12D driven tumor cell line). MIA PaCa-2 culture medium is prepared with DMEM/Ham's F12 (e.g., with stable glutamine, 10% FCS, and 2.5% horse serum. NCI-H1792 culture medium is prepared with RPMI 1640 (e.g., with stable glutamine) and 10% FCS.

[718] On a first day (e.g., Day 1), Softagar (Select Agar, Invitrogen, 3% in ddH_2O autoclaved) is boiled and tempered at 48 °C. Appropriate culture medium (i.e., medium) is tempered to 37 °C. Agar (3%) is diluted 1:5 in medium (=0.6%) and plated into 96 well plates (Corning, #3904), then incubated at room temperature for agar solidification. A 3% agar is diluted to 0.25% in medium (1:12 dilution) and tempered at 42 °C. Cells are trypsinized, counted, and tempered at 37 °C. The cells (e.g., MIA PaCa-2 at about 125-150 cells, NCI-H1792 at about 1000 cells) are resuspended in 100 mL 0.25% Agar and plated, followed by incubation at room temperature for agar solidification. The wells are overlaid with 50 mL of the medium. Sister wells in a separate plate are plated for time zero determination. All plates are incubated overnight at 37 °C and 5% CO_2.

[719] On a second day (e.g., Day 2), time zero values are measured. A 40 mL volume of Cell Titer 96 Aqueous Solution (Promega) is added to each well and incubated in the dark at 37 °C and 5% CO_2. Absorption can be measured at 490 nm and reference wavelength 660 nm. DMSO-prediluted test compounds are added to wells of interest, e.g., with HP Dispenser, to one or more desired concentrations (e.g., a final DMSO concentration of 0.3%).

[720] On a tenth day (e.g., Day 10), absorption by wells treated with the test compounds and control wells are measured with, for example, Cell Titer 96 AQueous and analyzed in comparison to the time zero measurements. The IC50 values are determined using the four parameter fit. The resulting IC50 value is a measurement of the ability of the test compound to reduce cell growth of Ras-driven cells (e.g., tumor cell lines) in vitro and/or in vivo.

b. Growth of cells with K-Ras G12D mutation

[721] ASPC-1 (ATCC CRL-1682), Panc-10.05 (ATCC CRL-2547), A427, and GP2d cell lines, or any other cell lines comprising a G12D mutation, can be used to assess Ras cellular signaling in vitro, e.g., in response to a compound described herein. For example, ASPC-1 culture medium is prepared with RPMI-1640 and 10% heat-inactivated FBS. Panc-10.05 culture medium is prepared with RPMI-1640, 10 units/mL human recombinant insulin, and 10% FBS. A427 cell culture is prepared with RPMI-1640 and 10% heat-inactivated FBS. A CellTiter-Glo (CTG) luminescent based assay (Promega) is used to assess growth of the cells, as a measurement of the ability of the compounds herein to inhibit Ras signaling in the cells. The cells (e.g., 800 per well) are seeded in their respective culture medium in standard tissue

culture-treated 384-well format plates (Falcon #08-772-116) or ultra-low attachment surface 384-well format plates (S-Bio # MS-9384UZ). The day after plating, cells are treated with a dilution series (e.g., a 9 point, 3-fold dilution series) of the compounds herein (e.g., approximately 40 μL final volume per well). Cell viability can be monitored (e.g., approximately 5 days later) according to the manufacturer's recommended instructions, where CellTiter-Glo reagent is added (e.g., approximately 10 μL), vigorously mixed, covered, and placed on a plate shaker (e.g., approximately for 20 min) to ensure sufficient cell lysis prior to assessment of luminescent signal. The IC50 values are determined using the four-parameter fit. The resulting IC50 value is a measurement of the ability of the test compound to reduce cell growth of Ras-driven cells (e.g., tumor cell lines) in vitro and/or in vivo.

c. Growth of cells with K-Ras G12S mutation

[722] Cell lines comprising a KRas G12S mutant protein, such as A549 (ATCC CRL-185) and LS123 (ATCC CRL-255) cell lines can be used to assess Ras cellular signaling in vitro, e.g., in response to treatment with a compound described herein. A549 culture medium is prepared with RPMI-1640 and 10% heat-inactivated FBS. LS123 culture medium is prepared with RPMI-1640 and 10% heat-inactivated FBS. A CellTiter-Glo (CTG) luminescent based assay (Promega) is used to assess growth of the cells, as a measurement of the ability of the compounds herein to inhibit Ras signaling in the cells. The cells (e.g., 800 per well) are seeded in their respective culture medium in standard tissue culture-treated 384-well format plates (Falcon #08-772-116) or ultra-low attachment surface 384-well format plates (S-Bio # MS-9384WZ). The day after plating, cells are treated with a dilution series (e.g., a 10 point, 3-fold dilution series) of the compounds herein (e.g., approximately 40 μL final volume per well). Cell viability can be monitored (e.g., approximately 6 days later) according to the manufacturer's recommended instructions, where CellTiter-Glo reagent is added (e.g., approximately 10 μL), vigorously mixed, covered, and placed on a plate shaker (e.g., approximately for 20 min) to ensure sufficient cell lysis prior to assessment of luminescent signal. The IC50 values are determined using the four parameter fit. The resulting IC50 value is a measurement of the ability of the test compound to reduce cell growth of Ras-driven cells (e.g., tumor cell lines) in vitro and/or in vivo.

[723] Example 9: Ras-SOS cellular growth inhibition assay

[724] The ability of any compound of the present disclosure to inhibit SOS1-mediated signaling and hence Ras protein signaling can be demonstrated by inhibiting growth of a given Kras mutant cell line. Cells comprising a KRAS mutant protein (e.g., MIA PaCa-2 (ATCC CRL-1420) and NCI-H1792 (ATCC CRL-5895) for G12C; ASPC-1 (ATCC CRL-1682), Panc-10.05 (ATCC CRL-2547), A427, and GP2d for G12D; A549 (ATCC CRL-185) and LS123 (ATCC CRL-255) for G12S) are grown as described above. For comparison of anti-growth activity, a CellTiter-Glo (CTG) luminescent based assay (Promega) is used. Cells (~300-1,200 per well) are seeded (using the same media) in standard tissue culture-treated 384-well format plates. The day after plating, cells are treated with a 9 point, 5-fold dilution series of indicated compounds (40 μL final volume per well) and growth inhibition is monitored over time until the end of the experiment for KRAS mutant cell lines, where 20 μL of CellTiter-Glo reagent is added, vigorously mixed, covered, and placed on a plate shaker for 20 min to ensure complete cell lysis prior to assessment of luminescent signal. Growth inhibition of cells treated with a SOS1 inhibitor of the present disclosure in combination with selected KRAS inhibitors are monitored as stated above. The experiment demonstrates a synergistic inhibition by a SOS1 inhibitor disclosed herein in combination with KRAS inhibitor.

[725] Growth of K-Ras mutant cell lines (e.g., as described above) can be used to assess Ras cellular signaling in vitro, e.g., in response to a subject compound of the present disclosure. This cellular assay can also be used to discern selective inhibition of subject compounds against certain types of Kras mutants. Cell culture medium (comprising, for example, KRAS mutant comprising cells) is prepared with DMEM/Ham's F12 (e.g., with stable Glutamine, 10% FCS,

and 2.5% Horse Serum). NCI-H1792 culture medium is prepared with RPMI 1640 (e.g., with stable Glutamine) and 10% FCS. A CellTiter-Glo (CTG) luminescent based assay (Promega) is used to assess growth of the cells, as a measurement of the ability of the compounds herein to inhibit Ras signaling in the cells. The cells (e.g., 800-1200 per well) are seeded in their respective culture medium in standard tissue culture-treated ultra-low attachment surface 96-well format plates (Corning Costar #3474). The day after plating, cells are treated with a dilution series (e.g., a 7 point 5-fold dilution series) of the compounds herein (e.g., approximately 125 μL final volume per well). Cell viability can be monitored (e.g., approximately 5 days later) according to the manufacturer's recommended instructions, where the CellTiter-Glo reagent is added (e.g., approximately 65 μL), vigorously mixed, covered, and placed on a plate shaker (e.g., approximately for 20 min) to ensure sufficient cell lysis prior to assessment of luminescent signal. The IC50 values are determined using the four-parameter fit. The resulting IC50 value is a measurement of the ability of the compounds herein to reduce cell growth of Ras-driven cells as representative tumor cells.

[726] Example 10: KRAS inhibitor with SOS Inhibitor

[727] This study explores the inhibition of a variety types of cancer cells (e.g., KRAS driven tumor cells) using a combination of KRAS inhibitor and SOS inhibitor. Cell lines from multiple indications are utilized and include MIA PaCa-2 (ATCC CRL-1420), NCI-H1792 (ATCC CRL-5895), A549 (ATCC CRL-185), LS123 (ATCC CRL-255), H358, H2122, and/or LU99. All cell lines contain a KRAS mutation. The cancer cell lines are cultured in vitro in a 3D proliferation assay where cells are grown in ultra-low attachment surface cell culture plates in RPMI medium containing ~10% FBS. Cells are incubated with different concentrations of a subject SOS inhibitor (e.g., Compound A) and with different concentrations of a subject KRAS inhibitor (e.g., Compound K) for a period of time. The amount of cell growth inhibition is calculated and reported whereby a 100% inhibition is equivalent to complete blockade of growth and 0% is no effect and <100% reflects a partial growth-inhibitory effect relative to vehicle (DMSO)-treated control (Ctrl) cells. In **FIG. 1A**, **FIG. 2A**, and **FIG. 3A**, the degree of enhanced cell growth inhibition is displayed for KRAS inhibitor alone, SOS inhibitor alone, or in combination with each other respectively. The degree of synergy for the combination across cell lines is calculated by using the Bliss independence model as described herein, and is shown in **FIG. 1B**, **FIG. 2B**, and **FIG. 3B**. The degree of excess over Bliss is the difference in cell growth inhibition between the experimentally observed and the predicted inhibition at various compound concentrations whereby values >0 are indicative of more than additive effects and are instead synergistic. The greater the departure from Bliss indicates more profound synergy: ≤0 indicates no synergism, 0.05-0.1 indicates mild synergy, 0.1-0.2 indicates moderate synergy, and ≥0.2 indicates robust synergy. KRAS inhibitors in combination with a SOS inhibitor are expected to display synergistic cell growth inhibition across a range of concentrations tested. For certain cancers including pancreatic, colorectal, and gastric cancers, robust synergy is expected to be observed, as assessed in accordance with the Bliss independence model exemplified herein.

[728] Example 11: Inhibition of tumor growth in animal models

[729] Mice are maintained under specific pathogen-free conditions, and food and water were provided *ad libitum*. For PDX models, BALB/c nude (NCr) mice are implanted with respective tumor fragments (2-3 mm in diameter) on the flank. To generate other animal models, KRAS mutant cell lines (1×10^6) (e.g. H358, H2122, LU99, or SW837) are harvested on the day of use and injected in growth-factor-reduced Matrigel/PBS (50% final concentration in 100 μL). One flank is inoculated subcutaneously per mouse. Mice are monitored daily, weighed twice weekly, and caliper measurements begin when tumors become visible. Animals are randomly assigned to treatment groups by an algorithm that assigns animals to groups to achieve best case distributions of mean tumor size with lowest possible standard deviation. Tumor volume is calculated by measuring two perpendicular diameters using the following formula:

(L x w^2) / 2, in which L and w refer to the length and width of the tumor diameter, respectively. When tumors reached an average size of 100-200 mm^3, mice are randomized and treated with vehicle or indicated compounds (e.g., SOS1 inhibitor, KRAS inhibitor, Compound A, Compound K, or combinations thereof) using a reported schedule. Results are expressed as mean and standard deviation of the mean. Possible toxicity and body weight changes are monitored. FIG. 4 shows that a SOS1 inhibitor of the present disclosure (Compound A) synergistically reduces tumor volume in combination with a subject KRAS inhibitor (e.g., Compound K) in a KRAS G12C-mediated colorectal cancer PDX model. FIG. 5 shows that a SOS1 inhibitor of the present disclosure (Compound A) synergistically reduces tumor volume in combination with a subject KRAS inhibitor (e.g., Compound K) in a KRAS G12C-mediated colorectal cancer xenograft model. FIG. 6 shows that a SOS1 inhibitor of the present disclosure (Compound A) synergistically reduces tumor volume in combination with a subject KRAS inhibitor (e.g., Compound K) in a KRAS G12C-mediated NSCLC PDX model that is refractory to sotorasib and adigrasib.

[730] Example 12: Rat Oral Exposure (%F)

[731] Pharmacokinetic profile for test compound is measured by single dosing in jugular vein cannulated male Sprague-Dawley rats. Animal weights are typically over 200 grams, and animals are allowed to acclimate to their new environment for at least 3 days prior to the initiation of any studies. One set of animals is dosed intravenous (IV) with test compound, 2 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to ~4 by citric acid. IV dosing solution concentration is 0.4 mg/ml test compound. Time of blood sampling is 5 minutes, 15 minutes, 30 minutes, 90 minutes, 360 minutes, and 24 hours following IV dosing. Another set of animals is dosed oral (po) with test compound, 10 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to ~4 by citric acid. Oral dosing solution concentration is 1 mg/ml test compound. Time of blood sampling is 15 minutes, 30 minutes, 90 minutes, 180 minutes, 360 minutes and 24 hours following oral (po) dosing. Blood samples (~0.2 mL/ sample) is collected via jugular vein and placed in tubes containing EDTA-K2 and stored on ice until centrifuged. The blood samples are centrifuged at approximately 6800g for 6 minutes at 2-8°C and the resulting plasma will be separated and stored frozen at approximately -80°C.

[732] All the plasma samples are analyzed using an Agilent Technologies 6430 Triple Quad LC/MS system, following the manufacture instructions. All the analytes are detected with positive-mode electrospray ionization (ES+). A standard curve for each test compound is generated and used to measure test compound concentrations in the rat plasma samples. Based on the time course sampling, an area under the curve is calculated for the oral dose group and the intravenous dose group. Percentage rat bioavailability is calculated based on equation 5.

Equation 5

$\%F\ (rat) = \frac{AUC_{po} * Dose_{IV}}{AUC_{IV} * Dose_{po}}$, where F is bioavailability, AUC_{po} is area under curve of oral drug, AUC_{IV} is area under curve of intravenous drug, $Dose_{IV}$ is the intravenous dose and $Dose_{po}$ is the oral dose.

[733] Example 13: Inhibition of tumor growth in sotorasib- or adagrasib-resistant animal model

[734] Mice are maintained under specific pathogen-free conditions, and food and water were provided *ad libitum*. Cells from a suitable KRAS-mutant cell line (1 x 10^6) are harvested on the day of use and injected in growth-factor-reduced Matrigel/PBS (50% final concentration in 100 µL). One flank is inoculated subcutaneously per mouse. Mice are monitored daily, weighed twice weekly, and caliper measurements begin when tumors become visible. Animals are randomly assigned to treatment groups by an algorithm that assigns animals to groups to achieve best case distributions of mean tumor size with lowest possible standard deviation. Tumor volume is calculated by measuring two perpendicular diameters using the following formula: (L x w^2) / 2, in which L and w refer to the length and width of the tumor diameter, respectively. When tumors reached an average size of 100-200 mm^3, mice are randomized and treated with vehicle, sotorasib, or adagrasib. Possible toxicity and body weight changes are monitored. Once tumors begin to

progress on sotorasib or adagrasib monotherapy, the animals are randomly assigned to new treatment groups by an algorithm that assigns animals to groups to achieve best case distributions of mean tumor size with lowest possible standard deviation. Animals are then treated with a subject KRAS inhibitor (e.g., Compound K) in combination with a SOS1 inhibitor of the present disclosure (e.g., Compound A). Possible toxicity and body weight changes are monitored.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS protein overexpression, the method comprising administering to the cells (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

2. The method of claim 1, wherein the cancer cells are non-small cell lung cancer cells, colorectal cancer cells, or pancreatic cancer cells.

3. A method of downregulating KRAS signaling output in a plurality of cancer cells, comprising:

(i) assessing KRAS mutation status in a biological sample comprising nucleic acid from the subject; and

(ii) administering an effective dose of (a) a SOS1 inhibitor and an effective dose of (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), if a KRAS mutation is detected in the sample, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

4. A method of treating cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

5. The method of claim 4, wherein the cancer is a mutant KRAS-mediated cancer.

6. The method of any one of claims 1 to 5, wherein the KRAS inhibitor is a compound, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), or (II-3).

7. The method of any one of the preceding claims, wherein the administration of (a) and (b) synergistically reduces proliferation of the cancer cells with a synergistic value of at least 0.05 as ascertained by Bliss independence criterion.

8. A method of treating an mutant KRAS-mediated cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), wherein (a) is administered prior to, concurrently with, or subsequent to administering (b), and wherein the administration of (a) and (b) synergistically reduces proliferation of the cancer cells with a synergistic value of at least 0.05 as ascertained by Bliss independence criterion.

9. The method of claim 7 or 8, wherein the synergistic value is ascertained by Bliss independence criterion in accordance with the formula:

$$Y_{AB,O} - Y_{AB,P}$$

wherein:

$Y_{AB,O}$ is observed percent growth inhibition of the cancer cells by the application of (a) and (b) comprising (a) at dose A and (b) at dose B;

$Y_{AB,P}$ is predicted percent growth inhibition of the cancer cells by the application of (a) and (b) comprising (a) at dose A and (b) at dose B, wherein $Y_{AB,P} = Y_A + Y_B - Y_A Y_B$;

Y_A is observed percent growth inhibition of the cancer cells by (a) alone at dose A;

Y_B is observed percent growth inhibition of the cancer cells by (b) alone at dose B; and

Y_AY_B is the product of Y_A and Y_B.

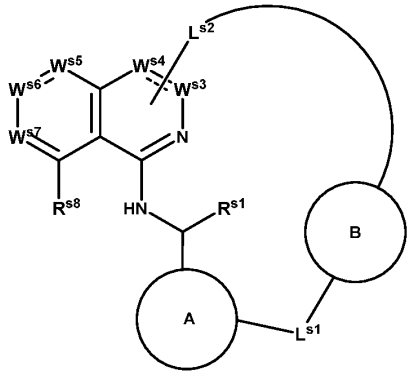
10. The method of any one of claims 7 to 9, wherein the synergistic value is at least 0.1.

11. The method of any one of claims 7 to 9, wherein the synergistic value is at least 0.4.

12. The method of any one of claims 7 to 9, wherein the synergistic value is at least 1.

13. The method of any one of claims 7 to 9, wherein the synergistic value is at least 5.

14. The method of any one of claims 1 to 13, wherein the SOS1 inhibitor is a compound of Formula (SI-1):



(SI-1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

is selected from C_{5-7} carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R^{s11};

is absent or selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{s11a};

L^{s1} is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^{s2} is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{s11b}, wherein L^{s2} is covalently bound to one of W^{s3}, W^{s4}, W^{s5}, W^{s6}, or W^{s7};

W^{s3} is selected from $N(R^{s3b})$, N, $C(R^{s3})$, and C(O);

W^{s4} is selected from $N(R^{s4b})$, N, $C(R^{s4})$, and C(O);

W^{s5} is selected from $N(R^{s5b})$, N, and $C(R^{s5})$;

W^{s6} is selected from $C(R^{s6})$ and C(O);

W^{s7} is $C(R^{s7})$;

R^{s1} is C_{1-3} alkyl optionally substituted with one or more R^{s11c};

R^{s8} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, -

$N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3}, R^{s4}, R^{s5}, R^{s6}, and R^{s7} are each independently selected from a bond to L^{s2}, hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s3b}, R^{s4b}, and R^{s5b} are each independently selected from a bond to L^{s2}, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, and $-CH_2S(O)_2N(R^{s12})(R^{s13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{s20};

R^{s11} and R^{s11a} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{s12}$, $-SR^{s12}$, $-N(R^{s12})(R^{s13})$, $-C(O)OR^{s12}$, $-OC(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)OR^{s15}$, $-N(R^{s14})S(O)_2R^{s15}$, $-C(O)R^{s15}$, $-S(O)R^{s15}$, $-OC(O)R^{s15}$, $-C(O)N(R^{s12})(R^{s13})$, $-C(O)C(O)N(R^{s12})(R^{s13})$, $-N(R^{s14})C(O)R^{s15}$, $-S(O)_2R^{s15}$, $-S(O)_2N(R^{s12})(R^{s13})$, $-S(=O)(=NH)N(R^{s12})(R^{s13})$, $-CH_2C(O)N(R^{s12})(R^{s13})$, $-CH_2N(R^{s14})C(O)R^{s15}$, $-CH_2S(O)_2R^{s15}$, $-CH_2S(O)_2N(R^{s12})(R^{s13})$, $-CH_2N(R^{s12})S(O)_2(R^{s13})$, and $-P(O)(R^{s17})(R^{s17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s11c} is independently selected at each occurrence from halogen, $-OR^{s12}$, and $-N(R^{s12})(R^{s13})$;

R^{s12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{s12} and R^{s13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{s20};

R^{s14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{s15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle,

and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{s20};

R^{s17} and R^{s17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{s20}; or R^{s17} and R^{s17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{s20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, -CH_2-(3- to 10-membered heterocycle), -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, -$OCH_2C(O)OR^{s22}$, and -$OC(O)R^{s25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{s21}, -SR^{s21}, -$N(R^{s22})(R^{s23})$, -$C(O)OR^{s22}$, -$C(O)N(R^{s22})(R^{s23})$, -$C(O)C(O)N(R^{s22})(R^{s23})$, -$OC(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)N(R^{s22})(R^{s23})$, -$N(R^{s24})C(O)OR^{s25}$, -$N(R^{s24})C(O)R^{s25}$, -$N(R^{s24})S(O)_2R^{s25}$, -$C(O)R^{s25}$, -$S(O)_2R^{s25}$, -$S(O)_2N(R^{s22})(R^{s23})$, and -$OC(O)R^{s25}$;

R^{s21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{s22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

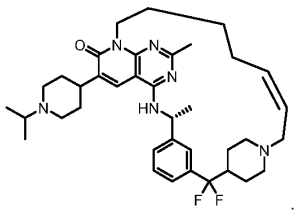
R^{s23} is independently selected at each occurrence from H and C_{1-6} alkyl;

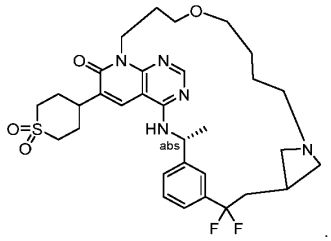
R^{s24} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{s25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

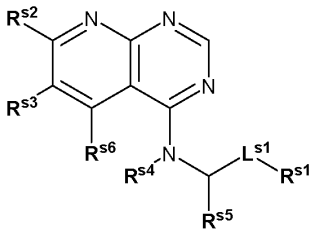
15. The method of any one of claims 1 to 14, wherein the SOS1 inhibitor is selected from BI-3406, MRTX0902, BAY 293, RMC-5845, and BI-1701963.

16. The method of any one of claims 1 to 14, wherein the SOS1 inhibitor is  .



17. The method of any one of claims 1 to 14, wherein the SOS1 inhibitor is .

18. The method of any one of claims 1 to 13, wherein the SOS1 inhibitor is a compound of Formula (SIV-1):



(SIV-1),

or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

L^{s1} is a bond;

R^{s1} is 6- to 10-membered aryl, wherein the 6- to 10-membered aryl is optionally substituted with one or more independently selected R^{s10} substituents;

R^{s2} is halogen or OR^{s2a};

R^{s2a} is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl is optionally substituted with one, two, or three independently selected R^{s20a} substituents;

R^{s3} is halogen, C_{1-6} alkyl, C_{3-14} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein the C_{1-6} alkyl, C_{3-14} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl is optionally substituted with one, two, or three independently selected R^{s20b} substituents;

R^{s4} is H, C_{1-6} alkyl, or C_{1-6} haloalkyl;

R^{s5} is H, C_{1-6} alkyl, or C_{1-6} haloalkyl;

R^{s6} is H, halogen, CN, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with one, two, or three independently selected R^{s20c} substituents;

each R^{s10} is independently halogen, CN, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein each C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three independently selected R^{s20d} substituents;

each R^{s20a} is independently halogen, CN, C_{1-6} alkyl, CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OCH_2C(O)OR^{s22}$, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, $S(O)_2NR^{s22}R^{s23}$, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$,

$NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$; and

wherein each CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$;

each R^{s20b} is independently halogen, CN, C_{1-6} alkyl, CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OCH_2C(O)OR^{s22}$, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, $S(O)_2NR^{s22}R^{s23}$, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$; and

wherein each CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$;

each R^{s20c} is independently halogen, CN, C_{1-6} alkyl, CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OCH_2C(O)OR^{s22}$, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, $S(O)_2NR^{s22}R^{s23}$, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$; and

wherein each CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$;

each R^{s20d} is independently halogen, CN, C_{1-6} alkyl, CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$,

$NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OCH_2C(O)OR^{s22}$, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, $S(O)_2NR^{s22}R^{s23}$, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl;

wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$; and

wherein each CH_2C_{3-10} cycloalkyl, CH_2C_{2-9} heterocycloalkyl, CH_2C_{6-10} aryl, C_{3-10} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{s25}$, $C(O)C(O)NR^{s22}R^{s23}$, $C(O)NR^{s22}R^{s23}$, $C(O)OR^{s22}$, $NR^{s22}R^{s23}$, $NR^{s24}C(O)R^{s25}$, $NR^{s24}C(O)NR^{s22}R^{s23}$, $NR^{s24}C(O)OR^{s25}$, $NR^{s24}S(O)_2R^{s25}$, =NH, OR^{s21}, $OC(O)R^{s25}$, $OC(O)NR^{s22}R^{s23}$, =O, SR^{s21}, $S(O)_2R^{s25}$, and $S(O)_2NR^{s22}R^{s23}$;

each R^{s21} is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein each C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen and C_{1-6} alkyl;

each R^{s22} is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein each C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen and C_{1-6} alkyl;

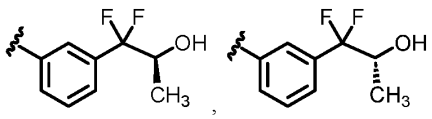
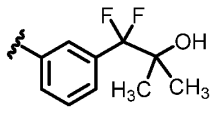
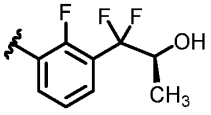
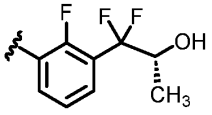
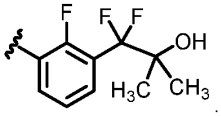
each R^{s23} is independently H or C_{1-6} alkyl;

each R^{s24} is independently H or C_{1-6} alkyl; and

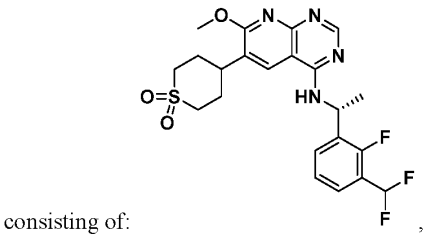
each R^{s25} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, or C_{1-9} heteroaryl, wherein each C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl is optionally and independently substituted with one, two, or three substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, OC_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl.

19. The method of claim 18, wherein R^{s3} is C_{2-9} heterocycloalkyl, wherein the C_{2-9} heterocycloalkyl is optionally substituted with one, two, or three independently selected R^{s20b} substituents.

20. The method of claim 18, wherein R^{s3} is C_{3-10} cycloalkyl, wherein the C_{3-10} cycloalkyl is optionally substituted with one, two, or three independently selected R^{s20b} substituents.

21. The method of any one of claims 18 to 20, wherein R^{s1} is:  , ,  ,  ,  , or  .

22. The method of any one of claims 1 to 13, wherein the SOS1 inhibitor is a compound selected from the group consisting of: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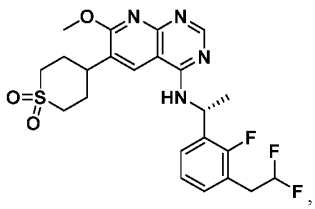
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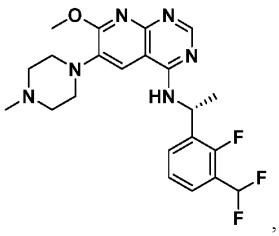
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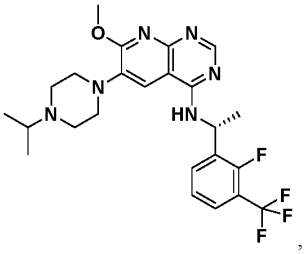
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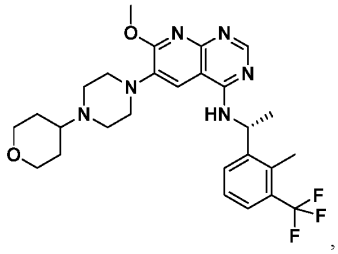
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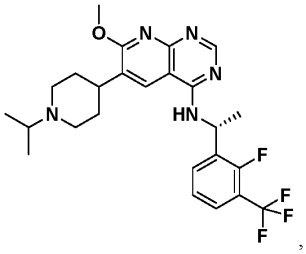
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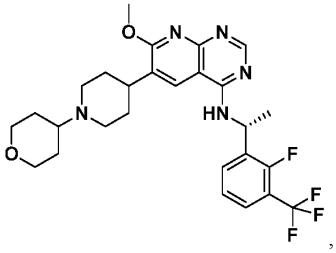
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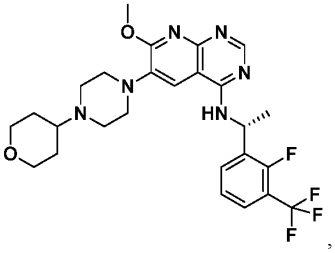
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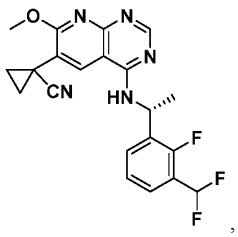
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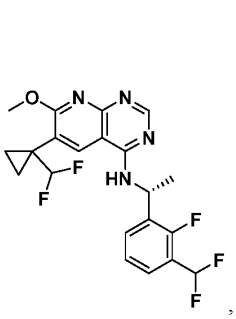
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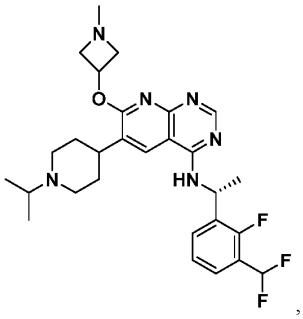
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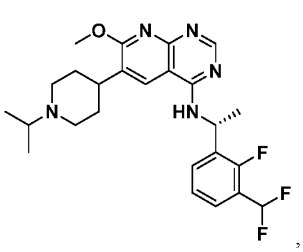
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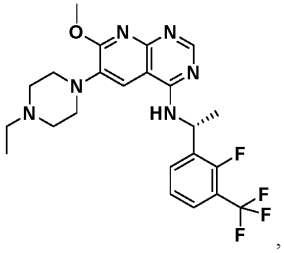
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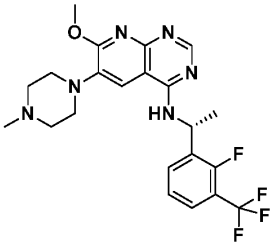
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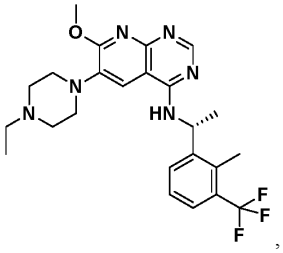
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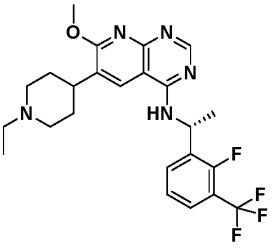
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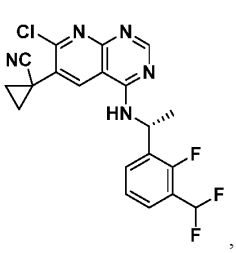
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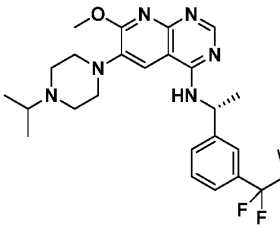
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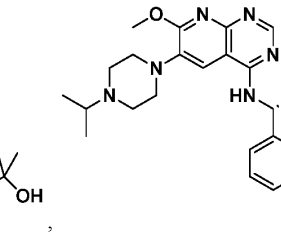
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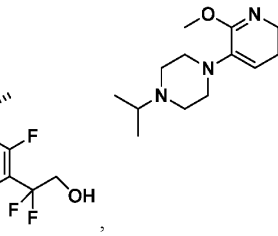
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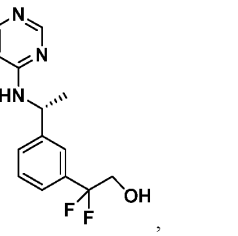
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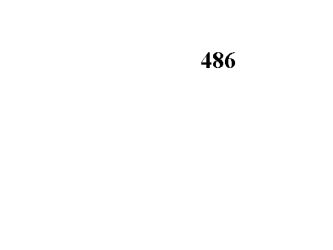
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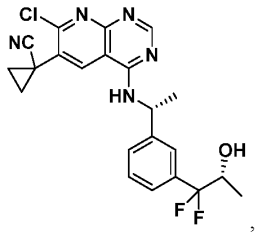
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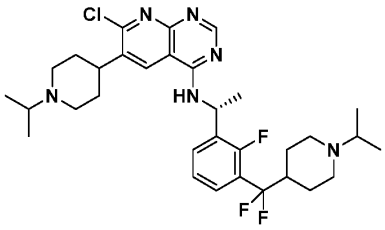
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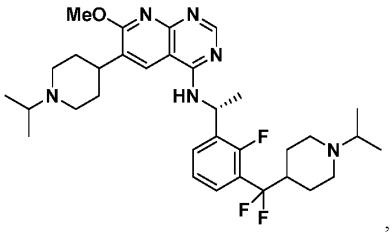
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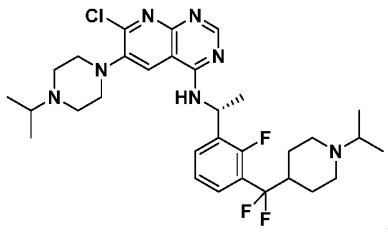
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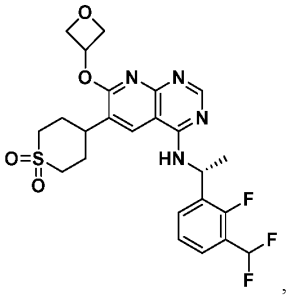
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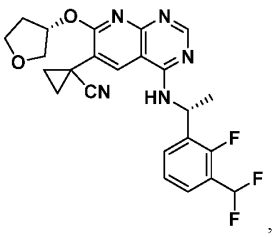
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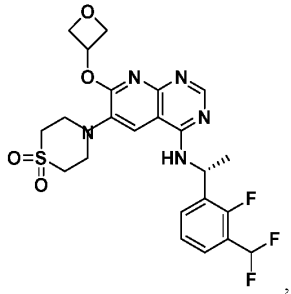
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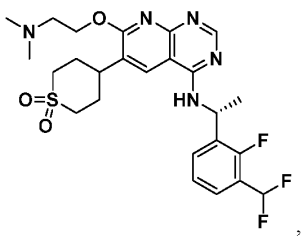
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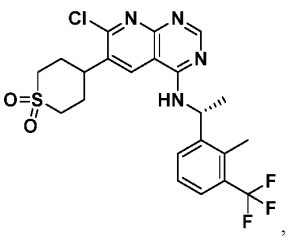
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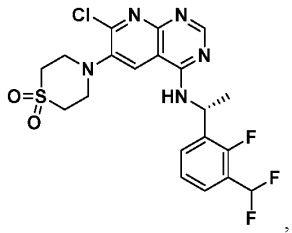
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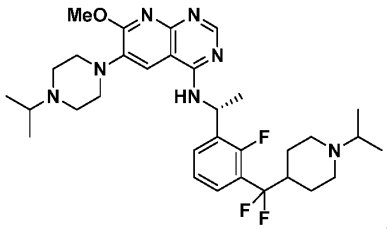
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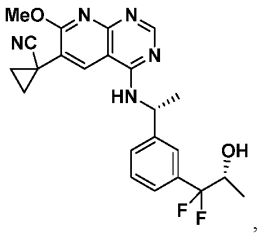
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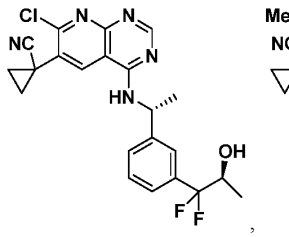
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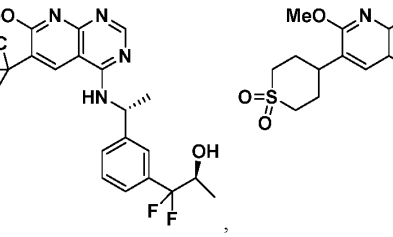
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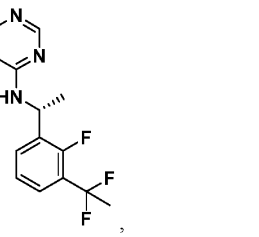
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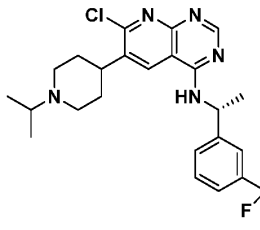
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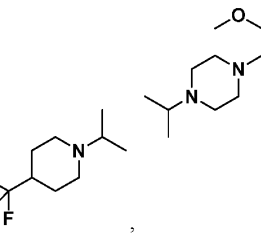
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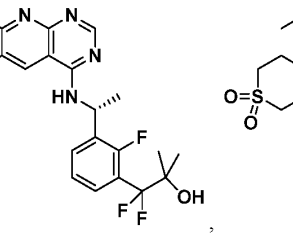
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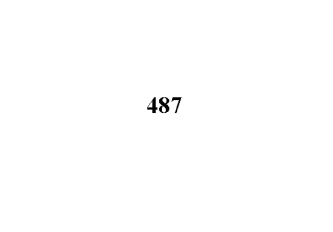
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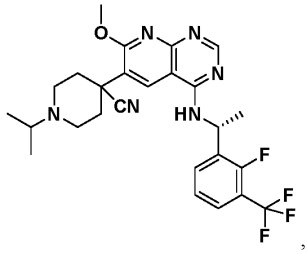
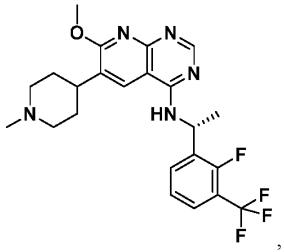
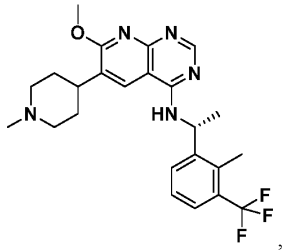
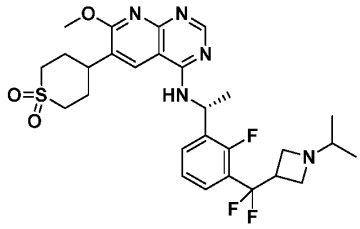
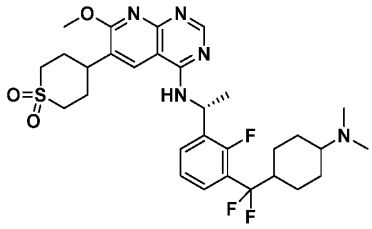
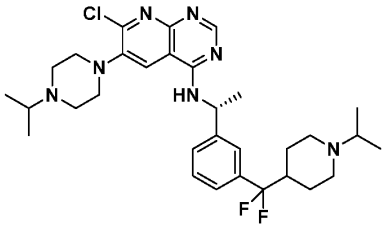
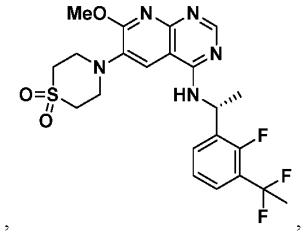
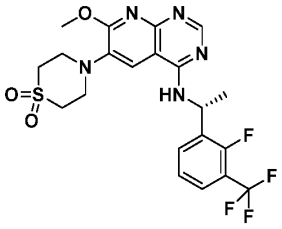
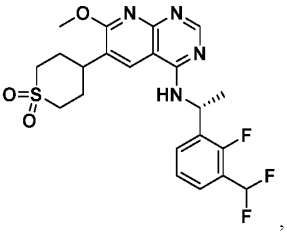
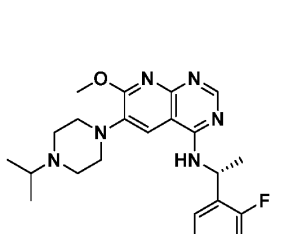
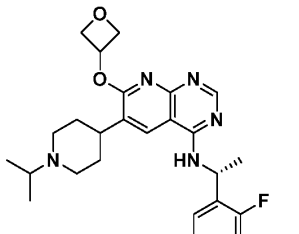
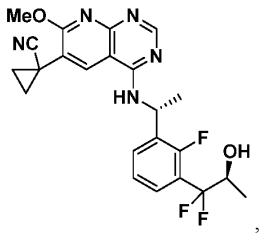
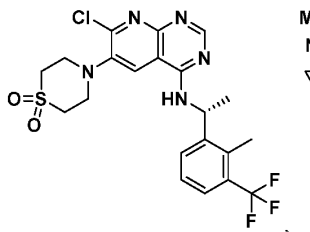
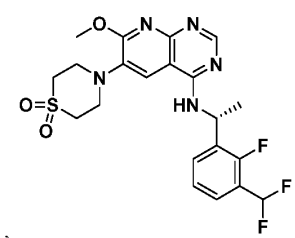
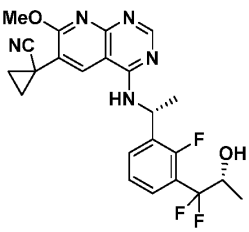
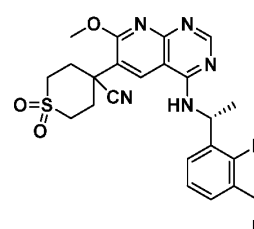
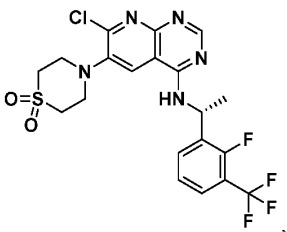
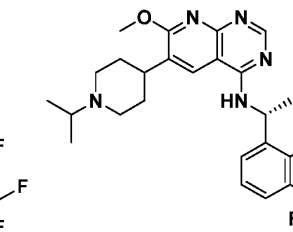
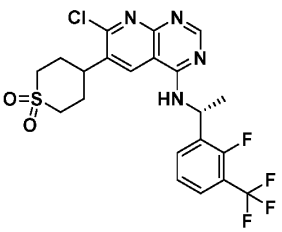
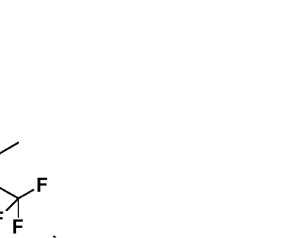

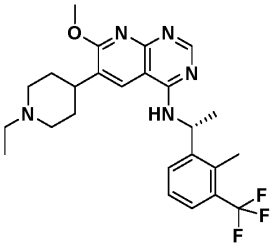
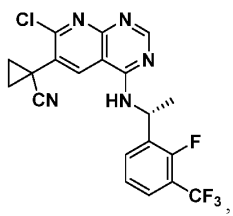
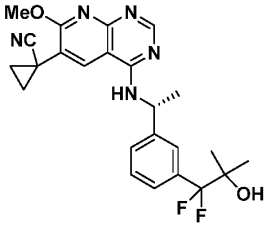
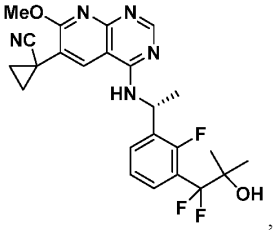
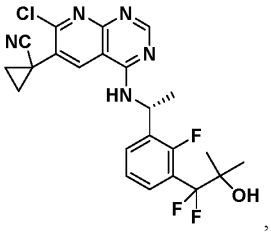
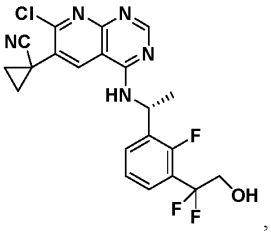
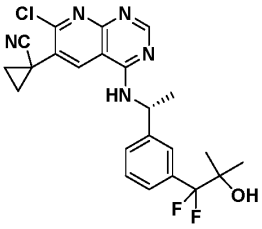
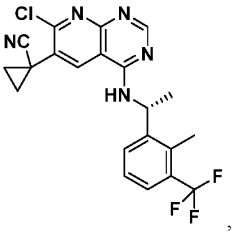
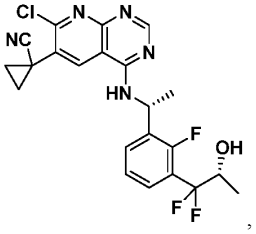
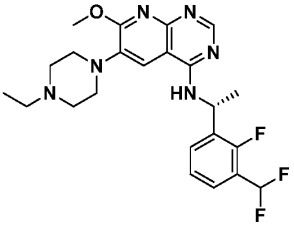
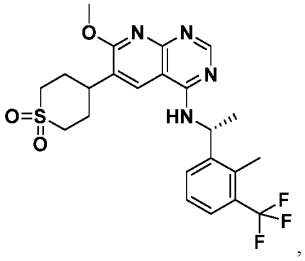
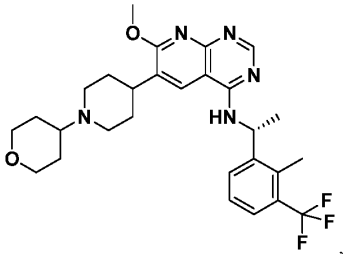
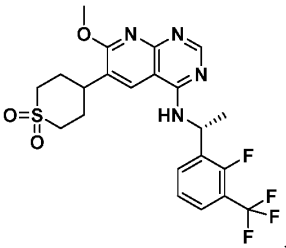
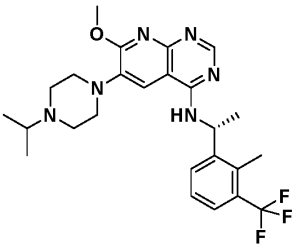
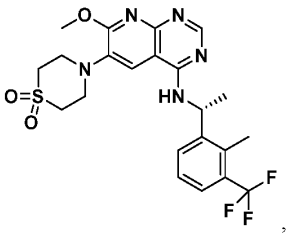
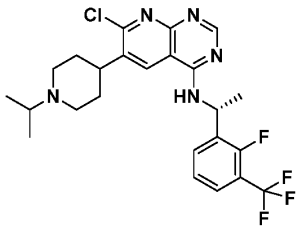
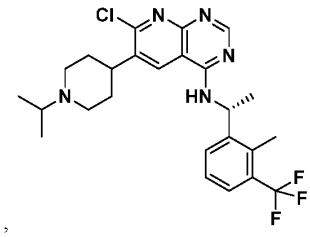
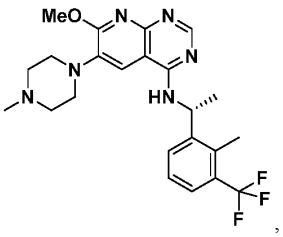
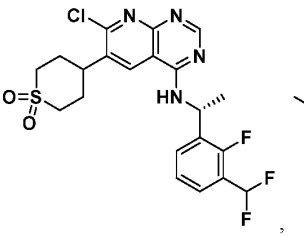
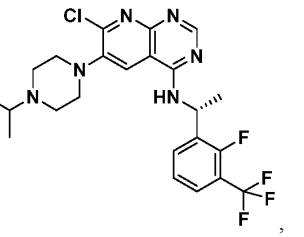

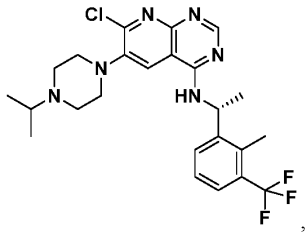
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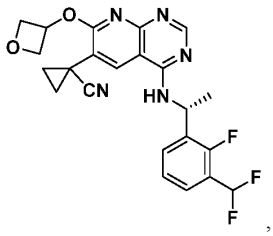
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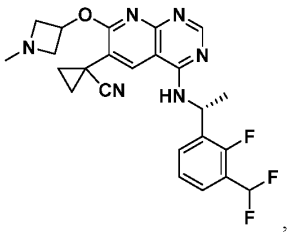
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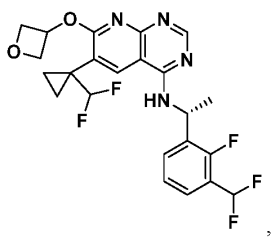
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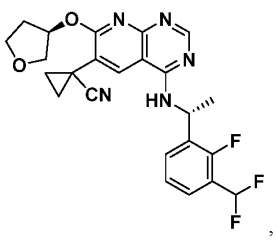
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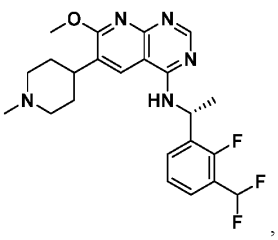
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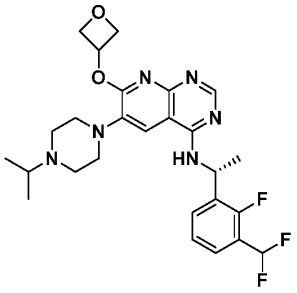
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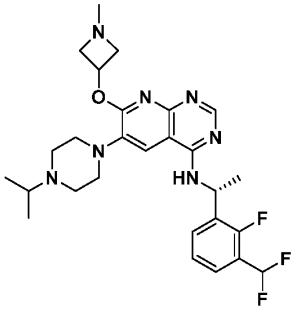
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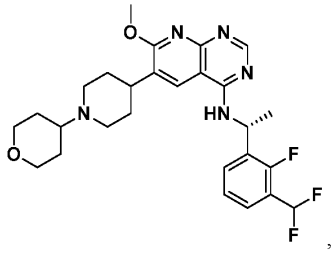
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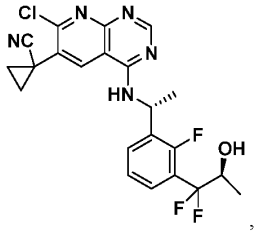
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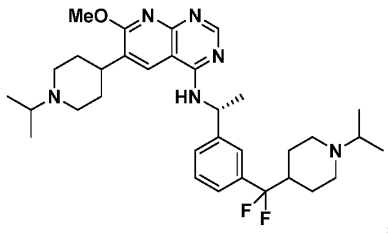
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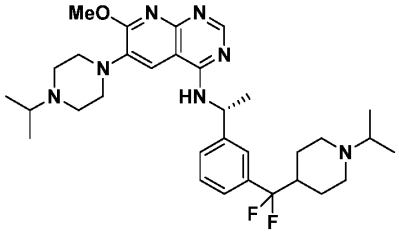
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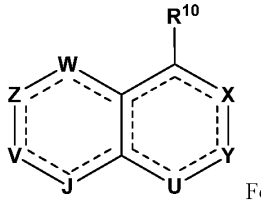
23. The method of any one of claims 1 to 22, wherein the KRAS inhibitor is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:


Formula (I);

wherein

W is a N, C(R^{18}), N(R^{18b}), C(R^{18})(R^{18a}), C(O), S(O), or $S(O)_2$;

Z is N, C(R^{8}), N(R^{8b}), C(R^{8})(R^{8a}), C(O), S(O), or $S(O)_2$; wherein W and Z are not both selected from C(O), S(O), and $S(O)_2$;

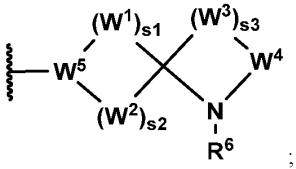
V and J are each independently selected from $C(R^{17})$, $C(R^{17})(R^{16a})$, $C(R^{16})$, $C(R^{16})(R^{16a})$, N, $N(R^{17b})$, and $N(R^{16b})$; wherein exactly one of V and J is $C(R^{17})$, $C(R^{17})(R^{16a})$, or $N(R^{17b})$;

Y is N, $C(R^2)$, $C(R^2)(R^{2c})$, $N(R^{2b})$, S(O), or $S(O)_2$;

U is N, $C(R^{2c})$, $C(R^{2c})(R^{2c})$, $N(R^{2b})$, S(O), $S(O)_2$, or C(O);

R^{10} is $-L^7-R^7$;

L^7 is a bond, -O-, $-N(R^{14})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, C_{1-4}alkyl, or 2-4 membered heteroalkyl linker, wherein the C_{1-4}alkyl and 2-4 membered heteroalkyl linker are each optionally substituted with one, two or three R^{20a};

R^7 is 

;

W^1 and W^3 are independently selected from $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^2 is independently selected from a $N(R^1)$, $N(R^4)$, $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, C(O), S, O, S(O), and $S(O)_2$;

W^4 is selected from $C(R^1)(R^1)$, $C(R^1)(R^4)$, $C(R^4)(R^4)$, S(O), and $S(O)_2$;

W^5 is selected from N, $C(R^1)$, and $C(R^4)$;

s1 is 1 and s2 is 0, 2, or 3; s1 is 2 and s2 is 0, 1, or 3; s1 is 3 and s2 is 0 to 3; s1 is 4 and s2 is 0 to 3; s1 is 5 and s2 is 0 to 3; or s1 is 6 and s2 is 0 to 3; or

s3 is an integer from 1 to 3;

each R^1 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{3-12}cycloalkyl, $-CH_2-C_{3-12}$cycloalkyl, C_{1-11}heterocycloalkyl, $-CH_2-C_{1-11}$heterocycloalkyl, C_{6-12}aryl, $-CH_2-C_{6-12}$aryl, $-CH_2-C_{1-11}$heteroaryl, and C_{1-11}heteroaryl are optionally substituted with one, two, or three R^{20a};

each R^4 is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $=C(R^{21b})_2$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{12}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{12}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-C(O)N(R^{12})(R^{13})$, $-(C_{1-6}$alkyl$)-N(R^{14})C(O)R^{12}$, $-(C_{1-6}$alkyl$)-S(O)_2R^{15}$, $-(C_{1-6}$alkyl$)-N(R^{12})(R^{13})$, and $-(C_{1-6}$alkyl$)-S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20a};

R^6 is $-L^2-R^5$, wherein R^6 is optionally capable of forming a covalent bond with a Ras amino acid;

L^2 is a bond, -O-, $-N(R^{4d})$-, -C(O)-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{4d}$-, $CR^{4c}R^{4c}$, $-OCR^{4c}R^{4c}$-, $-N(R^{4d})CR^{4c}R^{4c}$-, $-C(O)CR^{4c}R^{4c}$-, $-SCR^{4c}R^{4c}$-, $-S(O)_2CR^{4c}R^{4c}$-, $-S(O)CR^{4c}R^{4c}$-, $-P(O)R^{4d}CR^{4c}R^{4c}$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}$, $-CR^{4c}R^{4c}O$-, $-CR^{4c}R^{4c}N(R^{4d})$-, $-CR^{4c}R^{4c}C(O)$-, $-CR^{4c}R^{4c}S$-, $-CR^{4c}R^{4c}S(O)_2$-, $-CR^{4c}R^{4c}S(O)$-, $-CR^{4c}R^{4c}P(O)R^{4d}$-, $-N(R^{4d})C(O)$-, $-N(R^{4d})S(O)_2$-, $-N(R^{4d})S(O)$-, $-N(R^{4d})P(O)R^{4d}$-, $-C(O)N(R^{4d})$-, $-S(O)_2N(R^{4d})$-, $-S(O)N(R^{4d})$-, $-P(O)R^{4d}N(R^{4d})$-, -OC(O)-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{4d}$-, -C(O)O-, $-S(O)_2O$-, -S(O)O-, $-P(O)R^{4d}O$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}CR^{4c}R^{4c}$-, $-OCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-N(R^{4d})CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-C(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-SCR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-S(O)_2CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-S(O)CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-P(O)R^{4d}CR^{4c}R^{4c}CR^{4c}R^{4c}$ -, $-CR^{4c}R^{4c}CR^{4c}R^{4c}O$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}N(R^{4d})$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}C(O)$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)_2$-, $-CR^{4c}R^{4c}CR^{4c}R^{4c}S(O)$-, or -

$CR^{4c}R^{4c}CR^{4c}R^{4c}P(O)R^{4d}$-;

each R^{4c} is independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -C(O)OR^{14}, -C(O)N(R^{14})(R^{14}), -C(O)C(O)N(R^{14})(R^{14}), -OC(O)N(R^{14})(R^{14}), -C(O)R^{14a}, -$S(O)_2R^{14}$, -$S(O)_2$N(R^{14})(R^{14}), -OCH_2C(O)OR^{14}, -OC(O)R^{14a}, -N(R^{14})(R^{14}), -N(R^{14})C(O)N(R^{14})(R^{14}), -N(R^{14})C(O)OR^{14}, -N(R^{14})C(O)R^{14a}, and -N(R^{14})$S(O)_2R^{14}$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -N(R^{14})(R^{14}), -C(O)OR^{14}, -C(O)N(R^{14})(R^{14}), -C(O)C(O)N(R^{14})(R^{14}), -OC(O)N(R^{14})(R^{14}), -N(R^{14})C(O)N(R^{14})(R^{14}), -N(R^{14})C(O)OR^{14}, -N(R^{14})C(O)R^{14}, -N(R^{14})$S(O)_2R^{14}$, -C(O)R^{14a}, -$S(O)_2R^{14}$, -$S(O)_2$N(R^{14})(R^{14}), and -OC(O)R^{14a};

each R^{4d} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, -OR^{14}, -SR^{14}, -C(O)OR^{14}, -C(O)N(R^{14})(R^{14}), -C(O)C(O)N(R^{14})(R^{14}), -OC(O)N(R^{14})(R^{14}), -C(O)R^{14a}, -$S(O)_2R^{14}$, -$S(O)_2$N(R^{14})(R^{14}), -OCH_2C(O)OR^{14}, and -OC(O)R^{14a}, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, and -CH_2-C_{2-9}heterocycloalkyl, are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{14}, -SR^{14}, -N(R^{14})(R^{14}), -C(O)OR^{14}, -C(O)N(R^{14})(R^{14}), -C(O)C(O)N(R^{14})(R^{14}), -OC(O)N(R^{14})(R^{14}), -N(R^{14})C(O)N(R^{14})(R^{14}), -N(R^{14})C(O)OR^{14}, -N(R^{14})C(O)R^{14}, -N(R^{14})$S(O)_2R^{14}$, -C(O)R^{14a}, -$S(O)_2R^{14}$, -$S(O)_2$N(R^{14})(R^{14}), and -OC(O)R^{14a};

R^5 is a 5 or 6 membered partially unsaturated heterocycloalkyl or a 5 or 6 membered heteroaryl, each optionally substituted with one, two or three R^{20k}, wherein the partially unsaturated 5 or 6 membered heterocycloalkyl or 5 or 6 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and the 5 or 6 membered partially unsaturated heterocycloalkyl or 5 or 6 membered heteroaryl is each bonded to L^2 through a ring nitrogen;

R^8 and R^{8a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})$S(O)_2R^{15}$, -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)R^{15}, -$S(O)_2R^{15}$, -$S(O)_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{8b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -$S(O)_2R^{15}$, -$S(O)_2$N(R^{12})(R^{13})-, S(=O)(=NH)N(R^{12})(R^{13}), -CH_2C(O)N(R^{12})(R^{13}), -CH_2N(R^{14})C(O)R^{15}, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2$N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20c};

R^{17} is -L^1-R^{19};

R^{17b} is -L^{1b}-R^{19};

L^1 is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -O-, -N(R^{14})-, -C(O)-, -N(R^{14})C(O)-, -C(O)N(R^{14})-, -S-, -$S(O)_2$-, -S(O)-, -$S(O)_2$N(R^{14})-, -S(O)N(R^{14})-, -N(R^{14})S(O)-, -N(R^{14})$S(O)_2$-, -OCON(R^{14})-, -N(R^{14})C(O)O-, N(R^{1e}), C(O)N(R^{1c}), $S(O)_2$N(R^{1c}), S(O)N(R^{1c}), C(R^{1f})(R^{1g})O, C(R^{1f})(R^{1g})N(R^{1c}), and C(R^{1f})(R^{1g});

wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

L^{1b} is selected from a bond, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, -C(O)-, -C(O)N(R^{14})-, C(O)N(R^{1c}), C(R^{1f})(R^{1g})O, C(R^{1f})(R^{1g})N(R^{1c}), and C(R^{1f})(R^{1g}); wherein the C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl are optionally substituted with one, two, or three R^{20i};

R^{1e}, R^{1f}, and R^{1g} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -$CH_2$C(O)N($R^{12}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, and -$CH_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1f} and R^{1g} are joined to form a 4-7 membered heterocycloalkyl ring or a 4-7 membered cycloalkyl ring, wherein the 4-7 membered heterocycloalkyl ring or 4-7 membered cycloalkyl ring are optionally substituted with one, two, or three R^{20i};

R^{1c} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{19} is selected from a C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl, wherein the C_{3-12}cycloalkyl, C_{2-11}heterocycloalkyl, C_{6-12}aryl, and C_{2-12}heteroaryl are optionally substituted with one, two, three, four, five, six, or seven R^{1i};

each R^{1i} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -$CH_2$C(O)N($R^{12}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, and -$CH_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i};

R^{16} and R^{16a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -N(R^{12})(R^{13}), -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -N(R^{14})C(O)N(R^{12})(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12}$)($R^{13}$), -C(O)C(O)N($R^{12}$)($R^{13}$), -N($R^{14}$)C(O)$R^{15}$, -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -$CH_2$C(O)N($R^{12}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, and -$CH_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^{16b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -C(O)OR^{12}, -OC(O)N(R^{12})(R^{13}), -C(O)R^{15}, -S(O)R^{15}, -OC(O)R^{15}, -C(O)N(R^{12})(R^{13}), -C(O)C(O)N(R^{12})(R^{13}), -S(O)$_2$$R^{15}$, -S(O)$_2$N($R^{12}$)($R^{13}$)-, S(=O)(=NH)N($R^{12}$)($R^{13}$), -$CH_2$C(O)N($R^{12}$)($R^{13}$), -$CH_2$N($R^{14}$)C(O)$R^{15}$, -$CH_2$S(O)$_2$$R^{15}$, and -$CH_2$S(O)$_2$N($R^{12}$)($R^{13}$), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20g};

R^2 is selected from halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -O$R^{12'}$, -S$R^{12'}$, -N($R^{12''}$)(R^{13}), -N=(R^{15}), -C(O)O$R^{12'}$, -OC(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)N($R^{12'}$)(R^{13}), -N(R^{14})C(O)OR^{15}, -N(R^{14})S(O)$_2$$R^{15}$, -C(O)$R^{15}$, -S(O)$R^{15}$, -OC(O)$R^{15}$, -C(O)N($R^{12'}$)($R^{13}$), -

$C(O)C(O)N(R^{12'})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3\text{-}10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{4\text{-}9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6\text{-}10}\text{aryl})\text{-}R^{12b}$, and $-(C_{1\text{-}9}\text{heteroaryl})\text{-}R^{12b}$, wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2c} is independently hydrogen, halogen, -CN, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}9}$heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3\text{-}10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2\text{-}9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6\text{-}10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1\text{-}9}\text{heteroaryl})\text{-}R^{12b}$, wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{2b} is independently hydrogen, -CN, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}9}$heteroaryl, $-OR^{12'}$, $-SR^{12'}$, $-C(O)OR^{12'}$, $-OC(O)N(R^{12'})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12'})(R^{13})$, $-C(O)C(O)N(R^{12'})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12'})(R^{13})$-, $S(=O)(=NH)N(R^{12'})(R^{13})$, $-CH_2C(O)N(R^{12'})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12'})(R^{13})$, $-(C_1\text{-}C_6\text{alkyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkenyl})\text{-}R^{12b}$, $-(C_{2\text{-}6}\text{alkynyl})\text{-}R^{12b}$, $-(C_{3\text{-}10}\text{cycloalkyl})\text{-}R^{12b}$, $-(C_{2\text{-}9}\text{heterocycloalkyl})\text{-}R^{12b}$, $-(C_{6\text{-}10}\text{aryl})\text{-}R^{12b}$, or $-(C_{1\text{-}9}\text{heteroaryl})\text{-}R^{12b}$, wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

R^{12b} is selected from hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-CH_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-CH_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}9}$heteroaryl, wherein $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-CH_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-CH_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

X is $C(R^3)$, $C(R^3)(R^3)$, $N(R^3)$, or N;

each R^3 is independently selected from hydrogen, halogen, -CN, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}9}$heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20b};

each R^{12} is independently selected from hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-CH_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-CH_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}9}$heteroaryl, wherein $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-CH_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-CH_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{6\text{-}10}$aryl, $-CH_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}9}$heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12'}$ is independently selected from hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-C(R^{12c})_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-C(R^{12c})_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-C(R^{12c})_2\text{-}C_{6\text{-}10}$aryl, $-C(R^{12c})_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}9}$heteroaryl, wherein $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}10}$cycloalkyl, $-C(R^{12c})_2\text{-}C_{3\text{-}10}$cycloalkyl, $C_{2\text{-}9}$heterocycloalkyl, $-C(R^{12c})_2\text{-}C_{2\text{-}9}$heterocycloalkyl, $C_{6\text{-}10}$aryl, $-C(R^{12c})_2\text{-}C_{6\text{-}10}$aryl, $-C(R^{12c})_2\text{-}C_{1\text{-}9}$heteroaryl, and $C_{1\text{-}$

$_9$heteroaryl are optionally substituted with one, two, or three R^{20d};

each $R^{12''}$ is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -$C(R^{12c})_2$-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$C(R^{12c})_2$-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -$C(R^{12c})_2$-C_{6-10}aryl, -$C(R^{12c})_2$-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20d};

each R^{12c} is independently selected from hydrogen and R^{20m};

each R^{13} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl; or R^{12} and R^{13}, together with the nitrogen to which they are attached, form a C_{2-9}heterocycloalkyl ring optionally substituted with one, two, or three R^{20e};

each R^{14} is independently selected from hydrogen, C_{1-6}alkyl, and C_{1-6}haloalkyl;

each R^{14a} is independently selected from C_{1-6}alkyl and C_{1-6}haloalkyl;

each R^{15} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20f};

R^{18} and R^{18a} are independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$N(R^{12})(R^{13})$, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)OR^{15}$, -$N(R^{14})S(O)_2R^{15}$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$N(R^{14})C(O)R^{15}$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

R^{18b} is independently selected from hydrogen, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, -OR^{12}, -SR^{12}, -$C(O)OR^{12}$, -$OC(O)N(R^{12})(R^{13})$, -$C(O)R^{15}$, -$S(O)R^{15}$, -$OC(O)R^{15}$, -$C(O)N(R^{12})(R^{13})$, -$C(O)C(O)N(R^{12})(R^{13})$, -$S(O)_2R^{15}$, -$S(O)_2N(R^{12})(R^{13})$-, S(=O)(=NH)$N(R^{12})(R^{13})$, -$CH_2C(O)N(R^{12})(R^{13})$, -$CH_2N(R^{14})C(O)R^{15}$, -$CH_2S(O)_2R^{15}$, and -$CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20h};

each R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{20e}, R^{20f}, R^{20g}, R^{20h}, R^{20i}, R^{20k}, and R^{20m} is independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, C_{1-9}heteroaryl, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, =$C(R^{21b})_2$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{21}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{21}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$; wherein two R^{20k} bonded to the same or adjacent atoms may optionally be joined to form a C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, or C_{1-9}heteroaryl; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, -CH_2-C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -CH_2-C_{2-9}heterocycloalkyl, C_{6-10}aryl, -CH_2-C_{6-10}aryl, -CH_2-C_{1-9}heteroaryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three groups independently selected from halogen, oxo, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$;

each R^{21} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

R^{21b} is independently selected at each occurrence from hydrogen, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, or two R^{21b} are taken together with the carbon atom to which they are attached to form C_{3-10}cycloalkyl or C_{2-9}heterocycloalkyl; each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

each R^{22} is independently selected from H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

each R^{23} is independently selected from H and C_{1-6}alkyl;

each R^{24} is independently selected from H and C_{1-6}alkyl;

each R^{25} is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl;

indicates the location of attachment of the depicted chemical formula or atom to a substituent, a further component of a molecule, or an atom; and

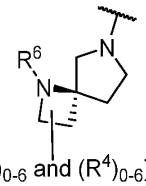
indicates a single or double bond such that all valences are satisfied.

24. The method of claim 23, wherein R^5 is a 5 membered heteroaryl optionally substituted with one, two or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and the 5 membered heteroaryl is bonded to L^2 through a ring nitrogen.

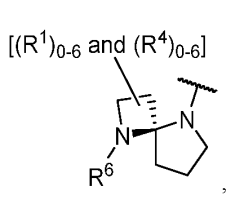
25. The method of claim 23, wherein L^2 is -C(O)-; and R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms; and L^2 is directly bonded to an N ring atom of R^5.

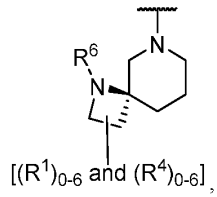
26. The method of any one of claims 23 to 25, wherein L^7 is a bond.

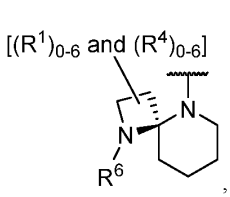
27. The method of any one of claims 23 to 26, wherein s1 is 2 and s2 is 0, 1, or 3.

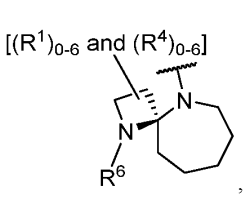
28. The method of any one of claims 23 to 26, wherein R^7 is selected from 

[(R1)0-6 and (R4)0-6],



, 

, 

, 

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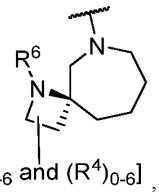
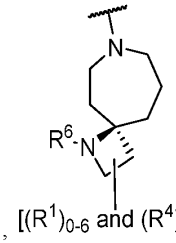
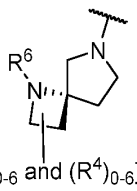
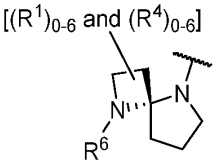
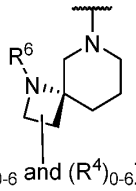


, 

, 

, 

, 

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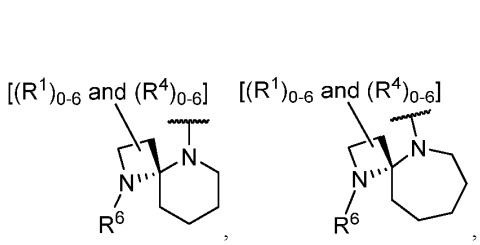
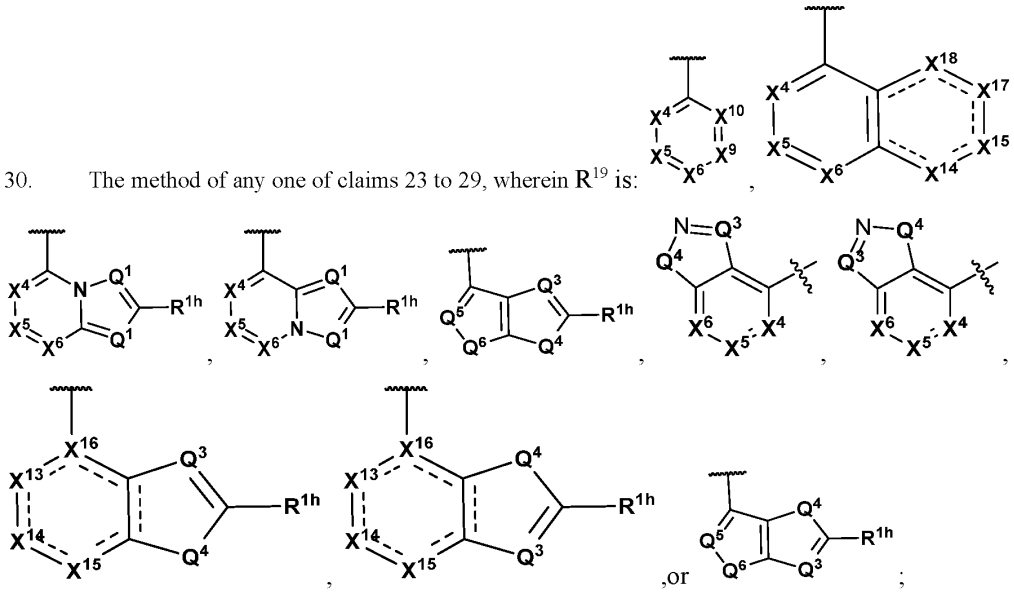


; wherein R^1 and R^4 substituents may be bonded to either spirocyclic ring.

29. The method of any one of claims 23 to 28, wherein R^{17} is $-L^1-R^{19}$ or $-L^{1b}-R^{19}$; L^1 is a bond, and L^{1b} is a bond.

30. The method of any one of claims 23 to 29, wherein R^{19} is:



,or ;

Q^1, Q^3, and Q^5 are independently selected from N and $C(R^{1d})$;

Q^4 and Q^6 are independently selected from O, S, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

X^4, X^5, X^6, X^9, X^{10} are independently selected from $C(R^{1a})$ and N;

X^{13} is selected from a bond, $C(R^{1a})$, N, C(O), $C(R^{1a})(R^{1b})$, $C(O)C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})C(R^{1a})(R^{1b})$, $C(R^{1a})(R^{1b})N(R^{1c})$, and $N(R^{1c})$;

X^{14}, X^{15}, X^{17}, X^{18} are independently selected from a C(O), $C(R^{1a})$, N, $C(R^{1a})(R^{1b})$, and $N(R^{1c})$;

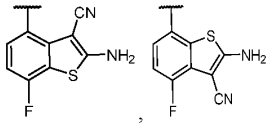
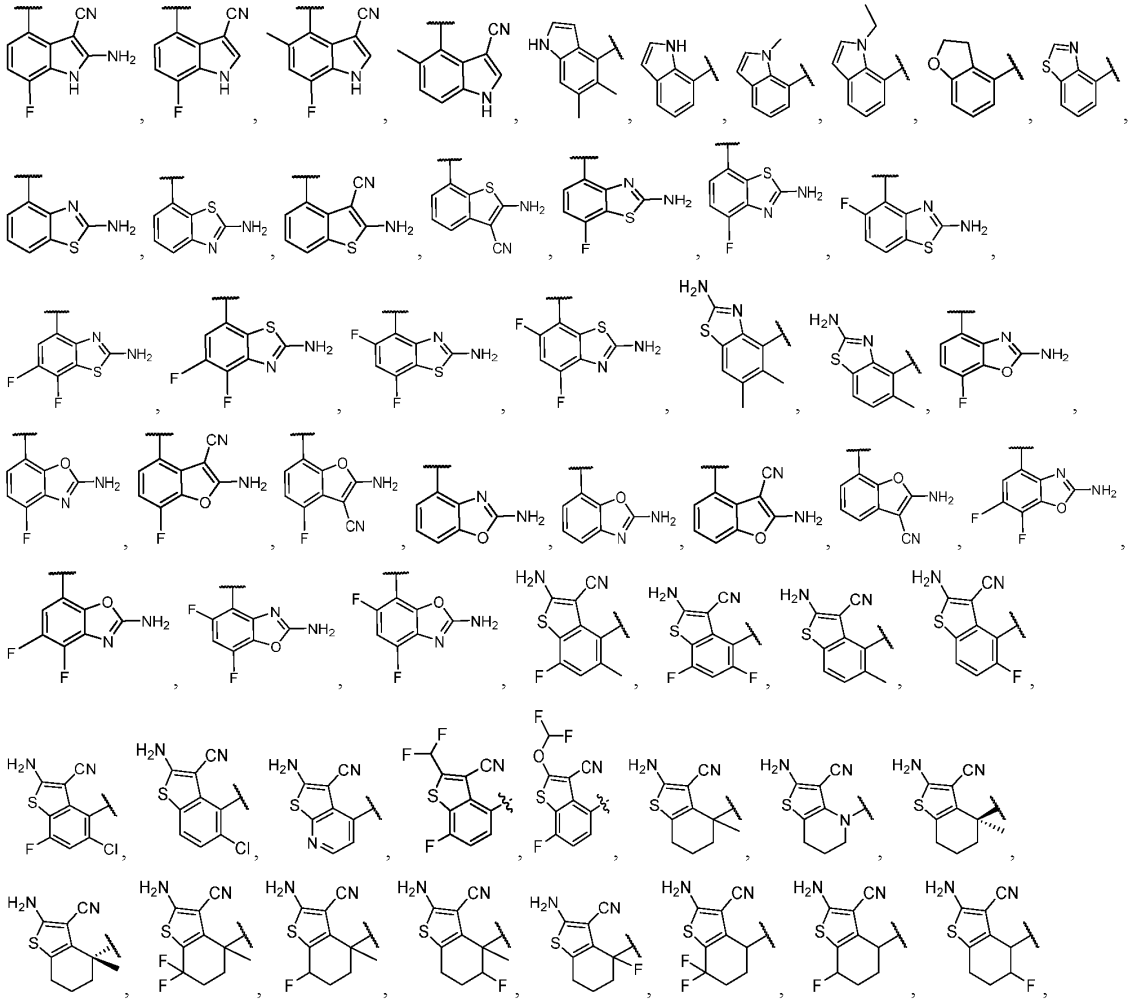
X^{16} are independently selected from C, N, and $C(R^{1a})$;

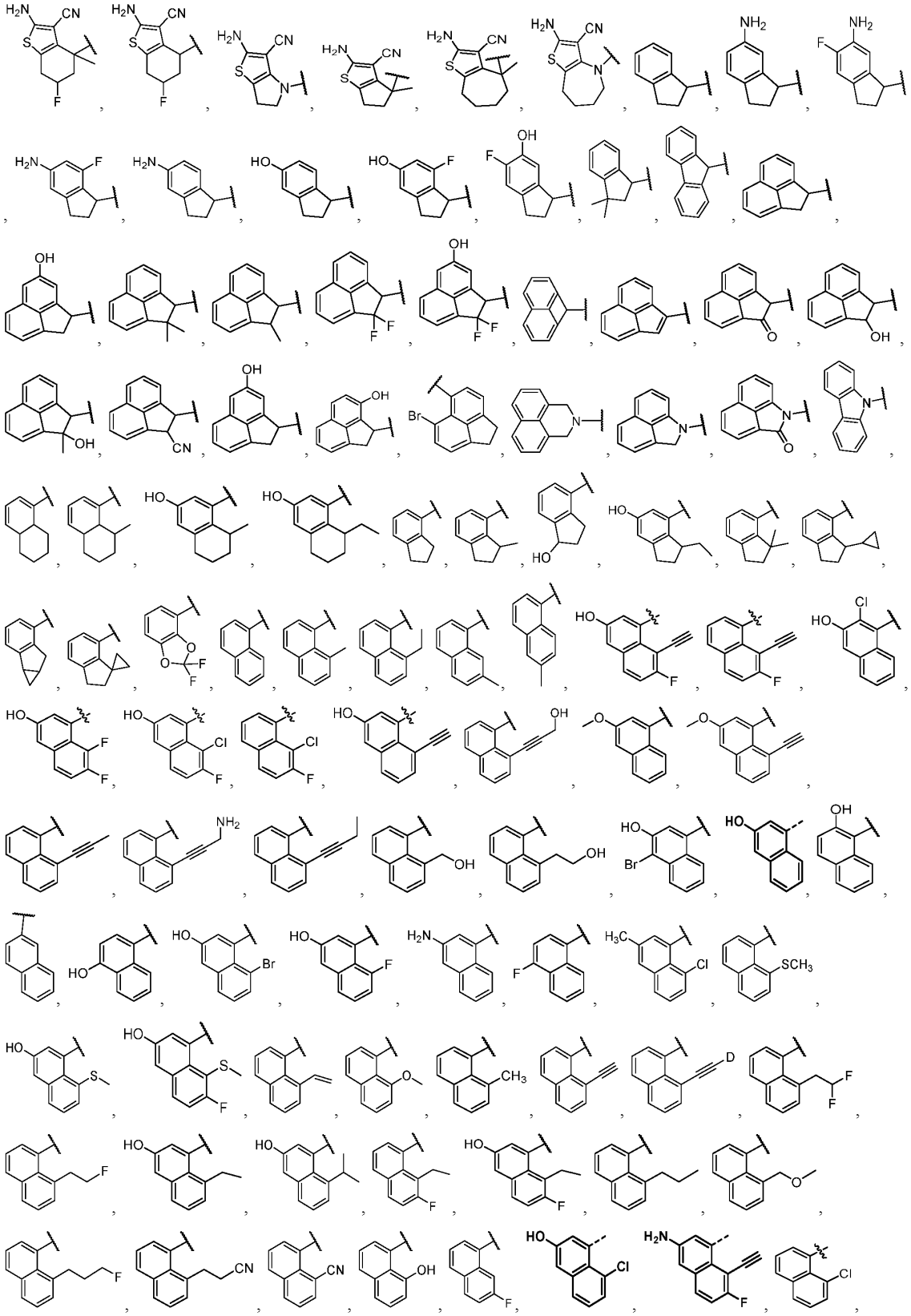
each R^{1a}, R^{1b}, R^{1d}, and R^{1h} are each independently selected from hydrogen, halogen, -CN, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, C_{1-9}heteroaryl, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$-, $S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}; or R^{1a} and R^{1b} bonded to the same carbon are joined to form a 3-10 membered heterocycloalkyl ring or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or two R^{1a} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-}

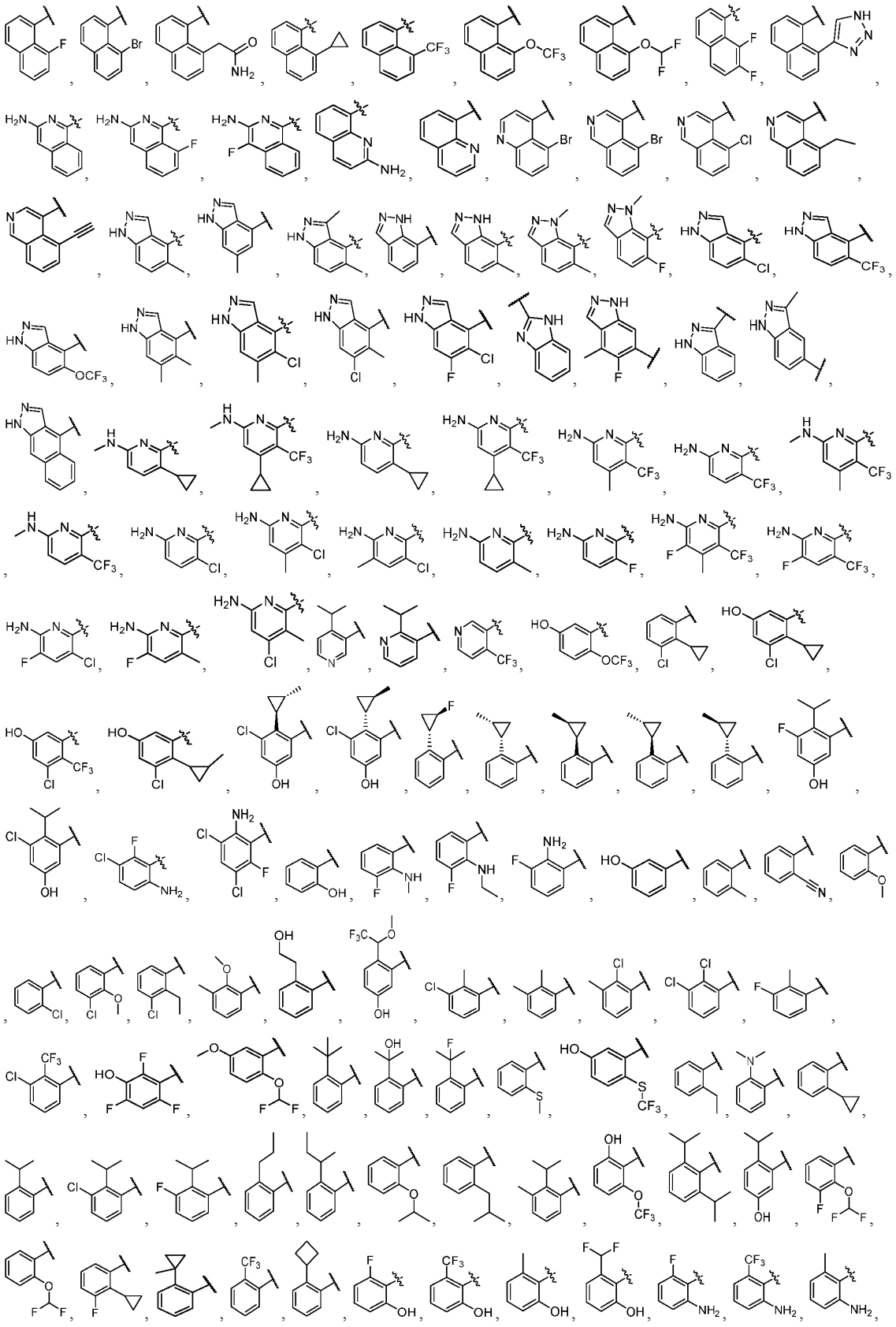
$_{10}$cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, C_{6-10}aryl ring, 5-12 membered heteroaryl ring, or C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; or R^{1h} and one of R^{1a}, R^{1b}, R^{1c}, and R^{1d} bonded to adjacent atoms are joined to form a 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, or a C_{3-10}cycloalkyl ring, wherein the 3-10 membered heterocycloalkyl ring, a C_{6-10}aryl ring, a 5-12 membered heteroaryl ring, and C_{3-10}cycloalkyl ring are optionally substituted with one, two, or three R^{20i}; and

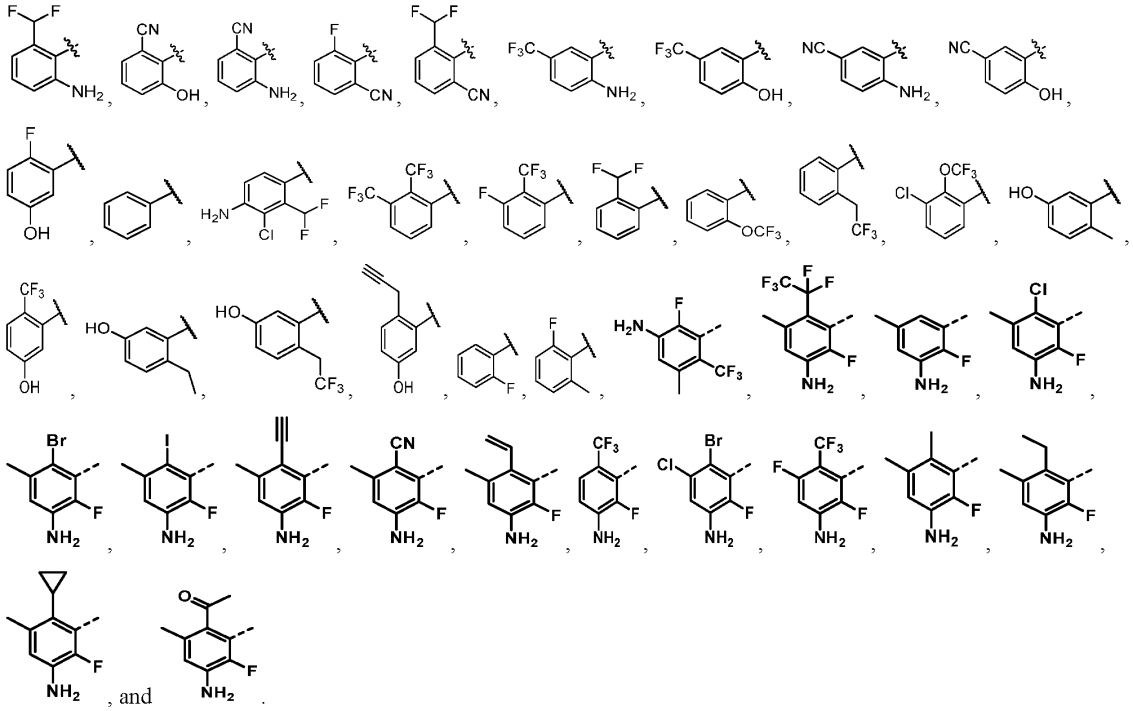
each R^{1c} is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, C_{6-10}aryl, and C_{1-9}heteroaryl are optionally substituted with one, two, or three R^{20i}.

31. The method of any one of claims 23 to 29, wherein R^{19} is selected from

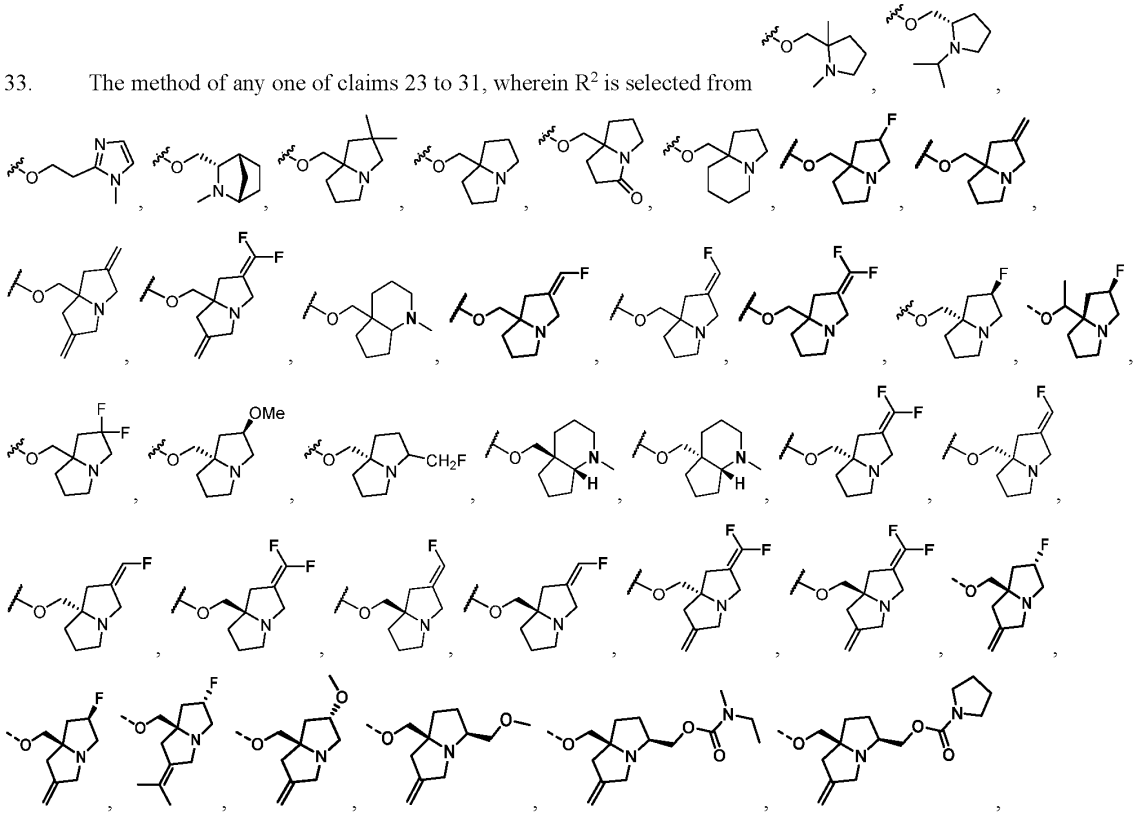


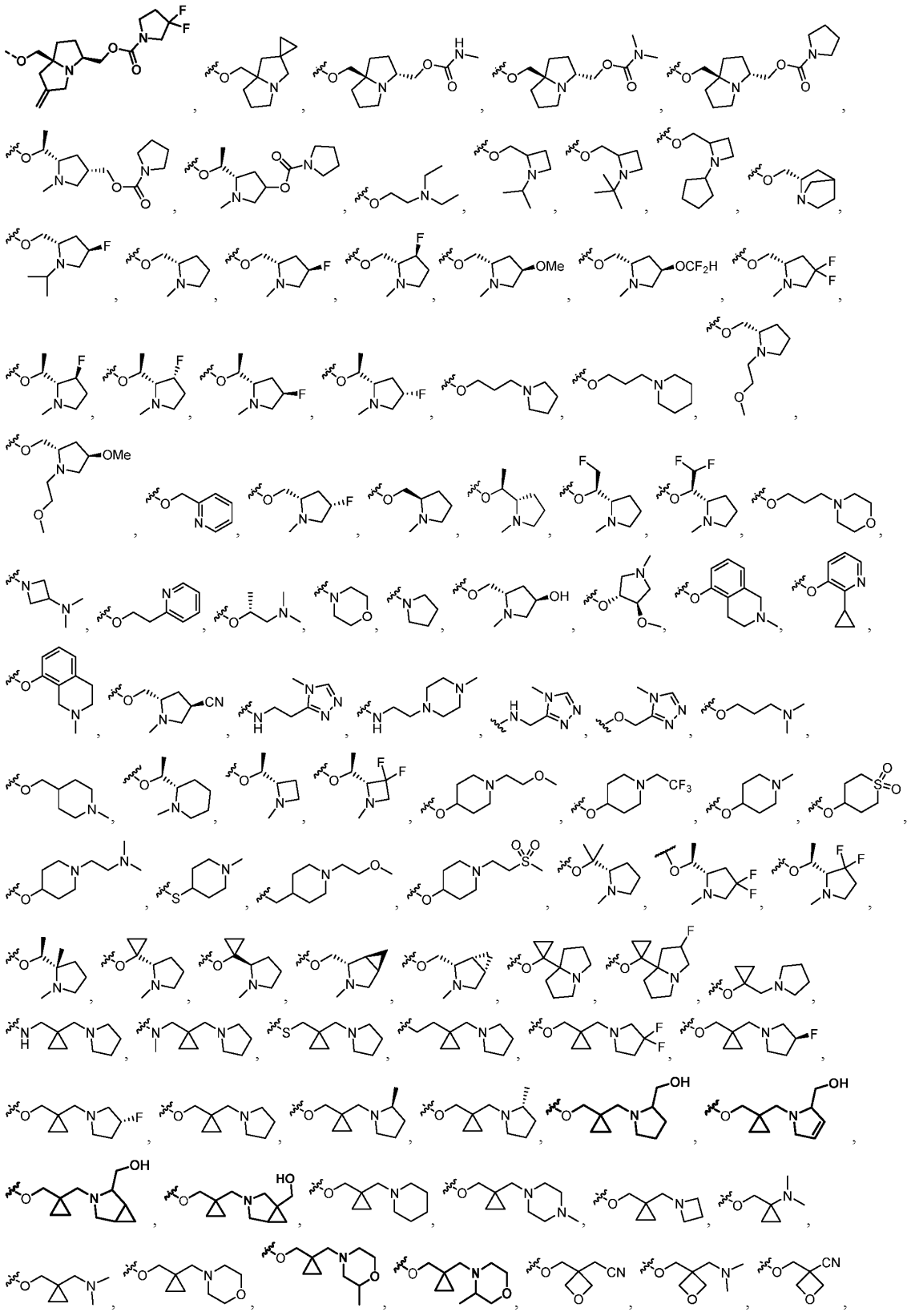


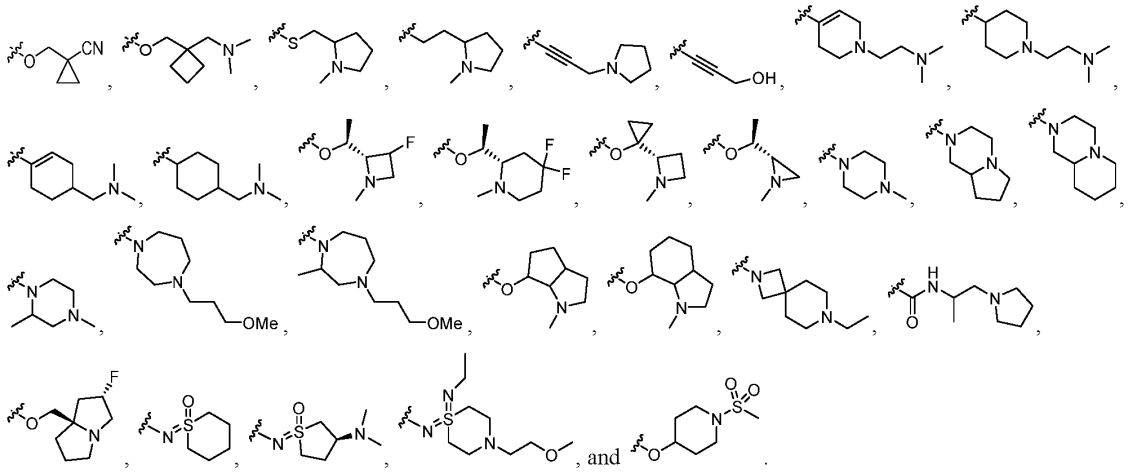


32. The method of any one of claims 23 to 31, wherein R^2 is $-OR^{12'}$.

33. The method of any one of claims 23 to 31, wherein R^2 is selected from







34. The method of claim 23, wherein

W is a C(R^{18}) or C(O); Z is N, C(R^{8}), or N(R^{8b}); V is C(R^{17}); J is C(R^{16}); Y is C(R^{2}); U is N; X is N;

L^1 is a bond;

L^7 is a bond;

W^1, W^2, and W^3 are independently selected from C(R^1)(R^1), C(R^1)(R^4), C(R^4)(R^4), and O; W^4 is selected from C(R^1)(R^1), C(R^1)(R^4), and C(R^4)(R^4); W^5 is selected from N and CH;

L^2 is -C(O)-; R^5 is a 5 membered heteroaryl, optionally substituted with one, two, or three R^{20k}, wherein the 5 membered heteroaryl comprises one, two, or three ring nitrogen atoms and further wherein when R^5 is directly bonded to a C(O) of L^2, L^2 is directly bonded to an N ring atom of R^5;

R^2 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -$OR^{12'}$, -$SR^{12'}$, and -N($R^{12''}$)(R^{13}), wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20d};

R^8 is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -OR^{12}, -SR^{12}, and -N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20e};

R^{8b} is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20e};

R^{16} is independently selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{2-9}heterocycloalkyl, -OR^{12}, -SR^{12}, and -N(R^{12})(R^{13}), wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or three R^{20g}; and

R^{18} is hydrogen.

35. The method of claim 34, wherein

W^1, W^2, and W^3 are independently selected from CH_2 and O; W^4 is CH_2; W^5 is selected from N and CH;

R^2 is -$OR^{12'}$;

R^8 is independently selected halogen and C_{1-6}haloalkyl;

R^{8b} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl, wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, and C_{2-9}heterocycloalkyl are optionally substituted with one, two, or

three R^{20c}; and

R^{16} is halogen.

36. The method of any one of claims 4 to 35, wherein the cancer is lung cancer.

37. The method of any one of claims 4 to 35, wherein the cancer is a non-small cell lung cancer.

38. The method of any one of claims 4 to 35, wherein the cancer is colorectal cancer.

39. The method of any one of claims 4 to 35, wherein the cancer is pancreatic cancer.

40. The method of any one of claims 4 to 35, wherein the cancer is a solid cancer.

41. The method of any one of claims 4 to 40, wherein cancer cells of the subject comprise a KRAS G12C mutant protein.

42. The method of any one of claims 4 to 40, wherein cancer cells of the subject are refractory to at least one KRAS G12C inhibitor.

43. The method of any one of claims 4 to 40, wherein cancer cells of the subject comprise a KRAS G12S mutant protein.

44. The method of any one of claims 1 to 43, wherein cancer cells of the subject comprise overexpression of KRAS.

45. The method of any one of the preceding claims, wherein the subject exhibits relapse of the cancer.

46. The method of any one of the preceding claims, wherein the subject has previously been treated with a KRAS G12C inhibitor.

47. The method of any one of the preceding claims, further comprising administering (c) an additional agent or additional therapy.

48. The method of claim 47, wherein the additional agent is selected from an immunomodulatory agent, an anti-nausea agent, an antiemetic, a pain reliever, a chemotherapeutic agent, a SHP2 inhibitor, a PI3K inhibitor, a CDK4/6 inhibitor, a RAF inhibitor, a MEK inhibitor, an ERK inhibitor, an EGFR inhibitor, and an AKT inhibitor.

49. The method of claim 47, wherein the additional agent is selected from an immunomodulatory agent, a cytokine blockade agent, and a checkpoint immune blockade agent.

50. The method of claim 47, wherein the additional agent is selected from an anti-PD-L1 antibody, an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-LAG3 antibody, an anti-TIM3 antibody, and combinations thereof.

51. The method of claim 47, wherein the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation.

52. The method of any one of the preceding claims, wherein the administration of (a) and (b) reduces incidence of one or more adverse events associated with the SOS1 inhibitor or the KRAS inhibitor.

53. The method of claim 52, wherein the adverse event is selected from diarrhea, rash, nausea, vomiting, decreased appetite, fatigue, musculoskeletal pain, dyspnea, and acute kidney injury.

54. The method of claim 52, wherein the adverse event is selected from diarrhea, rash, and nausea.

55. The method of any one of the preceding claims, wherein the administration of (a) and (b) exhibits a synergistic effect.

56. The method of claim 54, wherein the synergistic effect is characterized by a synergistic value of at least 0.05 as ascertained by Bliss independence criterion.

57. The method of any one of the preceding claims, wherein one or both of (a) and (b) are administered at a sub-therapeutic dose but achieve a therapeutic effect at least comparable to administering (a) or (b) alone at its therapeutically effective amount.

58. The method of any one of the preceding claims, wherein KRAS inhibitor is administered at a dose less than about 25% the standard monotherapy dose.

59. The method of any one of the preceding claims, wherein (a) and (b) are administered in the same formulation.

60. The method of any one of the preceding claims, wherein (a) and (b) are administered in separate formulations.

61. A kit for use in reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS overexpression, the kit comprising:

(1) a composition comprising a SOS1 inhibitor of Formula (SI-1);

(2) a composition comprising a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H); and

(3) instructions for using the composition(s) of (1) and (2).

62. A kit for use in reducing proliferation of cancer cells comprising a KRAS mutant protein or KRAS overexpression, the kit comprising:

(1) a composition comprising a SOS1 inhibitor of Formula (SIV-1);

(2) a composition comprising a KRAS inhibitor of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H); and

(3) instructions for using the composition(s) of (1) and (2).

63. The kit of any one of claims 61 to 62, wherein the SOS1 inhibitor and the KRAS inhibitor are formulated in the same unit dosage form.

64. The kit of any one of claims 61 to 62, wherein the SOS1 inhibitor and the KRAS inhibitor are formulated in different unit dosage forms.

65. A pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

66. A method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SI-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

67. A pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SIV-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

68. A method of treating a mutant KRAS-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (SIV-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) a KRAS inhibitor, or a pharmaceutically acceptable salt or solvate thereof, of Formula (I), (I-1), (I-2), (II), (II-1), (II-2), (II-3), (IV), (IV-1), (IV-2), (A), (B), (C), (D), (E), (F), (G), or (H), and (iii) a pharmaceutically acceptable excipient.

69. The method of claim 1, 3, 4, 8, 66, or 68, wherein the subject is a naïve subject that has not been treated with a KRAS inhibitor prior to administering (a) and (b).

70. The method, kit, or pharmaceutical composition of any one of claim 1-69, wherein the SOS1 inhibitor is a compound of Table 2a, or a pharmaceutically acceptable salt or solvate thereof.

71. The method, kit, or pharmaceutical composition of any one of claim 1-69, wherein the SOS1 inhibitor is a compound of Table 2b, or a pharmaceutically acceptable salt or solvate thereof.

72. The method, kit, or pharmaceutical composition of any one of claim 1-71, wherein the KRAS inhibitor is a compound of Table 1a, or a pharmaceutically acceptable salt or solvate thereof.

73. The method, kit, or pharmaceutical composition of any one of claim 1-71, wherein the KRAS inhibitor is a compound of Table 1b, or a pharmaceutically acceptable salt or solvate thereof.