

COMBINATIONS OF SOS-1 INHIBITORS WITH OSIMERTINIB AND/OR MET
INHIBITORS TO TREAT CANCER

CROSS-REFERENCE

[001] This application claims the benefit of U.S. Provisional Application No. 63/593,222, filed October 25, 2023, U.S. Provisional Application No. 63/572,068, filed March 29, 2024, and U.S. Provisional Application No. 63/683,193, filed August 14, 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_775_601_SL.xml and is 4,097 bytes in size.

BACKGROUND

[003] The ErbB family of receptor tyrosine kinases includes EGFR (HER1/ErbB1), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4), each of which is a mediator of normal cell growth and development. In particular, phosphorylation of EGFR activates downstream signaling pathways—including the PI3K/AKT/mTOR, STAT, and RAS/MAPK pathways—that involve cell proliferation, angiogenesis, apoptosis, and metastasis. Overexpression of EGFR is frequently observed in a variety of tumors, including brain, breast, cervical, colorectal, esophageal, head and neck, kidney, lung, ovarian, and stomach cancers.

[004] EGFR mutations have been detected in over 40% of non-small cell lung cancer (NSCLC) cases in Asia and over 10% of NSCLC cases in North America and Europe, making them the most prevalent genetic alterations in NSCLC. The L858R point mutation and exon 19 deletions are often referred to as classical EGFR activating mutations and result in constitutive activation of EGFR and downstream signaling pathways, particularly in non-small cell lung cancer (NSCLC). These mutants have a greater affinity for ATP-competitive EGFR inhibitors, which, combined with the increased reliance of the tumor cells on EGFR signaling, creates a large therapeutic window for EGFR inhibition, making it an effective treatment for NSCLC patients with classical EGFR mutations. However, certain exon 20 mutations, including T790M and exon 20 insertions, activate EGFR while affording the tumor resistance to first- and second-generation EGFR inhibitors targeting the classical EGFR mutations, such as gefitinib, erlotinib, and afatinib. Lung cancer is the leading cause of cancer-related death worldwide, due in part to these resistance mechanisms. In 2023, an estimated 238,000 people will be diagnosed with lung and bronchus cancer and approximately 127,000 people will die from lung and bronchus cancer in the United States.

[005] Osimertinib is a third-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that has been approved for treating patients with NSCLC with EGFR activating mutations (exon 19 deletions and exon 21 L858R mutations) in the adjuvant and metastatic setting and in patients with exon 20 T790M mutations NSCLC who have progressed after EGFR therapy. While osimertinib has improved clinical outcome in these patients, their tumors eventually progress, and subsequent therapy has limited efficacy. *See* V. Di Noia, et al., *ESMO Open*, 2021, 6(6), 100280 (doi: 10.1016/j.esmoop.2021.100280).

[006] 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. SOS1-activation of RAS-family proteins can also be mediated by the interaction of SOS1/Grb2 with the BCR-ABL oncoprotein commonly found in chronic myelogenous leukemia.

SUMMARY

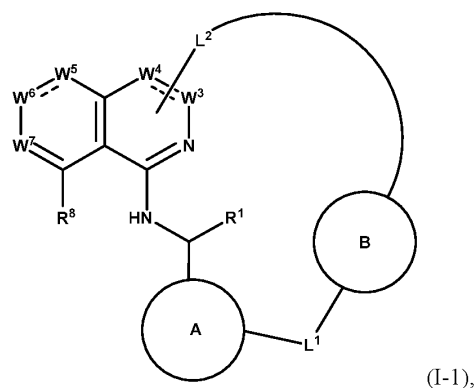
[007] There exists a considerable need for identifying relevant monotherapy as well as combination therapy to address the long-felt need for gaining sustained therapeutic benefit against EGFR-mediated diseases, including various types of cancer. The present invention addresses these needs and provides related advantages as well.

[008] In certain aspects, the present disclosure provides a method of reducing proliferation of cancer cells comprising an epidermal growth factor receptor (EGFR) exon 20 insertion, the method comprising administering to the cells (a) a SOS1 inhibitor and (b) osimertinib, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b). In some embodiments, the cancer cells are non-small cell lung cancer cells. In certain aspects, the present disclosure provides a method of downregulating EGFR signaling output in a plurality of non-small cell lung cancer cells, comprising: (i) assessing EGFR 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) osimertinib if an EGFR exon 20 insertion is detected in the sample, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

[009] In certain aspects, the present disclosure provides a method of treating cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a MET inhibitor, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b). In some embodiments, the cancer is an EGFR-mediated cancer. In some embodiments, the cancer exhibits MET amplification. In some embodiments, the MET inhibitor is savolitinib. In some embodiments, the method further comprises administering (c) an additional agent or additional therapy. In some embodiments, the additional agent is an EGFR inhibitor. In some embodiments, the EGFR inhibitor is selected from gefitinib, erlotinib, afatinib, lazertinib, osimertinib, dacomitinib, neratinib, cetuximab, panitumumab, lapatinib, necitumumab, nazartinib, vandetanib, poziotinib, mobocertinib, zipalartinib, sunvozertinib, BAY-2927088, BLU-451, BLU-945, STX-721, and zorifertinib. In some embodiments, the EGFR inhibitor is osimertinib. In some embodiments, the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation. In some embodiments, the administration of (a) and (b) synergistically reduces proliferation of the cancer cells with a synergistic value of at least 0.1 as ascertained by Bliss independent criterion.

[010] In certain aspects, the present disclosure provides a method of treating an EGFR-mediated cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) osimertinib, 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 0.1 as ascertained by Bliss independent criterion. In some embodiments, the synergistic value is ascertained by Bliss independent 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 . In some embodiments, the synergistic value is at least 0.4, such as at least 1 or at least 5.

[011] In practicing any of the subject methods, the SOS1 inhibitor may be selected from BI-3406, MRTX0902, BAY 293, RMC-5845, and BI-1701963. In some embodiments, the SOS1 inhibitor is a compound of Formula (I-1):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



is selected from C₅₋₇ carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R¹¹;



is absent or selected from C₃₋₈ carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{11a};

L¹ is selected from a bond, C₁₋₆ alkylene, and C₁₋₆ haloalkylene;

L² is selected from C₅₋₂₅ alkylene, C₅₋₂₅ alkenylene, C₅₋₂₅ alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}, wherein L² is covalently bound to one of W³, W⁴, W⁵, W⁶, or W⁷;

W³ is selected from N(R^{3b}), N, C(R³), and C(O);

W⁴ is selected from N(R^{4b}), N, C(R⁴), and C(O);

W⁵ is selected from N(R^{5b}), N, and C(R⁵);

W⁶ is selected from C(R⁶) and C(O);

W⁷ is C(R⁷);

R¹ is C₁₋₃ alkyl optionally substituted with one or more R^{11c};

R⁸ is selected from hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰;

R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³),

wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R^{3b}, R^{4b}, and R^{5b} are each independently selected from a bond to L², hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R¹¹ and R^{11a} are each independently selected at each occurrence from halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R^{11c} is independently selected at each occurrence from halogen, -OR¹², and -N(R¹²)(R¹³);

R¹² is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R¹³ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; or R¹² and R¹³, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R²⁰;

R¹⁴ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R¹⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R¹⁷ and R^{17a} are each independently selected at each occurrence from C₁₋₆ alkyl and C₃₋₆ cycloalkyl, wherein C₁₋₆ alkyl and C₃₋₆ cycloalkyl are optionally substituted with one, two or three R²⁰; or R¹⁷ and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle,

-CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), and -OC(O)R²⁵.

R²¹ is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²³ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁴ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

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

[012] In practicing any of the subject methods, the cancer may be lung cancer, such as non-small cell lung cancer. In some embodiments, cancer cells of the subject comprise an EGFR mutation. In some embodiments, the EGFR mutation is selected from an L858R mutation, a T790M mutation, an exon 19 deletion, and an exon 20 insertion, such as an exon 20 insertion. In some embodiments, cancer cells of the subject comprise overexpression of MET. In some embodiments, cancer cells of the subject comprise MET-amplification. In some embodiments, the subject exhibits relapse of the cancer. In some embodiments, the subject has previously been treated with platinum-based chemotherapy. In some embodiments, the subject has previously been treated with a tyrosine kinase inhibitor (TKI) against EGFR prior to administering (a) and (b). In some embodiments, the subject has previously been treated with a non-exon 20 insertion EGFR TKI, such as gefitinib, erlotinib, afatinib, lazertinib, osimertinib, dacomitinib, neratinib, cetuximab, panitumumab, lapatinib, necitumumab, nazartinib, vandetanib, BLU-945, or zorifertinib. In some embodiments, the subject has previously been treated with an EGFR exon 20 insertion TKI, such as poziotinib, mobocertinib, amivantamab, zipalertinib, sunvozertinib, BAY-2927088, BLU-451, or STX-721. In some embodiments, the subject exhibits resistance or intolerance to the TKI. Resistance to the TKI may be characterized by one or more changes selected from (1) progression of the cancer, (2) *EGFR* gene mutation, (3) loss of EGFR T790M mutation, (4) *EGFR* gene amplification, (5) *MET* amplification, (6) *HER2* amplification, (7) RAS-MAPK pathway activation, (8) PI3K pathway activation, (9) cell-cycle gene alteration, (10) oncogenic fusion, (11) histologic transformation, and (12) phenotypic transformation.

[013] A method described herein may further comprise administering (c) an additional agent or additional therapy. In some embodiments, the additional agent is selected from an EGFR TKI other than osimertinib, an immunomodulatory agent, an anti-nausea agent, an antiemetic, a pain reliever, a steroid, and a chemotherapeutic agent. In some embodiments, the additional agent is selected from an immunomodulatory agent, a cytokine blockade

agent, and a checkpoint immune blockade agent. In some 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 some embodiments, the additional agent is a MET inhibitor, such as savolitinib. In some embodiments, the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation.

[014] In practicing any of the subject methods, administration of (a) and (b) may reduce incidence of one or more adverse event associated with osimertinib. In some embodiments, the adverse event is selected from diarrhea, rash, nausea, stomatitis, vomiting, paronychia, fatigue, dry skin, anorexia, headache, anemia, pneumonia, pruritus, constipation, and cough. In some embodiments, the adverse event is selected from diarrhea, rash, nausea, dry skin, and paronychia.

[015] In practicing any of the subject methods, administration of (a) and (b) may exhibit a synergistic effect. In some embodiments, the synergistic effect is characterized by a synergistic value of at least 0.05 as ascertained by Bliss independent criterion. In some 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 some embodiments, osimertinib is administered at a dose less than about 25% the standard monotherapy dose. In some embodiments, (a) and (b) are administered in the same formulation. In some embodiments, (a) and (b) are administered in separate formulations.

[016] In certain aspects, the present disclosure provides a kit for use in reducing proliferation of cancer cells comprising an epidermal growth factor receptor (EGFR) exon 20 insertion, the kit comprising: (1) a composition comprising a SOS1 inhibitor of Formula (I-1); (2) a composition comprising osimertinib; and (3) instructions for using the composition(s) of (1) and (2). In some embodiments, the SOS1 inhibitor and the osimertinib are formulated in a same unit dosage form. In some embodiments, the SOS1 inhibitor and the osimertinib are formulated in different unit dosage forms.

[017] In certain aspects, the present disclosure provides a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (I-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) osimertinib, and (iii) a pharmaceutically acceptable excipient. In certain aspects, the present disclosure provides a method of treating an EGFR-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (I-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) osimertinib, and (iii) a pharmaceutically acceptable excipient. In practicing any of the subject methods, the subject may be a naïve subject that has not been treated with a TKI against EGFR prior to administering (a) and (b).

INCORPORATION BY REFERENCE

[018] 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

[019] 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:

[020] **FIG. 1A** shows a degree of growth inhibition of Ba/F3-EGFR_Ex20_ASV insertion cells upon treatment with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A, at various concentrations) alone, (ii) osimertinib alone, or (iii) a combination of (i) and (ii) at various concentrations.

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

[022] **FIG. 2A** shows a degree of growth inhibition of Ba/F3-EGFR_L858R/T790M cells upon treatment with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A, at various concentrations) alone, (ii) osimertinib alone, or (iii) a combination of (i) and (ii) at various concentrations.

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

[024] **FIG. 3A** shows a degree of growth inhibition of PC9-EGFR Ex19 E746_A750 deletion cells upon treatment with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A, at various concentrations) alone, (ii) osimertinib alone, or (iii) a combination of (i) and (ii) at various concentrations.

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

[026] **FIG. 4A** shows a degree of growth inhibition of H1975-EGFR L858R/T790M cells upon treatment with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A, at various concentrations) alone, (ii) osimertinib alone, or (iii) a combination of (i) and (ii) at various concentrations.

[027] **FIG. 4B** shows a degree of synergy across the combinations in **FIG. 4A**, as calculated using the BLISS independent model.

[028] **FIG. 5** depicts a western blot showing the degree of inhibition of EGFR signaling as measured by the level of phosphorylated ERK (p-ERK) in H1975-EGFR L858R/T790M cells treated for 24 hours with (i) osimertinib alone or (ii) osimertinib in combination with a SOS1 inhibitor of the present disclosure (e.g., Compound A) at the indicated concentrations (nM). The data demonstrate that the combination of a SOS1 inhibitor of the present disclosure with osimertinib prevents refractory and residual p-ERK signaling that is observed with single agent osimertinib (note arrows). Such synergistic effect yields greater apoptosis (increased cleaved PARP).

[029] **FIG. 6** shows results of a study in which mice bearing Ba/F3-EGFR-V769_D770insASV allograft tumors were treated with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A) alone, (ii) osimertinib 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 osimertinib in the tumor model.

[030] **FIG. 7** shows results of a study in which LU0858 mice (an NSCLC patient-derived xenograft (PDX) model exhibiting EGFR-L858R mutation with amplified MET) were treated with vehicle or a SOS1 inhibitor of the present disclosure (e.g., Compound A). The results demonstrate that the SOS1 inhibitor disclosed herein alone is effective in reducing tumor volume in EGFR-mediated lung cancer, particularly MET amplified lung cancer.

[031] **FIG. 8** shows results of a study in which LU0387 mice (an NSCLC PDX model exhibiting EGFR-Exon 20 D770_N771_insNPH mutation) were treated with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A) alone, (ii) osimertinib 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 osimertinib in EGFR-Exon 20 insertion tumors.

[032] **FIG. 9** shows results of a study in which mice bearing Ba/F3-EGFR-L858R/T790M allograft tumors were treated with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A) alone, (ii) osimertinib 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 osimertinib in the tumor model.

[033] **FIG. 10** shows results of a study in which mice bearing H1975 xenograft tumors (an NSCLC model exhibiting EGFR L858R/T790M mutations) were treated with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A) alone, (ii) osimertinib 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 osimertinib in the tumor model.

[034] **FIG. 11** shows results of a study in which mice bearing a squamous NSCLC PDX model exhibiting an EGFR-Exon 20 D772_N773insDNP mutation were treated with (i) a SOS1 inhibitor of the present disclosure (e.g., Compound A) alone, (ii) osimertinib 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 osimertinib in the tumor model.

DETAILED DESCRIPTION

[035] 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)).

[036] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure 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. Chemical structures are named herein according to IUPAC conventions as implemented in ChemDraw® software (Perkin Elmer, Inc., Cambridge, MA). The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. As used in the specification and claims, the singular forms “a”, “an” and “the” include plural references unless the context clearly dictates otherwise.

[037] “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 $\pm 10\%$ of a stated number or value.

[038] 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.

[039] “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., C₁₋₁₂ alkyl), such as one to eight carbon atoms (C₁₋₈ alkyl) or one to six carbon atoms (C₁₋₆ alkyl). Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, 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.

[040] “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.

[041] “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., C₂₋₁₂ alkenyl), such as two to eight carbon atoms (C₂₋₈ alkenyl) or two to six carbon atoms (C₂₋₆ 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.

[042] “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., C₂₋₁₂ alkynyl), such as two to eight carbon atoms (C₂₋₈ alkynyl) or two to six carbon atoms (C₂₋₆ 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.

[043] “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., C₁₋₁₂ alkylene), such as one to eight carbon atoms (C₁₋₈ alkylene) or one to six carbon atoms (C₁₋₆ 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.

[044] “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.

[045] “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.

[046] “Carbocycle” refers to a saturated, unsaturated or aromatic ring in which each atom of the ring is a carbon atom. Carbocycle may include C₃₋₁₀ monocyclic rings, C₆₋₁₂ bicyclic rings, C₆₋₁₂ spirocyclic rings, and C₆₋₁₂ bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. In some embodiments, the carbocycle is a C₆₋₁₂ aryl group, such as C₆₋₁₀ aryl. In some embodiments, the carbocycle is a C₆₋₁₂ cycloalkyl group. In some embodiments, the carbocycle is a C₆₋₁₂ 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, adamantyl, phenyl, indanyl, and naphthyl. Unless stated otherwise specifically in the specification, a carbocycle is optionally substituted by one or more substituents such as those substituents described herein.

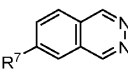
[047] “Heterocycle” refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms, for example 1, 2 or 3 heteroatoms selected from O, S and N. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, 6- to 12-membered spirocyclic rings, and 6- 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.

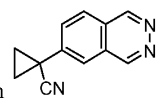
[048] “Heteroaryl” refers to a 5- to 12-membered aromatic ring that comprises at least one heteroatom, such as 1, 2 or 3 heteroatoms, selected from O, S and N. As used herein, the heteroaryl ring may be selected from monocyclic or bicyclic—including fused, spirocyclic and bridged ring systems—wherein 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.

[049] Unless stated otherwise, hydrogen atoms are implied in structures depicted herein as necessary to satisfy

the valence requirement.

[050] A wavy 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 R⁷ is 1-

cyclopropyl-1-carbonitrile as in , then R⁷ may be depicted as “CN” or “CN”.

[051] 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.

[052] A compound disclosed herein, such as a compound of Formula (I), is optionally substituted by one or more, such as 1, 2 or 3 substituents selected from:

halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²⁴)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), and -OC(O)R²⁵,

R²¹ is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²³ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁴ is independently selected at each occurrence from H and C₁₋₆ alkyl; and

R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered

heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle.

[053] In some embodiments, a compound disclosed herein, such as a compound of Formula (I), is optionally substituted by one or more, such as 1, 2 or 3 substituents selected from:

halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, and -N(R²²)(R²³);

R²¹ is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²³ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁴ is independently selected at each occurrence from H and C₁₋₆ alkyl; and

R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle.

[054] In some embodiments, a compound disclosed herein, such as a compound of Formula (I), is optionally substituted by one or more, such as 1, 2 or 3 substituents selected from halogen, oxo, =NH, -CN, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OH, -OCH₃, -OCH₂CH₃, -NH₂, -NHCH₃, and -NHCH₂CH₃, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, -NO₂, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -C(CH₃)₃, -OH, -OCH₃, -OCH₂CH₃, -NH₂, -NHCH₃, and -NHCH₂CH₃.

[055] 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.

[056] 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., -CH₂O- is also intended to encompass -OCH₂-.

[057] “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.

[058] 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 anhydrides), conformational polymorphs, amorphous forms of the compounds, and mixtures thereof.

[059] 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 compound of Formula (I) 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) 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.

[060] 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.

[061] 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.

[062] 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.

[063] 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.

[064] 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.

[065] “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 alkanolic acids, hydroxy alkanolic 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, isobutyrate, 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.

[066] “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, chlorprocaine, 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.

[067] 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.

[068] 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.

[069] 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.

[070] 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.

[071] 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.

[072] 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.

[073] 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.

[074] 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) *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.

[075] 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) *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.

[076] 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). 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.

[077] 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.

[078] 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.

[079] 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.

[080] 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.

[081] 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.

[082] 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.

[083] As used herein, “expression” refers to the process by which a polynucleotide is transcribed from a DNA template (such as into 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.

[084] 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).

[085] 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.

[086] 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).

[087] “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)). 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.

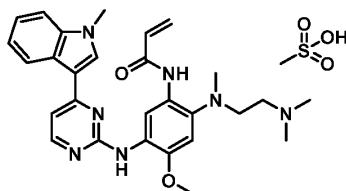
[088] The term “in vivo” refers to an event that takes place in a subject’s body. The term “ex vivo” refers to an event that first takes place outside of the subject’s body for a subsequent in vivo application into a subject’s body. For example, an ex vivo preparation may involve preparation of cells 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.

[089] 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.

[090] 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.

[091] “Osimertinib” refers to a kinase inhibitor for oral use. The molecular formula for osimertinib mesylate is $C_{28}H_{33}N_7O_2 \cdot CH_4O_3S$, and the molecular weight is 596 g/mol. The chemical name of osimertinib mesylate is N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide mesylate salt. Osimertinib has the following structural formula (as osimertinib mesylate):



Osimertinib is sold under the brand name Tagrisso and is indicated for: (a) adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test; (b) first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test; (c) in combination with pemetrexed and platinum-based chemotherapy, the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test; and (d) treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy. Tagrisso tablets contain 40 or 80 mg of osimertinib, equivalent to 47.7 and 95.4 mg of osimertinib mesylate, respectively. Inactive ingredients in the tablet core are mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and sodium stearyl fumarate. The tablet coating consists of polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, ferric oxide yellow, ferric oxide red, and ferric oxide black. References to osimertinib herein include osimertinib and pharmaceutically acceptable salts thereof, including osimertinib mesylate.

Methods

[092] The SOS1 inhibitors and the pharmaceutical compositions thereof, as disclosed herein, are particularly useful in treating epidermal growth factor receptor (EGFR)-mediated diseases and the symptoms associated therewith. Common EGFR mutations, including variable deletions of at least three amino acid residues in exon 19 (exon 19 deletion), L858R point mutation in exon 21, and exon 20 insertion mutations (ex20ins), are activating mutations that result in constitutive activation of EGFR and downstream signaling pathways, particularly in non-

small cell lung cancer (NSCLC). Cancers harboring exon 19 deletions and L858R mutations are typically more sensitive to EGFR inhibitors, such as gefitinib and erlotinib, as compared to cancers in which no EGFR mutations are detected. However, insertions in exon 20 result in constitutive activation of EGFR, are associated with resistance to EGFR inhibitors, and correlate with a poor patient prognosis. Even though osimertinib, a third-generation irreversible EGFR inhibitor, has been approved for treating certain EGFR activating mutations (exon 19 deletions and exon 21 L858R) in the adjuvant and metastatic setting and in exon 20 T790M mutation, the treated patients often eventually develop resistance to osimertinib resulting in relapse of cancer. Moreover, osimertinib alone may have limited efficacy in exon 20 mutant NSCLC at the standard dose of 80 mg, with evidence suggesting that higher doses (e.g., 160 mg osimertinib) may be needed to demonstrate a clinical benefit. The compositions and methods disclosed herein open a new avenue for overcoming osimertinib drug resistance for EGFR-mediated cancers, as well as the possibility of front-line treatment with a sustained and long-term efficacy. In some embodiments, the subject compositions and methods are particularly useful for treating NSCLC in which an exon 19 deletion, L858R mutation, T790M mutation, C797S mutation, and/or exon 20 insertion is detected. The combination of osimertinib and the SOS1 inhibitors described herein may overcome resistance and provide synergistic benefits in the treatment of EGFR mutant NSCLC.

[093] In one aspect, the present disclosure provides a method of reducing proliferation of cancer cells comprising an epidermal growth factor receptor (EGFR) exon 20 insertion, the method comprising administering to the cells (a) a SOS1 inhibitor and (b) osimertinib, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b). In some embodiments, the cancer cells are non-small cell lung cancer cells.

[094] In another aspect, the present disclosure provides a method of downregulating EGFR signaling output in a plurality of non-small cell lung cancer cells, comprising: (i) assessing EGFR 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) osimertinib if an EGFR exon 20 insertion is detected in the sample, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).

[095] In another aspect, the present disclosure provides a method of adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test, the method comprising administering to the subject (a) a SOS1 inhibitor and (b) osimertinib. In certain aspects, the present disclosure provides a method of first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test, the method comprising administering to the subject (a) a SOS1 inhibitor and (b) osimertinib. In certain aspects, the present disclosure provides a method of treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy, the method comprising administering to the subject (a) a SOS1 inhibitor and (b) osimertinib. In certain aspects, the present disclosure provides a method of treatment of adult patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test, the method comprising administering to the subject (a) a SOS1 inhibitor, (b) osimertinib, (c) pemetrexed, and (d) platinum-based chemotherapy.

[096] In yet another aspect, the present disclosure provides a method of treating an EGFR-mediated disease or condition or ameliorating the symptoms thereof in a subject in need thereof. The method may comprise administering to the subject (a) a SOS1 inhibitor and (b) osimertinib.

[097] In still another aspect, provided herein is a method of treating an EGFR-mediated cancer in a subject. The method comprises administering to the subject (a) a SOS1 inhibitor and (b) osimertinib, 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 0.1 as ascertained by Bliss independent criterion.

[098] In another aspect, the present disclosure provides a method of treating EGFR mutant NSCLC that has progressed on osimertinib in a subject, the method comprising administering to the subject (a) a SOS1 inhibitor and (b) osimertinib. The EGFR mutant NSCLC may have progressed on osimertinib in the locally advanced metastatic setting or recurred in the adjuvant setting.

[099] Any method described herein that comprises administering (a) a SOS1 inhibitor and (b) osimertinib may further comprise administering (c) an additional agent or additional therapy. Suitable agents that can be administered in combination with (a) the SOS1 inhibitor and (b) osimertinib 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 some embodiments, the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation. In some embodiments, a method described herein comprises administering (a) a SOS1 inhibitor, (b) osimertinib, (c) pemetrexed and (d) platinum-based chemotherapy. In some embodiments, a method described herein comprises administering (a) a SOS1 inhibitor, (b) osimertinib, and (c) pemetrexed. In some embodiments, a method described herein comprises administering (a) a SOS1 inhibitor, (b) osimertinib, and (c) platinum-based chemotherapy.

[100] In yet still another aspect, provided is a method of treating an EGFR-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (I-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) osimertinib, and (iii) a pharmaceutically acceptable excipient.

[101] In practicing one or more of the subject methods disclosed herein, the disease or condition may be a cancer comprising an EGFR mutation, including but not limited to an exon 19 deletion, an L858R mutation, a T790M mutation, a C797S mutation, and/or an exon 20 insertion. In some embodiments, the cancer comprises an exon 20 insertion. In some embodiments, the cancer comprises a G719x mutation, an S768I mutation, and/or an L861Q mutation. In practicing one or more of the subject methods disclosed herein, the disease or condition may be NSCLC comprising an EGFR mutation, including but not limited to an exon 19 deletion, an L858R mutation, a T790M mutation, a C797S mutation, a G719x mutation, an S768I mutation, an L861Q mutation, and/or an exon 20 insertion.

[102] The EGFR-mediated disease or condition may be any disease or condition in which the EGFR signaling pathway contributes to the progression of the disease or condition. In some embodiments, the disease or condition is characterized by aberrant activation of EGFR, optionally due to EGFR amplification, EGFR overexpression, overexpression of EGFR ligands, and/or occurrence of one or more EGFR mutation. EGFR-mediated diseases or conditions include, but are not limited to: cancer, such as lung adenocarcinoma, squamous cell lung carcinoma, non-small cell lung cancer, anal cancer, ovarian cancer, breast cancer, colorectal cancer, bladder cancer, esophageal cancer, glioblastoma, and head and neck carcinomas; inflammatory disease, such as psoriasis, eczema, atopic dermatitis, and atherosclerosis; and renal disease, such as renal fibrosis, chronic kidney disease, acute kidney injury, obstructive nephropathy, diabetic nephropathy, hypertensive nephropathy, and glomerulonephritis. In some embodiments, the EGFR-mediated disease or condition is an EGFR-mediated cancer. In some embodiments, the

cancer is lung cancer, such as non-small cell lung cancer (NSCLC). In some embodiments, the NSCLC is locally advanced or metastatic NSCLC. In some embodiments, the lung cancer is not predominant squamous NSCLC and/or small cell lung cancer. In some embodiments, the cancer is metastatic, such as metastatic NSCLC. In some embodiments, the cancer comprises an EGFR mutation, such as a mutation selected from L858R, T790M, C797S, G719X, S768I, L861Q, an exon 19 deletion, and an exon 20 insertion. In some embodiments, the cancer comprises an EGFR mutation, such as a mutation selected from L858R, T790M, C797S, an exon 19 deletion, and an exon 20 insertion. In some embodiments, the cancer comprises an exon 20 insertion. In some embodiments, the cancer comprises a double or triple EGFR mutant, such as T790M/C797S, L858R/T790M, del19/T790M/C797S, or L858R/T790M/C797S. In some embodiments, the cancer comprises aberrant MET expression, such as overexpression of MET or MET amplification.

[103] Determining whether a tumor or cancer comprises an EGFR mutation can be undertaken by assessing the nucleotide sequence encoding the protein, by assessing the amino acid sequence of the protein, or by assessing the characteristics of a putative protein. 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 are 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 *EGFR*. Where desired, one or more nucleic acids can be employed to detect a genetic aberration resulting in formation of *EGFR* gene including but not limited to translation, as well as genetic mutations within the *EGFR* gene via point mutation, insertion, deletion, or frameshift.

[104] Additional methods for detecting a nucleotide sequence of a gene include, but are not limited to, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays, polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) assays, real-time PCR assays, PCR sequencing, mutant allele-specific PCR amplification (MASA) assays, direct sequencing, primer extension reactions, electrophoresis, oligonucleotide ligation assays, hybridization assays, TaqMan assays, SNP genotyping assays, high resolution melting assays, and microarray analyses. In some embodiments, the EGFR mutation is identified using a direct sequencing method of specific regions in the gene. This technique can identify all possible mutations in the region sequenced. Methods for detecting a mutant EGFR protein include, but are not limited to, detection of a mutant protein using a binding agent (e.g., an antibody) specific for the mutant protein, protein electrophoresis and Western blotting, and direct peptide sequencing. In some embodiments, the EGFR mutation is identified using a PCR-based or next-generation sequencing (NGS)-based diagnostic. In some embodiments, the EGFR mutation is identified using a PCR-based diagnostic. In some embodiments, the EGFR mutation is identified using a NGS-based diagnostic.

[105] In some embodiments, the presence of an EGFR mutation, such as an exon 19 deletion, an exon 21 L858R substitution mutation, and/or T790M, is determined in a tumor or plasma specimen using an FDA-approved test, such as the cobas EGFR Mutation Test v1 (Roche Molecular Systems, Inc.), cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.), FoundationOne CDx (Foundation Medicine, Inc.), FoundationOne Liquid CDx (Foundation Medicine, Inc.), Guardant360 CDx (Guardant Health, Inc.), ONCO/Reveal Dx Lung & Colon Cancer Assay (O/RDx-LCCA, Pillar Biosciences, Inc.), Oncomine Dx Target Test (Life Technologies Corporation), or theascreen EGFR RGQ PCR Kit (Qiagen Manchester, Ltd.). In some embodiments, the presence of an EGFR

mutation, such as L861Q, G719X, and/or S768I, is determined in a tumor or plasma specimen using an FDA-approved test, such as the Therascreen EGFR RGQ PCR Kit (Qiagen Manchester, Ltd.). In some embodiments, EGFR protein expression is assessed in a tumor or plasma specimen using an FDA-approved test, such as the Dako EGFR pharmDx Kit (Dako North America, Inc.). In some embodiments, the presence of an EGFR mutation, such as an exon 20 insertion mutation, is determined in a tumor or plasma specimen using an FDA-approved test, such as the FoundationOne Liquid CDx (Foundation Medicine, Inc.), Guardant360 CDx (Guardant Health, Inc.), or OncoPrint Dx Target Test (Life Technologies Corporation).

[106] Methods for determining whether a disease or condition is mediated by or exhibits dependence on a polypeptide such as EGFR or MET are known to those of skill in the art. These methods include, but are not limited to, cell proliferation assays, transcriptomic assays, such as RNA seq or hybridization assays, and protein detection assays, such as immunoassays. In some embodiments, an EGFR-mediated disease or condition is one comprising a known EGFR activating mutation, such as an exon 19 deletion, L858R, T790M, or an exon 20 insertion. A variety of techniques for protein analysis can also be applied for assessing the presence and/or overexpression of EGFR or mutants thereof, as well as expression of other proteins associated with EGFR TKI resistance. 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 EGFR polypeptides. A large number of anti-EGFR antibodies are available, including those provided by ThermoFisher and Abcam. Commercially available antibodies can also be used in immunoassays to ascertain a decrease in EGFR TKI binding affinity to EGFR as a result of a genetic mutation in the *EGFR* gene.

[107] Methods for determining whether a tumor or cancer comprises an EGFR mutation can use a variety of samples. In some embodiments, the sample is taken from a subject having a tumor or cancer. In some embodiments, the sample is a fresh tumor/cancer sample. In some embodiments, the sample is a frozen tumor/cancer sample. In some embodiments, the sample is a formalin-fixed paraffin-embedded sample. In some embodiments, the sample is processed to a cell lysate. In some embodiments, the sample is processed to DNA or RNA. In some embodiments, the sample is a plasma sample. In some embodiments, the sample comprises cell-free DNA (cfDNA). In some embodiments, the method utilizes circulating cfDNA from plasma of peripheral whole blood collected from the subject.

[108] In practicing a subject method, the presence of *EGFR* gene, mutations within the *EGFR* gene, or other genetic aberrations associated with resistance to an EGFR TKI, 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 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.

[109] 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.

[110] 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, 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).

[111] EGFR exon 20 insertions include in-frame insertions within exon 20 of EGFR. In some embodiments, an EGFR exon 20 insertion is found between residues E762 and C775. In some embodiments, an EGFR exon 20 insertion is found after E762, A763, Y764, V765, M766, A767, S768, V769, D770, N771, P772, H773, V774, or C775. In some embodiments, an EGFR exon 20 insertion is found after residue L747, A763, Y764, M766, A767, V769, D770, P772, or H773. In some embodiments, an EGFR exon 20 insertion is found after residue V769 or D770. In some embodiments, an EGFR exon 20 insertion is selected from A763_Y764ins, Y764_V765ins, M766_A767ins, A767_V769dup, V769_D770ins, D770_N771ins, delD770ins, P772_H773ins, P772_V774ins, and H773_V774ins. In some embodiments, an EGFR exon 20 insertion is selected from D770_N771ins and V769_D770ins. In some embodiments, an EGFR exon 20 insertion is selected from delL747_P753insS, A763_Y764insFQEA, Y764_V765insHH, M766_A767insAI, M766_A767insASV, A767_V769dupASV, V769_D770insASV, D770_N771insGL, D770_N771insGT, D770_N771insNPG, D770_N771insSVD, delD770insGY, P772_H773insYNP, P772_V774insPHV, H773_V774insH, and H773_V774insNPH. In some embodiments, an EGFR exon 20 insertion is selected from D770_N771insSVD and V769_D770insASV. In some embodiments, an EGFR exon 20 insertion consists of one to four amino acid residues, such as one, two, three or four amino acid residues. In some embodiments, a cancer comprising an EGFR exon 20 insertion is insensitive to treatment with gefitinib or erlotinib.

[112] In practicing one or more combination methods disclosed herein, a synergistic effect of a given combination 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., osimertinib or a MET inhibitor) for inducing growth inhibition of target cells (e.g., NSCLC cells), the Bliss independence criterion can utilize the following equation:

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

wherein:

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

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

wherein further:

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

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

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

The observed combined percent 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).

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

[113] When using the Bliss independence criterion, the percent 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, when the fractional scale is used, the difference between the observed combined percent inhibition $Y_{AB,O}$ and the predicted percent 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).

[114] In some embodiments, the combination treatment comprising a plurality of agents (e.g., a SOS1 inhibitor disclosed or exemplified herein and osimertinib, or SOS1 inhibitor disclosed or exemplified herein and a MET inhibitor disclosed or exemplified herein), can be utilized to reduce growth or proliferation of target cells, such as NSCLC 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 to about 5, about 5 to about 10, or about 10 to about 15. In some embodiments, the synergistic value is at least 0.4, such as at least 1. In some embodiments, the synergistic value is at least 5.

[115] 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 TKI against EGFR 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 non-osimertinib TKI against EGFR prior to administering (a) and (b). In some embodiments, the subject has not been treated with osimertinib as a TKI prior to administering (a) and (b).

[116] In some embodiments, a subject suitable for a treatment method of the present disclosure has previously been treated with one or more tyrosine kinase inhibitor (TKI) against EGFR prior to administering (a) and (b). In some embodiments, the subject has previously been treated with a first-generation EGFR TKI (e.g., gefitinib), a second generation EGFR TKI (e.g., afatinib), or a third generation EGFR TKI (e.g., osimertinib). In some embodiments, the subject has previously been treated with a non-exon 20 insertion EGFR TKI, such as gefitinib, erlotinib, afatinib, lazertinib, osimertinib, dacomitinib, neratinib, cetuximab, panitumumab, lapatinib, necitumumab, nazartinib, vandetanib, BLU-945, or zorifertinib. In some embodiments, the subject has previously been treated with gefitinib, erlotinib, or afatinib. In some embodiments, the subject has previously been treated with osimertinib. In some embodiments, the cancer has progressed on osimertinib. In some embodiments, the subject has an EGFR mutant NSCLC that has progressed on osimertinib. In some embodiments, the EGFR mutant NSCLC has progressed on osimertinib in the locally advanced metastatic setting or recurred in the adjuvant setting. In some embodiments, the subject has previously been treated with an EGFR exon 20 insertion TKI, such as poziotinib, mobocertinib, amivantamab, zipalertinib, sunvozertinib, BAY-2927088, BLU-451, or STX-721. In some embodiments, the subject has previously been treated with amivantamab. In some embodiments, the subject has previously been treated with an EGFR TKI selected from gefitinib, erlotinib, afatinib, lazertinib, osimertinib, dacomitinib, neratinib, cetuximab, panitumumab, lapatinib, necitumumab, nazartinib, vandetanib, BLU-945, zorifertinib, poziotinib, mobocertinib, amivantamab, zipalertinib, sunvozertinib, BAY-2927088, BLU-451, and STX-721. 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.

[117] Despite the remarkable progress via the advent of several generations of EGFR TKIs, drug resistance and/or intolerance to the earlier generations of TKIs severely limit treatment options to subjects who exhibit resistance or intolerance to one or more EGFR TKI, or relapse following treatment with one or more EGFR TKI. Resistance to an EGFR TKI may be characterized by one or more changes selected from (1) progression of the cancer, (2) *EGFR* gene mutation including point mutation, insertion, deletion and translocation, (3) loss of EGFR T790M mutation, (4) *EGFR* gene amplification, (5) *MET* amplification, (6) *HER2* amplification, (7) RAS-MAPK pathway activation, (8) PI3K pathway activation, (9) cell-cycle gene alteration, (10) oncogenic fusion, (11) histologic transformation, and (12) phenotypic transformation. In some embodiments, resistance to an EGFR TKI is characterized by an exon 20 insertion resulting in a decrease in TKI binding affinity to EGFR. In some embodiments, a subject resistant to an EGFR TKI comprises one or more mutation selected from L858R, T790M, C797S, an exon 19 deletion, and an exon 20 insertion. In some embodiments, a subject resistant to an EGFR TKI comprises a double or triple EGFR mutant, including but not limited to T790M/C797S, L858R/T790M, del19/T790M/C797S, and L858R/T790M/C797S.

[118] In some embodiments, a subject suitable for a treatment method of the present disclosure exhibits intolerance to an EGFR TKI. Osimertinib has a number of known side effects, including diarrhea, rash, nausea, decreased appetite, thrombocytopenia, leukopenia, epistaxis, alopecia, hand foot syndrome, increased creatinine, increased creatinine phosphokinase, stomatitis, vomiting, paronychia, fatigue, dry skin, anorexia, headache, anemia,

pneumonia, pruritus, constipation, and/or cough, any or all of which may render the subject intolerant to EGFR TKI treatment.

[119] A subject resistant to treatment with an EGFR TKI may exhibit progression of the disease or condition, such as cancer (e.g., NSCLC), despite treatment with the EGFR TKI. An exemplary EGFR-mediated cancer is NSCLC, which typically manifests one or more symptoms which may include a cough, coughing up blood, chest pain or discomfort, trouble breathing, wheezing, hoarseness, loss of appetite, unexplained weight loss, fatigue, trouble swallowing, and swelling in the face and/or veins in the neck. Progression of NSCLC may be observed using one or more imaging methods, such as CT, PET, or MRI scans or a bronchoscopy.

[120] 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 an EGFR-mediated cancer, such as NSCLC. 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 EGFR TKI.

[121] In some embodiments, a subject suitable for a treatment method of the present disclosure suffers from a relapse of an EGFR-mediated cancer, such as lung cancer. In some embodiments, the subject suffers from a relapse of NSCLC. 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 EGFR TKI.

[122] In practicing a subject method disclosed herein, administering 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 SOS1 inhibitor can be a small molecule, a nucleic acid agent, or a polypeptide (e.g., an endonuclease). The contacting, as disclosed herein, can occur *in vitro*, *ex vivo*, or *in vivo*.

[123] In some embodiments, the cell is contacted with (i) a SOS1 inhibitor disclosed herein and (ii) osimertinib and/or a MET inhibitor. 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 osimertinib or a MET inhibitor. For simultaneous contacting, a subject SOS1 inhibitor and osimertinib, or a subject SOS1 inhibitor and a MET inhibitor, or a subject SOS1 inhibitor, osimertinib and a MET inhibitor, 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 or three different compositions at the same time). For sequential contacting, the subject SOS1 inhibitor and osimertinib, the subject SOS1 inhibitor, osimertinib and a MET inhibitor, or the subject SOS1 inhibitor and the MET inhibitor 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, osimertinib, or the MET inhibitor) and a second contacting of the cell (e.g., with the MET inhibitor, osimertinib, 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. In practicing any of the subject methods, (a) and (b) may be administered in the same formulation. In some embodiments, (a) and (b) are administered in separate formulations.

[124] In certain aspects, the present disclosure provides a method of treating a MET-mediated cancer, such as

NSCLC, in a subject, comprising administering to the subject a SOS1 inhibitor. The method may further comprise administering (b) a MET inhibitor. In certain aspects, the present disclosure provides a method of treating cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) a MET inhibitor, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b). In some embodiments, the cancer is an EGFR-mediated cancer, such as an EGFR-mediated cancer described herein. In some embodiments, the MET inhibitor is selected from foretinib, AMG-458, tivantinib, crizotinib, cabozantinib, tepotinib, capmatinib, savolitinib, and glesatinib. In some embodiments, the MET inhibitor is selected from capmatinib, tepotinib, cabozantinib, and savolitinib. In some embodiments, the MET inhibitor is savolitinib. In some embodiments, the method further comprises administering (c) an additional agent or additional therapy in combination with (a) the SOS1 inhibitor and (b) the MET inhibitor. In some embodiments, the additional agent is an EGFR inhibitor, such as an EGFR inhibitor selected from gefitinib, erlotinib, afatinib, lazertinib, osimertinib, dacomitinib, neratinib, cetuximab, panitumumab, lapatinib, necitumumab, nazartinib, vandetanib, poziotinib, mobocertinib, zipalertinib, sunvozertinib, BAY-2927088, BLU-451, BLU-945, STX-721, and zorifertinib. In some embodiments, the EGFR inhibitor is osimertinib. In some embodiments, the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation.

[125] Suitable agents that can be administered in combination with a subject SOS1 inhibitor and MET inhibitor include osimertinib and other EGFR TKIs disclosed herein, 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.

[126] 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.

[127] 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 (e.g., alemtuzumab, gemtuzumab, rituximab, ofatumumab, tositumomab, brentuximab), 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 (e.g., aclacinomycin A, gliotoxin or bortezomib), an immunomodulator such as thalidomide or a thalidomide derivative (e.g., lenalidomide). Additional chemotherapeutic agents contemplated for use in combination include busulfan (Myleran®), busulfan

injection (Busulfex®), cladribine (Leustatin®), cyclophosphamide (Cytosan® 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, Cosmegen), dexamethasone, docetaxel (Taxotere®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitabine, Gemcitabine (difluorodeoxycytidine), 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®).

[128] In some embodiments, a method described herein that comprises administering (a) a SOS1 inhibitor and (b) osimertinib 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).

[129] The practice of any treatment methods disclosed herein may involve administering a SOS1 inhibitor and osimertinib or a MET inhibitor in combination or in conjunction with an additional therapy. Applicable therapies for treating EGFR-mediated diseases (including NSCLC) include surgery, radiotherapy, cell therapy, chemotherapy, bone marrow transplant, and radiation.

[130] The subject combination therapy comprising a plurality of different therapeutic agents (e.g. a SOS1 inhibitor and osimertinib or a MET inhibitor) can synergistically achieve one or more desired therapeutic actions or outcomes, including, but not limited to, reduced progression of NSCLC. In some embodiments, the reduced progression of EGFR-mediated cancer is evidenced by disease stabilization, disease regression, improved lung function, or improvement of one or more symptoms of the cancer, such as improvement in one or more symptoms selected from a cough, coughing up blood, chest pain or discomfort, trouble breathing, wheezing, hoarseness, loss of appetite, unexplained weight loss, fatigue, trouble swallowing, and swelling in the face and/or veins in the neck. 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, (iii) improved lung function, and (iv) 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.

[131] 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; and (iii) allowing for the use of an EGFR TKI that would otherwise be intolerable to the subject.

[132] Through the administration of a combination therapy disclosed herein, any of a range of undesirable side-effects associated with osimertinib may be reduced, including diarrhea, rash, nausea, stomatitis, vomiting, paronychia, fatigue, dry skin, anorexia, headache, anemia, pneumonia, pruritus, constipation, and cough. In some embodiments, diarrhea, rash, nausea, dry skin, and/or paronychia can be reduced. The combination treatment with a SOS1 inhibitor disclosed herein may allow administration of osimertinib when it would otherwise not be tolerable to the subject. The combination treatment with a subject SOS1 inhibitor may allow a more frequent dosage regimen of osimertinib that is otherwise too toxic or not tolerable to a subject in need of such treatment.

[133] The combination treatment as disclosed herein can utilize osimertinib at a therapeutically sub-optimal dose when used alone, but in combination with a SOS1 inhibitor disclosed herein yields 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 dose of osimertinib less than that approved for treating a human subject for a given indication (e.g., a sub-therapeutic dose). In some embodiments, the sub-therapeutic dose is less than 95% of the approved dose of osimertinib, 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 osimertinib. For example, a sub-therapeutic dose of osimertinib is less than the approved dose of 80 mg orally once daily for adjuvant treatment of early stage NSCLC. In some embodiments, a sub-therapeutic dose of osimertinib is less than the approved dose of 80 mg orally once daily for metastatic NSCLC. A sub-therapeutic dose of osimertinib may be less than 90% of the approved dose of 80 mg orally once daily for adjuvant treatment of early state NSCLC or less than 90% of the approved dose of 80 mg orally once daily for metastatic NSCLC, such as less than 72 mg orally once daily for adjuvant treatment of early state NSCLC or less than 72 mg orally once daily for metastatic NSCLC. In some embodiments, osimertinib is administered at a dose of 80 mg daily in combination with a SOS1 inhibitor disclosed herein. In some embodiments, osimertinib is administered at a dose of 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, or 240 mg daily in combination with a SOS1 inhibitor disclosed herein.

[134] 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 osimertinib. 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 osimertinib, such as in combination with 80 mg osimertinib. In some embodiments, the SOS1 inhibitor is administered once daily in an oral dosage form.

[135] In certain aspects, the present disclosure provides a method of treating cancer in a subject in need thereof. The method may comprise 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 NSCLC 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 utilizing the NSCLC cell line. In some embodiments, the SOS1 inhibitor inhibits an NSCLC cell line selected from the group consisting of Ba/F3-EGFR_Ex20_ASV insertion, Ba/F3-EGFR_L858R/T790M, PC9-EGFR Ex19 E746_A750 deletion, H1975-EGFR L858R/T790M, Ba/F3-EGFR-V769_D770insASV, Ba/F3-EGFR_D770_N771insNPH, H1993, LU0858, LU0387, LU3075, H3122, and H2228 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. In some embodiments, the SOS1 inhibitor inhibits growth of an NSCLC cell line with an IC₅₀ at least 10, 50, or 100 times less than that of BI3406 or that of MRTX0902. In some embodiments, the SOS1 inhibitor synergistically inhibits growth of an NSCLC cell line in combination with osimertinib. In some embodiments, the SOS1 inhibitor synergistically inhibits growth of an NSCLC cell line in combination with a MET inhibitor. In some embodiments, the SOS1 inhibitor is characterized in that it synergistically inhibits growth of NSCLC cells in combination with osimertinib to yield at least about 80% growth inhibition, when less than about 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, or 0.1 nM of the SOS1 inhibitor is applied in combination with osimertinib applied at its IC₅₀ molarity, in an in vitro growth inhibition assay using NSCLC cells. 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 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM of the SOS1 inhibitor is applied in combination with osimertinib applied at its IC₁₀ molarity, as ascertained in an in vitro growth inhibition assay using NSCLC cells. In some embodiments, the SOS1 inhibitor is characterized in that it synergistically increases percent of cell growth inhibition from about 50% to at least about 80%, when less than about 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM of the SOS1 inhibitor is applied in combination with osimertinib applied at its IC₅₀ molarity, in an in vitro growth inhibition assay using NSCLC cells.

[136] In yet another aspect, the present disclosure provides a method of reducing proliferation of a cell comprising EGFR mutation. The method comprises administering to the cell (a) a small molecule SOS1 inhibitor disclosed herein, and (b) osimertinib, wherein the administration of (a) and (b) synergistically inhibits growth of NSCLC 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 osimertinib is administered as compared to the amount required for osimertinib when administered alone. In some embodiments, osimertinib is administered in 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. In some embodiments, less than 80 mg/day, such as less than 75 mg/day, less than 70 mg/day, less than 65 mg/day, less than 60 mg/day, less than 55 mg/day, less than 50 mg/day, less than 45 mg/day, less than 40 mg/day, less than 35 mg/day, less than 30 mg/day, less than 25 mg/day, less than 20 mg/day, less than 15 mg/day, or less than 10 mg/day of osimertinib is administered. In some embodiments, 80 mg/day of osimertinib is administered.

Compounds

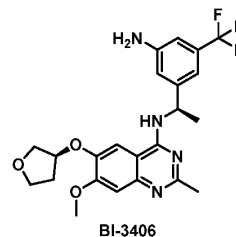
[137] A MET inhibitor for use in the present disclosure can be any MET inhibitor that is known in the art, and can include any entity that, upon administration to a subject, results in downregulation of MET in the subject. For example, a suitable MET inhibitor can be selected from a variety of types of molecules. In particular, the MET 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 MET inhibitor. Exemplary MET inhibitors for use in such combinations include one or more of foretinib, AMG-458, tivantinib, crizotinib, cabozantinib, tepotinib, capmatinib, savolitinib, and glesatinib. In some embodiments, the MET inhibitor is selected from capmatinib, tepotinib, cabozantinib, and savolitinib. In some embodiments, the MET inhibitor is savolitinib.

[138] 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).

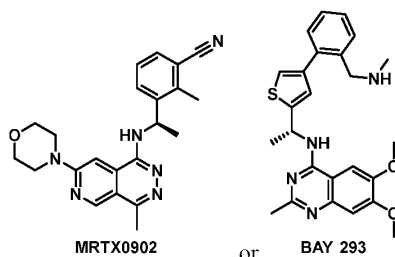
[139] In some embodiments, a small molecule SOS1 inhibitor may be conjugated to a degradation tag. A degradation tag may be configured to bind a degradation moiety having a capacity to degrade at least a portion of a target moiety that is bound by the degradation tag. In some embodiments, the target moiety is SOS1 or a substrate of SOS1.

[140] 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 3. 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 3. In some embodiments, a subject SOS1 inhibitor inhibits growth of a cancer cell, such as an NSCLC 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 NSCLC cell line. In some embodiments, the SOS1 inhibitor inhibits a NSCLC cell line selected from the group consisting of Ba/F3-EGFR_Ex20_ASV insertion,

Ba/F3-EGFR_L858R/T790M, PC9-EGFR Ex19 E746_A750 deletion, H1975-EGFR L858R/T790M, Ba/F3-EGFR-V769_D770insASV, Ba/F3-EGFR_D770_N771insNPH, H1993, LU0858, LU0387, LU3075, H3122, and H2228 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. 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 RMC-5845, BI-1701963,

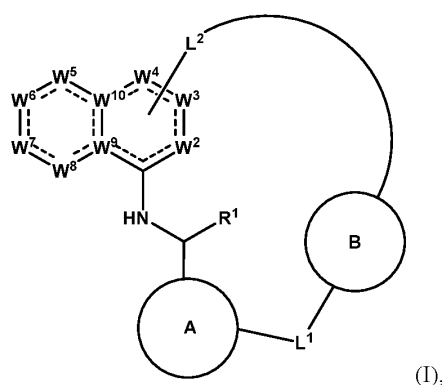


. In some embodiments, the SOS1 inhibitor inhibits growth of a NSCLC cell line with an IC₅₀ at least 10, 50, 100, 200, 300, 500, or 1000 times less than that of a SOS inhibitor described in WO2021092115, WO2018172250, WO2019201848, WO2019122129, WO2018115380, WO2021127429, WO2020180768, or WO2020180770, 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 an NSCLC cell line, in combination with osimertinib or a MET inhibitor.

[141] In some embodiments, the SOS1 inhibitor is characterized in it synergistically inhibits growth of NSCLC cells in combination with osimertinib or a MET inhibitor to yield at least about 80% growth inhibition when less than about 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, or 0.1 nM of the SOS1 inhibitor is applied in combination with osimertinib or the MET inhibitor applied at its IC₅₀ molarity, in an in vitro growth inhibition assay using NSCLC cells. 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 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM of the SOS1 inhibitor is applied in combination with osimertinib or the MET inhibitor applied at its IC₁₀ molarity, as ascertained in an in vitro growth inhibition assay using NSCLC cells. In some embodiments, the SOS1 inhibitor is characterized in that it synergistically increases percent of cell growth inhibition from about 50% to at least about 80%, when less than about 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, or 1 nM of the SOS1 inhibitor is applied in combination with osimertinib or the MET inhibitor applied at its IC₅₀ molarity, in an in vitro growth inhibition assay using NSCLC cells.

[142] The compounds of Formula (I) disclosed herein—including the compounds of Formula (I-A), (I-B), (I-1), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), (I-E1), (II-B), (II-C), and (III)—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.

[143] In certain aspects, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



is selected from C₅₋₇ carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R¹¹;



is absent or selected from C₃₋₈ carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{11a};

L¹ is selected from a bond, C₁₋₆ alkylene, and C₁₋₆ haloalkylene;

L² is selected from C₅₋₂₅ alkylene, C₅₋₂₅ alkenylene, C₅₋₂₅ alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}, wherein L² is covalently bound to one of W³, W⁴, W⁵, W⁶, or W⁷; or L² is -L³-D-L⁴, wherein L⁴ is covalently bound to one of W³, W⁴, W⁵, W⁶, or W⁷;

L³ is selected from C₁₋₁₀ alkylene, C₂₋₁₀ alkenylene, C₂₋₁₀ alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b};

D is absent or selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{11d};

L⁴ is selected from C₁₋₁₀ alkylene, C₂₋₁₀ alkenylene, C₂₋₁₀ alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b};

W² is selected from N(R^{2b}), N, C(R²), C(R²)(R^{2a}), and C(O);

W³ is selected from N(R^{3b}), N, C(R³), C(R³)(R^{3a}), and C(O);

W⁴ is selected from N(R^{4b}), N, C(R⁴), C(R⁴)(R^{4a}), and C(O);

W⁵ is selected from N(R^{5b}), N, C(R⁵), C(R⁵)(R^{5a}), and C(O);

W⁶ is selected from N(R^{6b}), N, C(R⁶), C(R⁶)(R^{6a}), and C(O);

W⁷ is selected from N(R^{7b}), N, C(R⁷), C(R⁷)(R^{7a}), and C(O);

W⁸ is selected from N(R^{8b}), N, C(R⁸), C(R⁸)(R^{8a}), and C(O);

W⁹ is selected from N, C(R⁹), and C;

W¹⁰ is selected from N, C(R¹⁰), and C;

R¹ is C₁₋₃ alkyl optionally substituted with one or more R^{11c};

R², R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R⁸, and R^{8a} are each independently selected from hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -

OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R^{2b} and R^{8b} are each independently selected from hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R^{3b}, R^{4b}, R^{5b}, R^{6b}, and R^{7b} are each independently selected from a bond to L², hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) is independently optionally substituted with one, two, or three R²⁰,

R¹¹, R^{11a}, and R^{11d} are each independently selected at each occurrence from halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle

are optionally substituted with one, two, or three R²⁰,

R^{11c} is independently selected at each occurrence from halogen, -OR¹², and -N(R¹²)(R¹³);

R¹² is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹³ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; or R¹² and R¹³, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R²⁰;

R¹⁴ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R¹⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹⁷ and R^{17a} are each independently selected at each occurrence from C₁₋₆ alkyl and C₃₋₆ cycloalkyl, wherein C₁₋₆ alkyl and C₃₋₆ cycloalkyl are optionally substituted with one, two or three R²⁰; or R¹⁷ and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), and -OC(O)R²⁵;

R²¹ is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

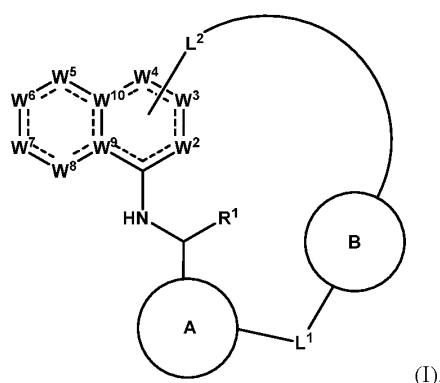
R²³ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁴ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

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

[144] In certain aspects, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



is selected from C₅₋₇ carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R¹¹;



is absent or selected from C₃₋₈ carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{11a};

L¹ is selected from a bond, C₁₋₆ alkylene, and C₁₋₆ haloalkylene;

L² is selected from C₅₋₂₅ alkylene, C₅₋₂₅ alkenylene, C₅₋₂₅ alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}, wherein L² is covalently bound to one of W³, W⁴, W⁵, W⁶, or W⁷;

W² is selected from N(R^{2b}), N, C(R²), C(R²)(R^{2a}), and C(O);

W³ is selected from N(R^{3b}), N, C(R³), C(R³)(R^{3a}), and C(O);

W⁴ is selected from N(R^{4b}), N, C(R⁴), C(R⁴)(R^{4a}), and C(O);

W⁵ is selected from N(R^{5b}), N, C(R⁵), C(R⁵)(R^{5a}), and C(O);

W⁶ is selected from N(R^{6b}), N, C(R⁶), C(R⁶)(R^{6a}), and C(O);

W⁷ is selected from N(R^{7b}), N, C(R⁷), C(R⁷)(R^{7a}), and C(O);

W⁸ is selected from N(R^{8b}), N, C(R⁸), C(R⁸)(R^{8a}), and C(O);

W⁹ is selected from N, C(R⁹), and C;

W¹⁰ is selected from N, C(R¹⁰), and C;

R¹ is C₁₋₃ alkyl optionally substituted with one or more R^{11c};

R², R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R⁸, and R^{8a} are each independently selected from hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰;

R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -

OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R^{2b} and R^{8b} are each independently selected from hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R^{3b}, R^{4b}, R^{5b}, R^{6b}, and R^{7b} are each independently selected from a bond to L², hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) is independently optionally substituted with one, two, or three R²⁰,

R¹¹ and R^{11a} are each independently selected at each occurrence from halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R^{11c} is independently selected at each occurrence from halogen, -OR¹², and -N(R¹²)(R¹³);

R¹² is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R¹³ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; or R¹² and R¹³, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally

substituted with one, two, or three R²⁰;

R¹⁴ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R¹⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹⁷ and R^{17a} are each independently selected at each occurrence from C₁₋₆ alkyl and C₃₋₆ cycloalkyl, wherein C₁₋₆ alkyl and C₃₋₆ cycloalkyl are optionally substituted with one, two or three R²⁰; or R¹⁷ and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), and -OC(O)R²⁵;

R²¹ is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

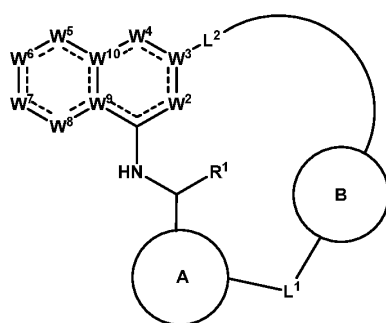
R²³ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁴ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

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

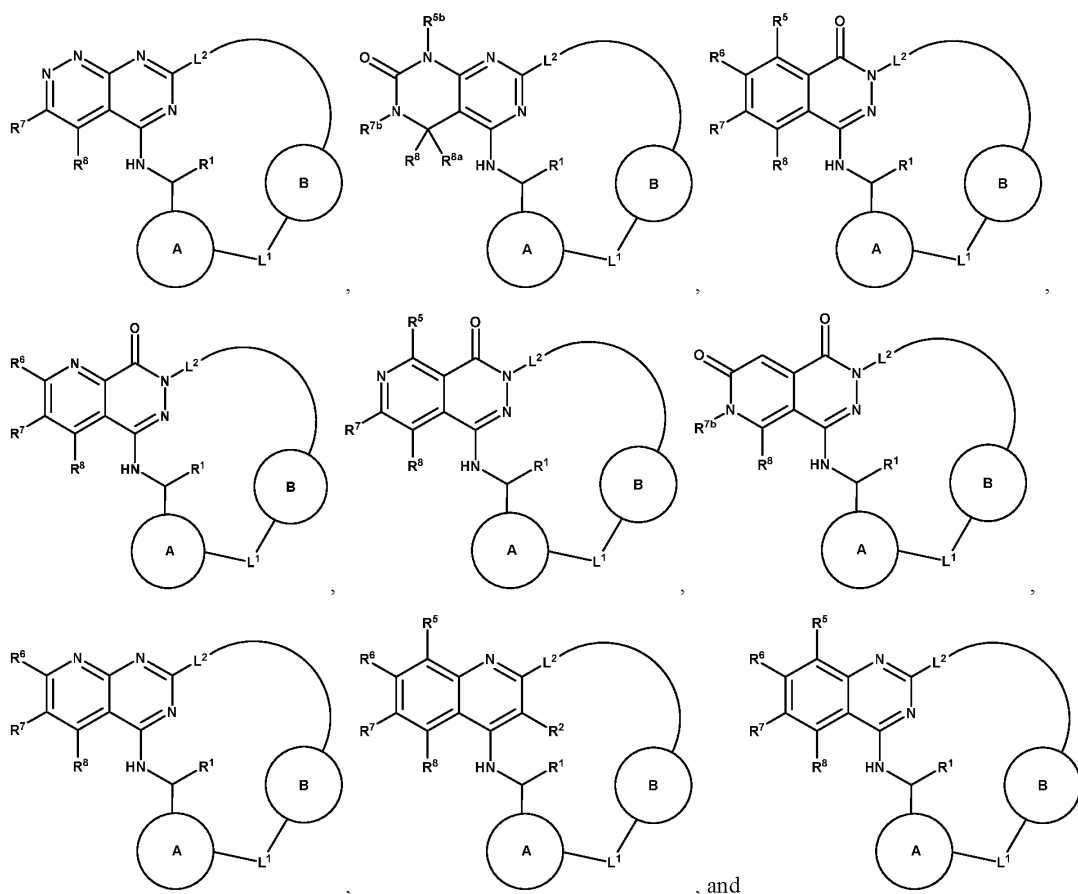
[145] In some embodiments, the compound of Formula (I) is a compound of Formula (I-A):



(I-A),

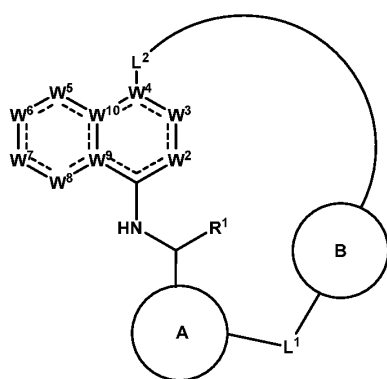
or a pharmaceutically acceptable salt or solvate thereof.

[146] In some embodiments, the compound of Formula (I-A) is a compound selected from:

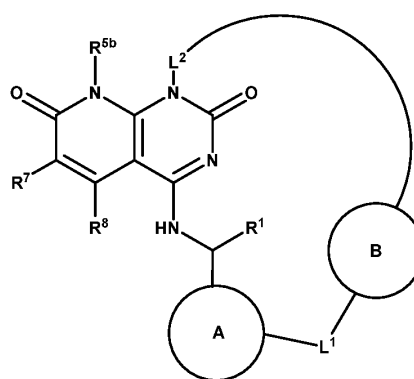


, and

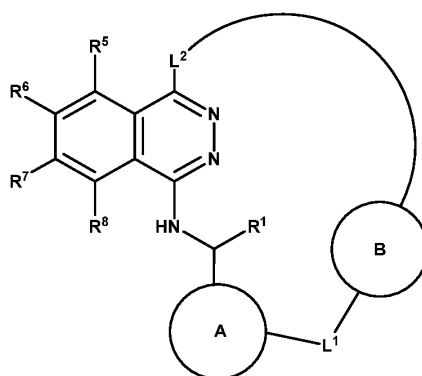
[147] In some embodiments, the compound of Formula (I) is a compound of Formula (I-B), such as a compound of Formula (I-B1) or (I-B2):



(I-B),



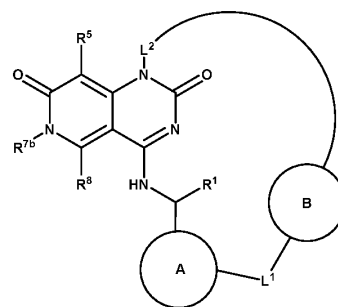
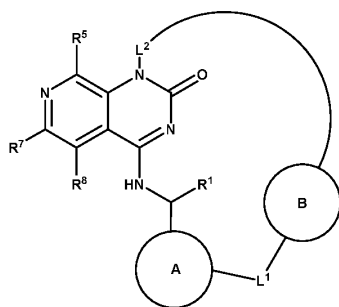
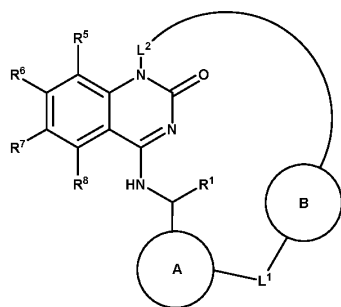
(I-B1), or



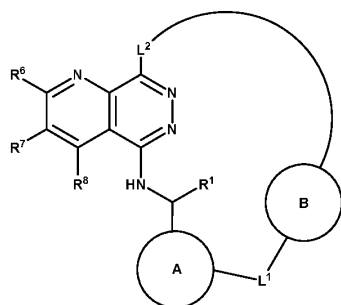
(I-B2),

or a pharmaceutically acceptable salt or solvate thereof.

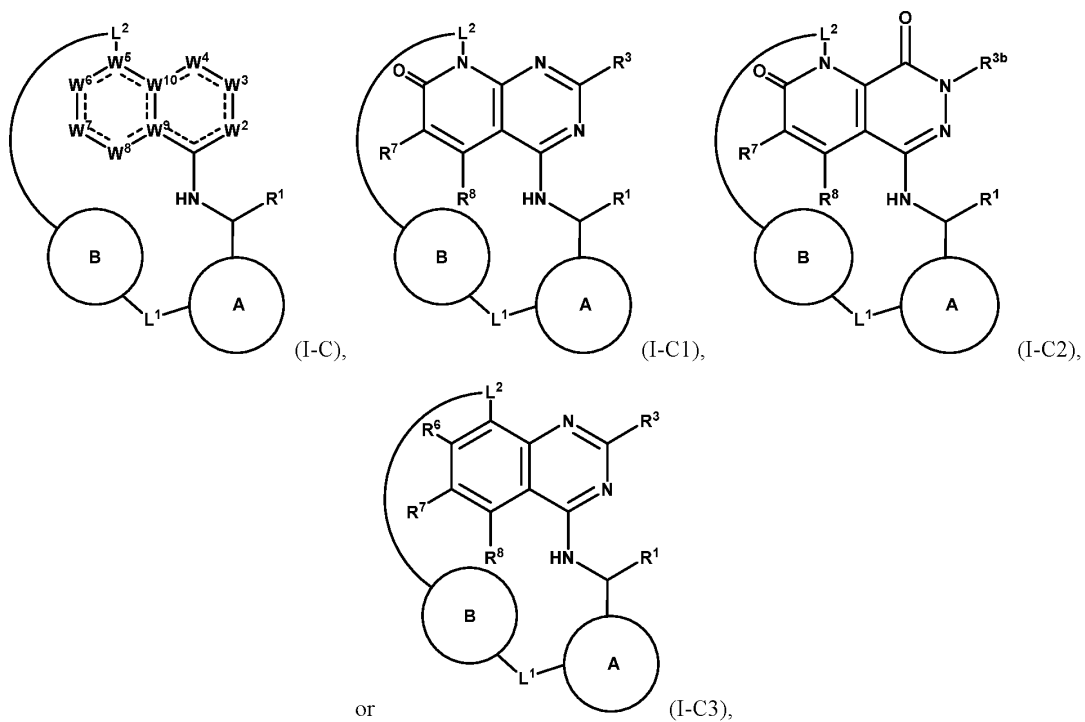
[148] In some embodiments, the compound of Formula (I-B) is a compound selected from:



, and

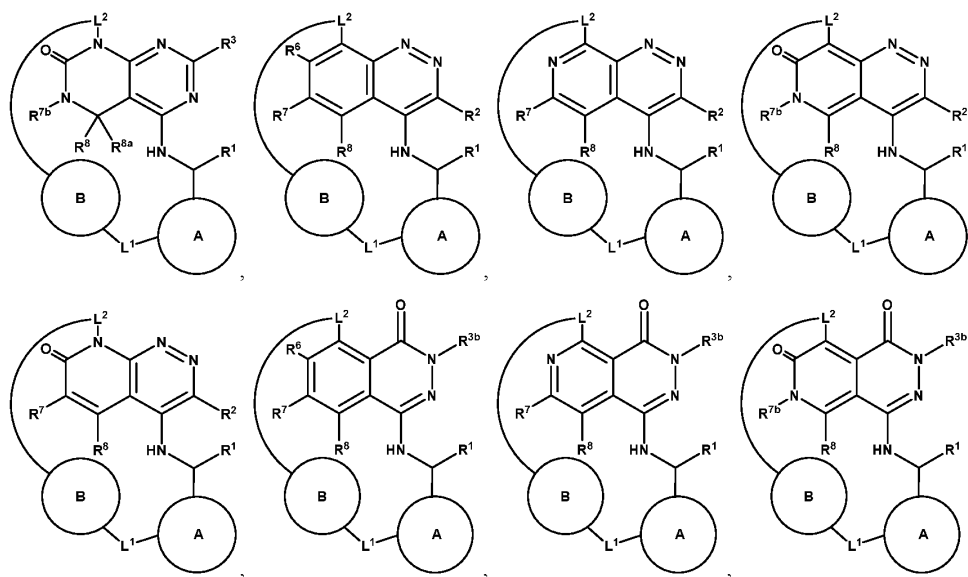


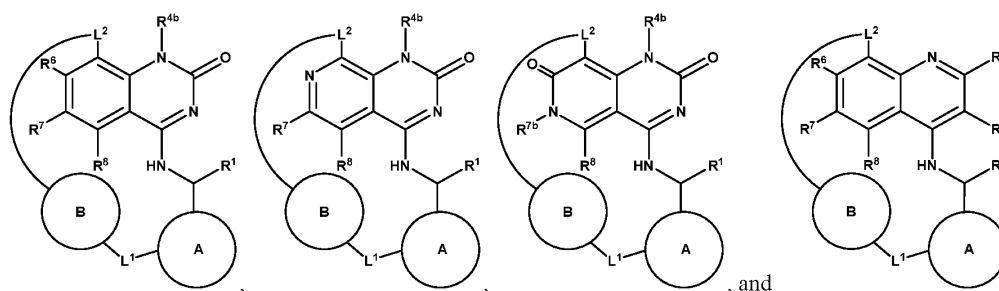
[149] In some embodiments, the compound of Formula (I) is a compound of Formula (I-C), such as a compound of Formula (I-C1), (I-C2), or (I-C3):



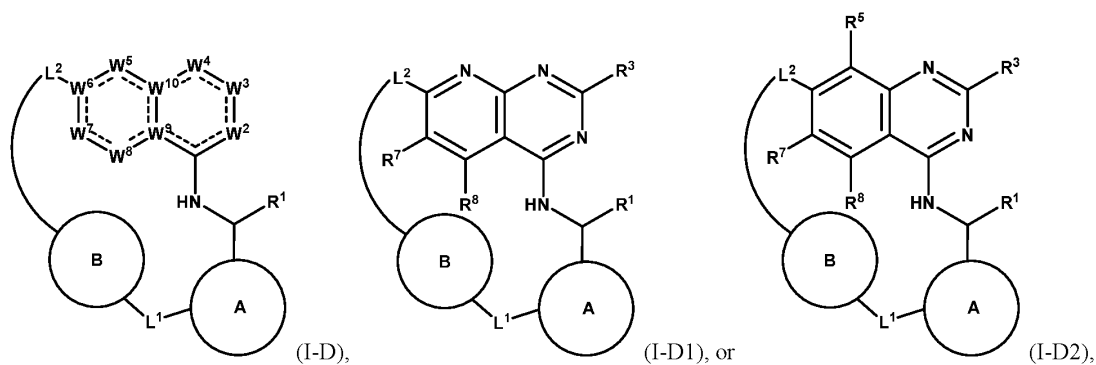
or a pharmaceutically acceptable salt or solvate thereof.

[150] In some embodiments, the compound of Formula (I-C) is a compound selected from:



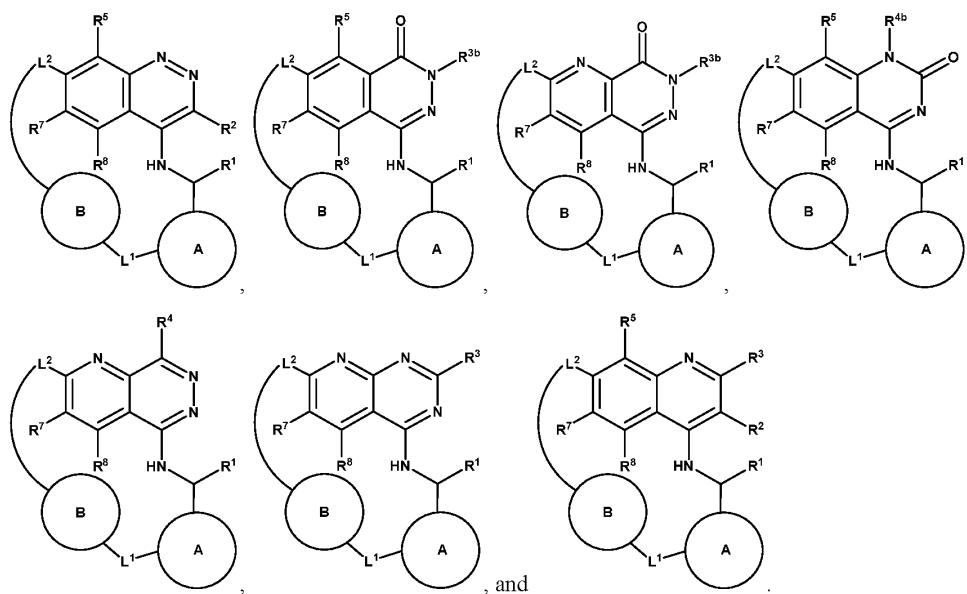


[151] In some embodiments, the compound of Formula (I) is a compound of Formula (I-D), such as a compound of Formula (I-D1) or (I-D2):

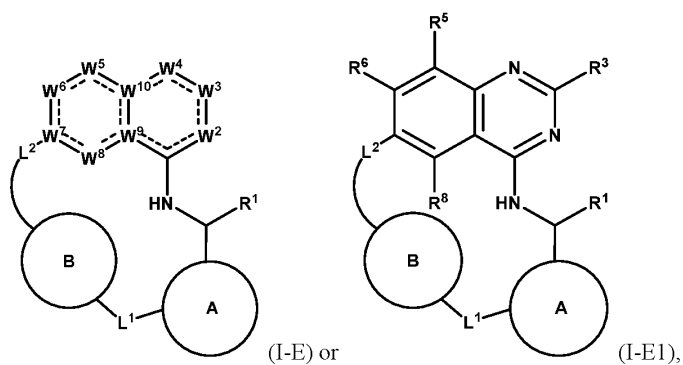


or a pharmaceutically acceptable salt or solvate thereof.

[152] In some embodiments, the compound of Formula (I-D) is a compound selected from:

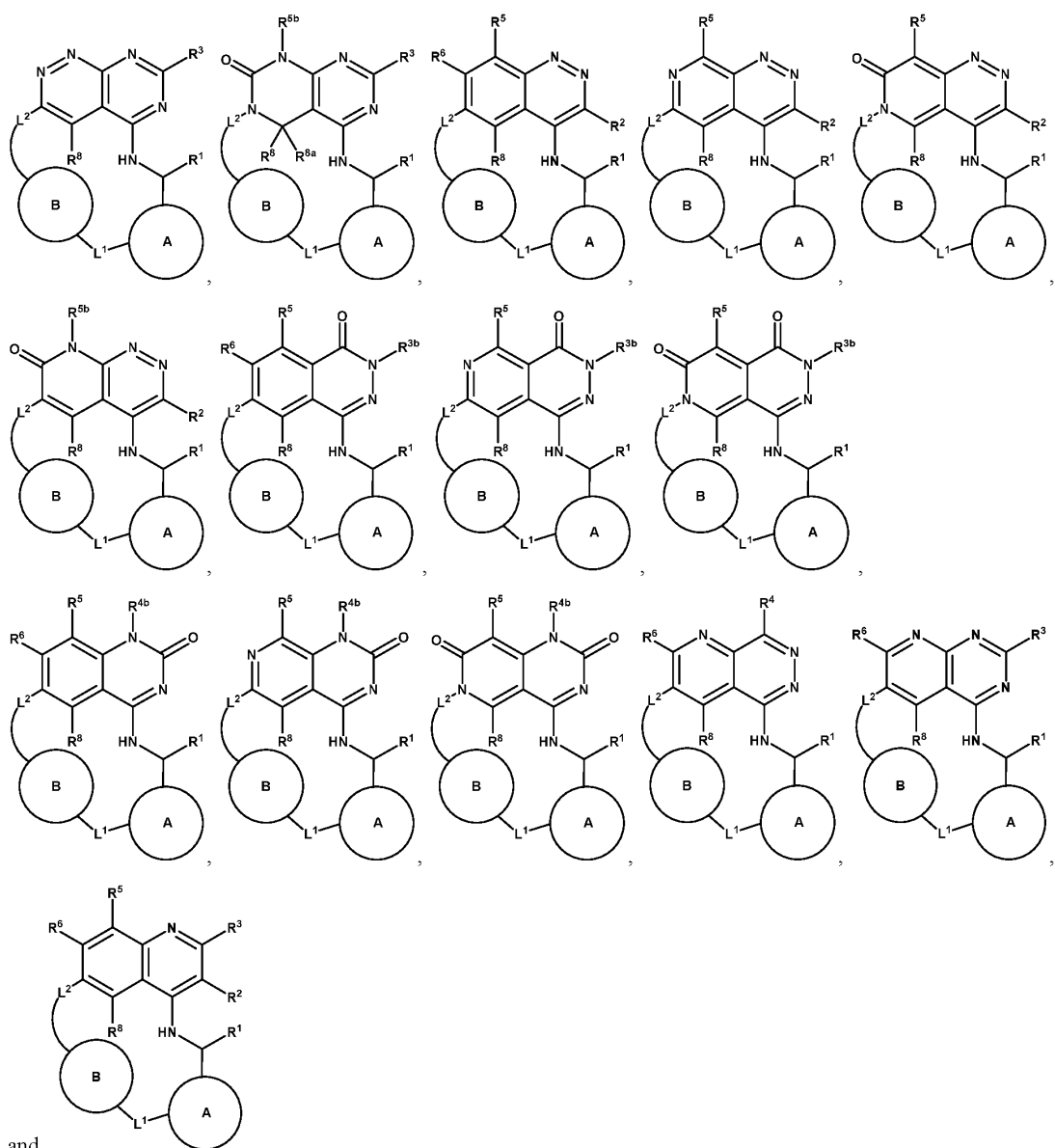


[153] In some embodiments, the compound of Formula (I) is a compound of Formula (I-E), such as a compound of Formula (I-E1):



or a pharmaceutically acceptable salt or solvate thereof.

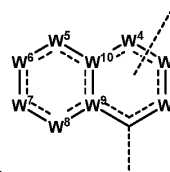
[154] In some embodiments, the compound of Formula (I-E) is a compound selected from:



[155] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (I-D), or (I-E), W^2 is N. In some embodiments, W^3 is selected from $N(R^{3b})$, N, $C(R^3)$, and C(O), such as NCH_3 , N, CH, CCH_3 , and C(O). In some embodiments, W^3 is selected from $C(R^3)$ and C(O), such as CH, CCH_3 and C(O). In some embodiments, W^3 is CH. In some embodiments, W^3 is CCH_3 . In some embodiments, W^4 is selected from $N(R^{4b})$, N, $C(R^4)$, and C(O), such as $N(R^{4b})$, N, $C(R^4)$, and C(O), wherein R^{4b} and R^4 are each independently a bond to L^2 . In some embodiments, W^4 is selected from $N(R^{4b})$ and N, such as $N(R^{4b})$, wherein R^{4b} is a bond to L^2 . In some embodiments, W^4 is N. In some embodiments, W^5 is selected from $N(R^{5b})$, N, $C(R^5)$, and C(O), such as $N(R^{5b})$, NCH_3 , N, CH, $C(R^5)$, and C(O), wherein R^{5b} and R^5 are each independently a bond to L^2 . In some embodiments, W^5 is selected from $N(R^{5b})$, N, and $C(R^5)$, such as $N(R^{5b})$, NCH_3 , N, CH, and $C(R^5)$, wherein R^{5b} and R^5 are each independently a bond to L^2 . In some embodiments, W^5 is selected from $N(R^{5b})$ and $C(R^5)$, such as $N(R^{5b})$, NCH_3 , and CH, wherein R^{5b} is a bond to L^2 . In some embodiments, W^5 is $N(R^{5b})$. In some embodiments, W^6 is selected from $C(R^6)$ and C(O), such as $COCH_3$, CH, $C(R^6)$, and C(O), wherein R^6 is a bond to L^2 . In some embodiments, W^6 is C(O). In some embodiments, W^7 is $C(R^7)$, such as W^7 is $C(R^7)$ wherein R^7 is a bond to L^2 . In some embodiments, W^7 is $C(R^7)$, wherein R^7 is not hydrogen, such as R^7 is selected from C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $-OR^{12}$, wherein C_{3-10} cycloalkyl and 3- to 10-membered heterocycloalkyl are optionally substituted with one, two, or three R^{20} . In some embodiments, W^8 is $C(R^8)$, such as W^8 is CH. In some embodiments, W^9 is C. In some embodiments, W^{10} is C.

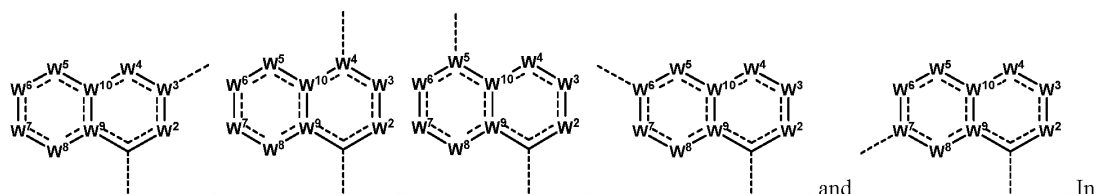
[156] In some embodiments, for a compound of Formula (I), (I-A), (I-C), (I-D), or (I-E), W^2 is N; W^3 is $N(R^{3b})$; W^4 is C(O); and W^9 and W^{10} are each C, such as W^2 is N; W^3 is NCH_3 ; W^4 is C(O); and W^9 and W^{10} are each C. In some embodiments, for a compound of Formula (I), (I-B), (I-C), (I-D), or (I-E), W^2 is N; W^3 is C(O); W^4 is $N(R^{4b})$; and W^9 and W^{10} are each C, such as W^2 is N; W^3 is C(O); W^4 is $N(R^{4b})$, wherein R^{4b} is a bond to L^2 , and W^9 and W^{10} are each C. In some embodiments, for a compound of Formula (I), (I-A), (I-C), (I-D), or (I-E), W^2 is N; W^3 is $C(R^3)$; W^4 is N; and W^9 and W^{10} are each C, such as W^2 is N; W^3 is CH or CCH_3 ; W^4 is N; and W^9 and W^{10} are each C. In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (I-D), or (I-E), W^5 is $C(R^5)$; W^6 is $C(R^6)$; W^7 is $C(R^7)$; W^8 is $C(R^8)$; and W^9 and W^{10} are each C, such as W^5 is CH or $C(R^5)$, wherein R^5 is a bond to L^2 ; W^6 is CH or $C(R^6)$, wherein R^6 is a bond to L^2 ; W^7 is $C(R^7)$; W^8 is CH; and W^9 and W^{10} are each C. In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), or (I-E), W^5 is $N(R^{5b})$; W^6 is C(O); W^7 is $C(R^7)$; W^8 is $C(R^8)$; and W^9 and W^{10} are each C, such as W^5 is NCH_3 or $N(R^{5b})$, wherein R^{5b} is a bond to L^2 ; W^6 is C(O); W^7 is $C(R^7)$; W^8 is CH; and W^9 and W^{10} are each C. In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-D), or (I-E), W^5 is N; W^6 is $C(R^6)$; W^7 is $C(R^7)$; W^8 is $C(R^8)$; and W^9 and W^{10} are each C, such as W^5 is N; W^6 is $COCH_3$, CH, or $C(R^6)$, wherein R^6 is a bond to L^2 ; W^7 is $C(R^7)$; W^8 is CH; and W^9 and W^{10} are each C. In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (I-D), or (I-E), W^2 is N; W^3 is selected from $N(R^{3b})$, N, $C(R^3)$, and C(O); W^4 is selected from $N(R^{4b})$, N, $C(R^4)$, and C(O); W^5 is selected from $N(R^{5b})$, N, and $C(R^5)$; W^6 is selected from $C(R^6)$ and C(O); W^7 is $C(R^7)$; W^8 is $C(R^8)$; and W^9 and W^{10} are each C, such as W^2 is N; W^3 is selected from NCH_3 , N, CH, CCH_3 , and C(O); W^4 is selected from $N(R^{4b})$, N, $C(R^4)$, and C(O), wherein R^{4b} and R^4 are each independently a bond to L^2 ; W^5 is selected from $N(R^{5b})$, NCH_3 , N, CH, and $C(R^5)$, wherein R^{5b} and R^5 are each independently a bond to L^2 ; W^6 is selected from $COCH_3$, CH, $C(R^6)$, and C(O), wherein R^6 is a bond to L^2 ; W^7 is $C(R^7)$; W^8 is CH; and W^9 and W^{10} are each C. In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (I-D), or (I-E), W^2 is N; W^3 is selected from $C(R^3)$ and C(O); W^4 is selected from $N(R^{4b})$ and N; W^5 is selected from $N(R^{5b})$ and $C(R^5)$; W^6 is selected from $C(R^6)$ and C(O); W^7 is $C(R^7)$; W^8 is CH; and W^9 and W^{10} are each C, such as W^2 is N; W^3 is selected from CH, CCH_3 , and C(O); W^4 is selected from $N(R^{4b})$ and N, wherein R^{4b} is a bond to L^2 ; W^5 is selected from $N(R^{5b})$, NCH_3 , CH, and $C(R^5)$, wherein R^{5b} and R^5 are each independently a

bond to L²; W⁶ is selected from COCH₃, CH, C(R⁶), and C(O), wherein R⁶ is a bond to L²; W⁷ is C(R⁷); W⁸ is CH; and W⁹ and W¹⁰ are each C.



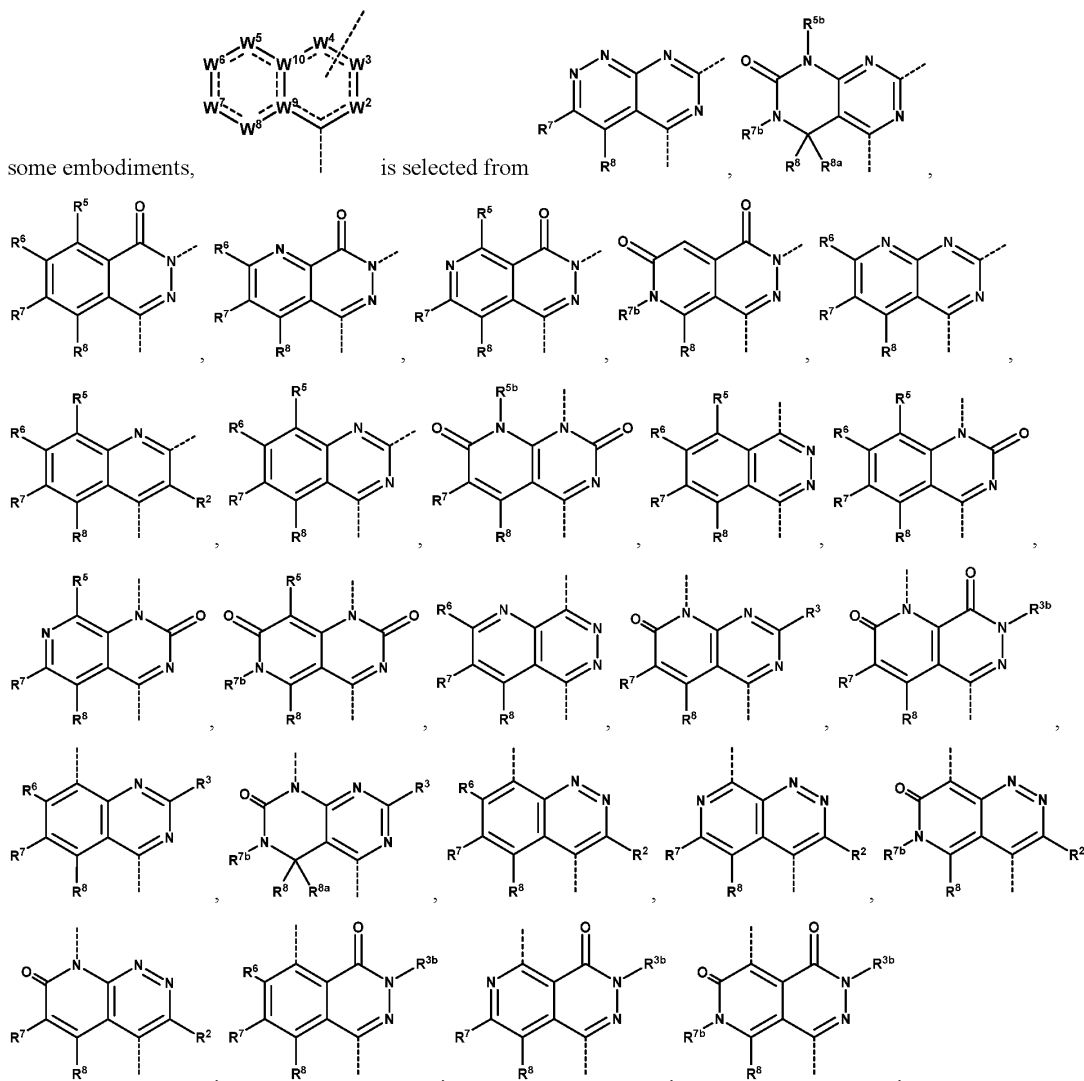
[157] In some embodiments, for a compound of Formula (I),

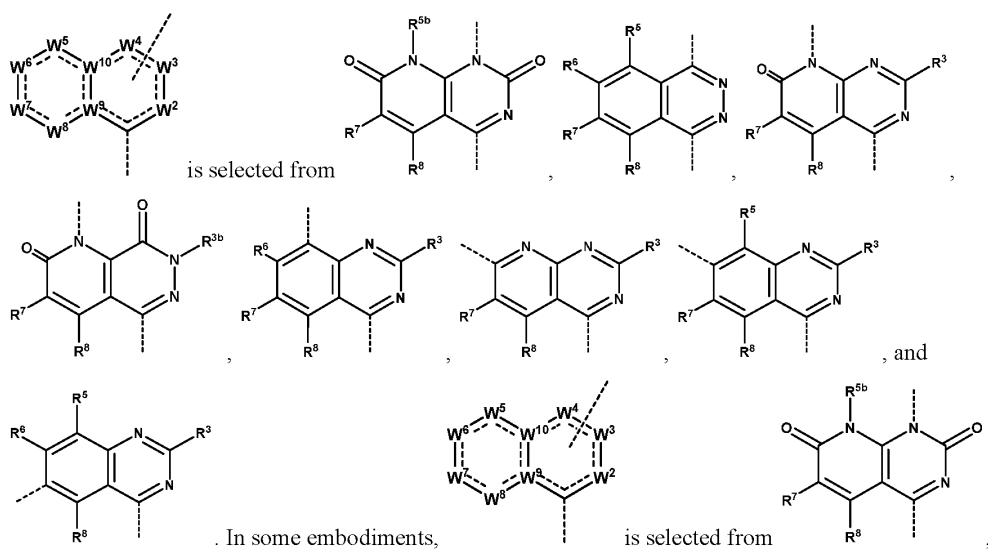
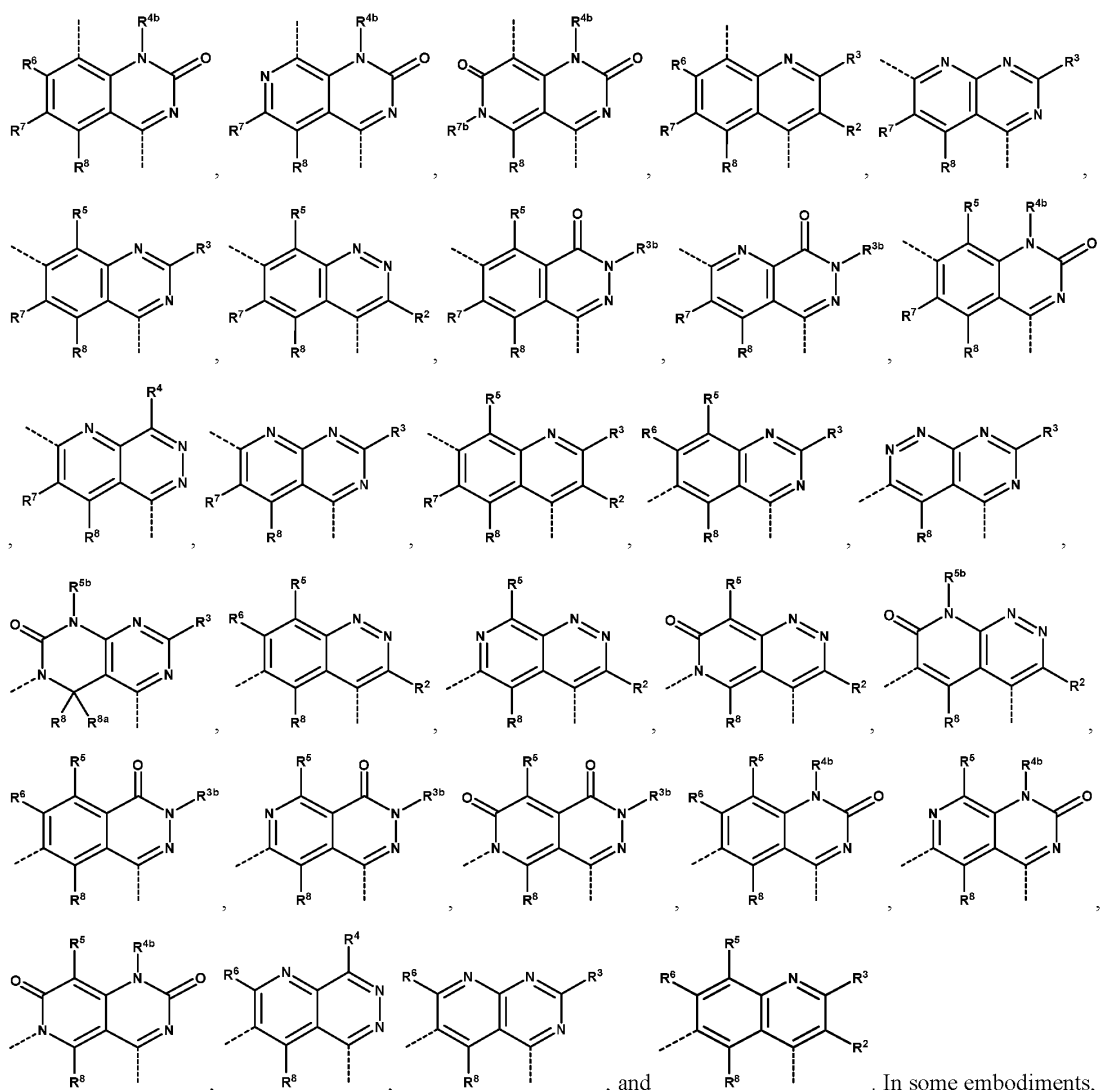
is selected from

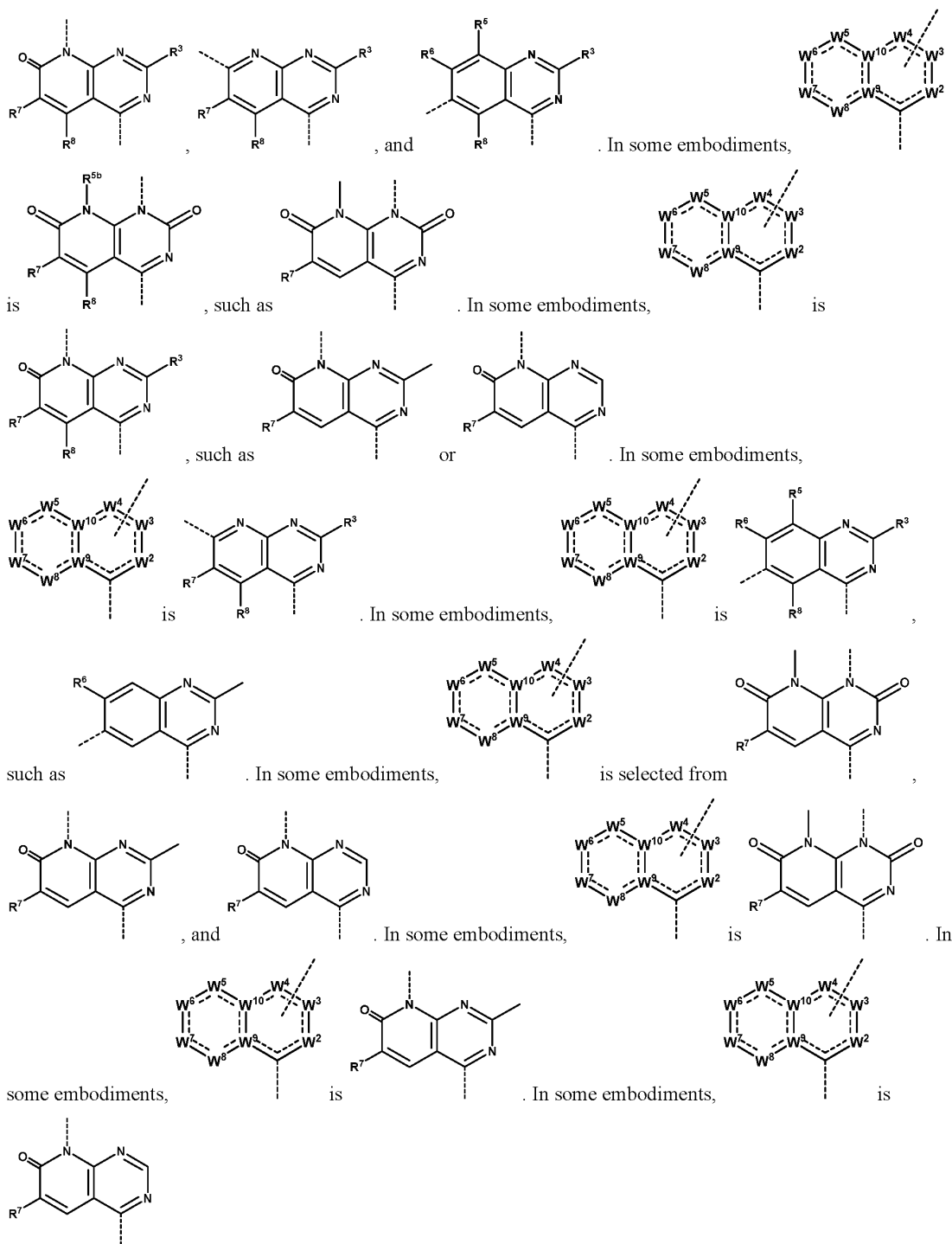


some embodiments,

is selected from







[158] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (I-D), or (I-E), R^2 , R^{2a} , R^{3a} , R^{4a} , R^{5a} , R^{6a} , R^{7a} , R^8 , and R^{8a} are each independently selected from hydrogen, halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, -OH, -NH₂, -NHCH₃, and -N(CH₃)₂. In some embodiments, R^2 , R^{2a} , R^{3a} , R^{4a} , R^{5a} , R^{6a} , R^{7a} , R^8 , and R^{8a} are each independently selected from hydrogen and -CH₃, such as hydrogen.

[159] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (I-D), or (I-E), R^3 , R^4 , R^5 , and R^6

are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₆ alkyl, C₃₋₆ carbocycle, 3- to 6-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, and -S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₃₋₆ carbocycle, and 3- to 6-membered heterocycle is independently optionally substituted with one, two, or three R²⁰, and R⁷ is selected from a bond to L², C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰. In some embodiments, R³, R⁴, R⁵, and R⁶ are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₃ alkyl, C₁₋₃ haloalkyl, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂, and R⁷ is selected from a bond to L², C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰. In some embodiments, R³, R⁴, R⁵, and R⁶ are each independently selected from a bond to L², hydrogen, -CH₃, and -OCH₃; and R⁷ is selected from a bond to L², C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰.

[160] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-C), (I-D), or (I-E), R^{2b} and R^{8b} are each independently selected from hydrogen and C₁₋₃ alkyl, such as hydrogen and -CH₃. In some embodiments, R^{3b}, R^{4b}, R^{5b}, R^{6b}, and R^{7b} are each independently selected from a bond to L², hydrogen, and C₁₋₃ alkyl, such as a bond to L², hydrogen, and -CH₃. In some embodiments, R^{3b}, R^{4b}, R^{5b}, R^{6b}, and R^{7b} are each independently selected from a bond to L² and -CH₃. In some embodiments, R^{3b}, R^{4b}, R^{5b}, R^{6b}, and R^{7b} are each independently selected from a bond to L². In some embodiments, R⁹ and R¹⁰ are each hydrogen.

[161] For a compound of Formula (I) wherein L² is -L³-D-L⁴, it is understood that the selection of “a bond to L²” for one of R³, R⁴, R⁵, R⁶, R⁷, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} inherently includes a bond to -L³-D-L⁴, specifically to L⁴. For the avoidance of doubt, any recitation of R³, R⁴, R⁵, R⁶, R⁷, R^{3b}, R^{4b}, R^{5b}, R^{6b}, and/or R^{7b} that includes “a bond to L²” also may be considered to include “a bond to L⁴”.

[162] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1), R¹ is selected from C₁₋₃ alkyl and C₁₋₃ haloalkyl, such as -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂F, -CHF₂, -CF₃, CH₂CH₂F, -CH₂CHF₂, and -CH₂CF₃. In some embodiments, R¹ is selected from C₁₋₃ alkyl, such as -CH₃ and -CH₂CH₃. In some embodiments, R¹ is -CH₃. In some embodiments, R¹ is (R)-CH₃. In some embodiments, R¹ is (S)-CH₃.

[163] In some embodiments, for a compound of Formula (I), (I-B), (I-C), (I-C1), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1), R³ is selected from hydrogen, halogen, -CN, C₁₋₆ alkyl, C₃₋₆ carbocycle, 3- to 6-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, and -S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₃₋₆ carbocycle, and 3- to 6-membered heterocycle is independently optionally substituted with one, two, or three R²⁰. In some embodiments, R³ is selected from hydrogen, halogen, -CN, C₁₋₃ alkyl, C₁₋₃ haloalkyl, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂. In some embodiments, R³ is selected from hydrogen, halogen, -CN, -OR¹², and C₁₋₆ alkyl optionally substituted with one, two, or three R²⁰. In some embodiments, R³ is C₁₋₆ alkyl optionally substituted with one, two, or three R²⁰. In some embodiments, R³ is hydrogen or -CH₃. In some embodiments, R³ is hydrogen. In some embodiments, R³ is -CH₃.

[164] In some embodiments, for a compound of Formula (I), (I-B), (I-C), (I-C2), (I-D), or (I-E), R^{3b} is selected from hydrogen and C₁₋₃ alkyl, such as hydrogen and -CH₃. In some embodiments, R^{3b} is -CH₃. In some

embodiments, R^{3b} is hydrogen.

[165] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B2), (I-D), (I-D2), (I-E), or (I-E1), R⁵ is selected from hydrogen, halogen, -CN, C₁₋₆ alkyl, C₃₋₆ carbocycle, 3- to 6-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, and -S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₃₋₆ carbocycle, and 3- to 6-membered heterocycle is independently optionally substituted with one, two, or three R²⁰. In some embodiments, R⁵ is selected from hydrogen, halogen, -CN, C₁₋₃ alkyl, C₁₋₃ haloalkyl, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂. In some embodiments, R⁵ is selected from hydrogen, -OR¹², and C₁₋₆ alkyl optionally substituted with one, two, or three R²⁰. In some embodiments, R⁵ is hydrogen or -CH₃. In some embodiments, R⁵ is hydrogen. In some embodiments, R⁵ is -CH₃.

[166] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-D), or (I-E), R^{5b} is selected from hydrogen and C₁₋₃ alkyl, such as hydrogen and -CH₃. In some embodiments, R^{5b} is selected from hydrogen and C₁₋₆ alkyl optionally substituted with one, two, or three R²⁰. In some embodiments, R^{5b} is -CH₃. In some embodiments, R^{5b} is hydrogen. In some embodiments, R^{5b} is a bond to L².

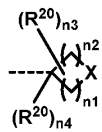
[167] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B2), (I-C), (I-C3), (I-E), or (I-E1), R⁶ is selected from hydrogen, halogen, -CN, C₁₋₆ alkyl, C₃₋₆ carbocycle, 3- to 6-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, and -S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₃₋₆ carbocycle, and 3- to 6-membered heterocycle is independently optionally substituted with one, two, or three R²⁰. In some embodiments, R⁶ is selected from hydrogen, halogen, -CN, C₁₋₃ alkyl, C₁₋₃ haloalkyl, -OH, -OCH₃, -NH₂, -NHCH₃, and -N(CH₃)₂. In some embodiments, R⁶ is selected from hydrogen, -OR¹², and C₁₋₆ alkyl optionally substituted with one, two, or three R²⁰, and wherein R¹² is selected from C₁₋₆ alkyl. In some embodiments, R⁶ is selected from hydrogen and -OCH₃. In some embodiments, R⁶ is hydrogen. In some embodiments, R⁶ is -OCH₃.

[168] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), or (I-D2), R⁷ is selected from C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰. In some embodiments, R⁷ is selected from C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰. In some embodiments, R⁷ is selected from C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocycloalkyl, and -N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocycloalkyl are optionally substituted with one, two, or three R²⁰. In some embodiments, R⁷ is 3- to 10-membered heterocycloalkyl optionally substituted with one, two, or three R²⁰, such as R⁷ is 4- to 6-membered heterocycloalkyl optionally substituted with one, two, or three R²⁰. In some embodiments, R⁷ is 3- to 10-membered heterocycloalkyl optionally substituted with one, two, or three R²⁰, 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, R⁷ is 3- to 6-membered heterocycloalkyl optionally substituted with one, two, or three R²⁰, wherein the heterocycloalkyl comprises S(O)₂. In some embodiments, R⁷ is C₃₋₁₀ cycloalkyl optionally substituted with one, two, or three R²⁰, such as R⁷ is C₃₋₆ cycloalkyl optionally substituted with one, two, or three R²⁰. In some embodiments, R⁷ is C₃₋₄ cycloalkyl optionally substituted with one R²⁰, optionally wherein R²⁰ is -CN. In some embodiments, R⁷ is C₁₋₆ alkyl optionally substituted with one, two, or three R²⁰, such as R⁷ is C₁₋₆ alkyl substituted

with one or two R^{20} . In some embodiments, R^7 is $-N(R^{12})(R^{13})$. In some embodiments, R^7 is $-OR^{12}$, such as $-O(3\text{- to }6\text{-membered heterocycloalkyl})$. In some embodiments, R^7 is substituted with at least one $-CN$. In some embodiments, R^7 is unsubstituted. In some embodiments, R^7 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^{20} . In some embodiments, R^7 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^7 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^7 is C_{3-4} cycloalkyl substituted with one, two, or three substituents selected from oxo, $-CN$, and C_{1-3} alkyl.

[169] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), or (I-D2), R^7 is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)(NR^{12})R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)(NR^{12})R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, 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^{20} . In some embodiments, R^7 is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)(NR^{12})R^{15}$, and $-SO_2N(R^{12})(R^{13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{20} . In some embodiments, R^7 is 3- to 6-membered heterocycloalkyl optionally substituted with one, two, or three R^{20} , wherein the heterocycloalkyl comprises $S(O)(NR^{12})$.

[170] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-



C3), (I-D), (I-D1), or (I-D2), R^7 is $(R^{20})_{n4}$, wherein:

$n1$ is an integer from 1 to 3;

$n2$ is an integer from 0 to 2;

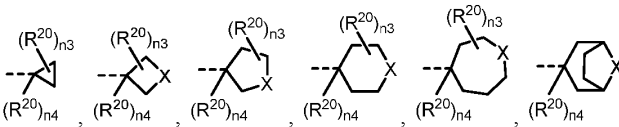
$n3$ is an integer from 0 to 2;

$n4$ is 0 or 1; and

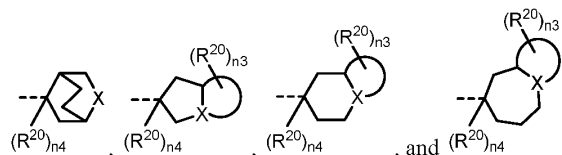
X is selected from $-O-$, $-S(O)_2-$, $-P(O)-$, $-CH_2-$, $-CH(OH)-$, $-CH(OR^{12})-$, $-CH(R^{20})-$, $-C(R^{20})_2-$, $-NR^{12}-$, $-CH(N(R^{12})(R^{13}))-$, $-CH(C(O)N(R^{12})(R^{13}))-$, and $-CH(S(O)_2N(R^{12})(R^{13}))-$,

wherein R^{12} , R^{13} , and R^{20} are as defined elsewhere herein, and

optionally wherein two R^{20} groups, or R^{20} and R^{12} , join together with the atom(s) to which they are attached to form a ring.



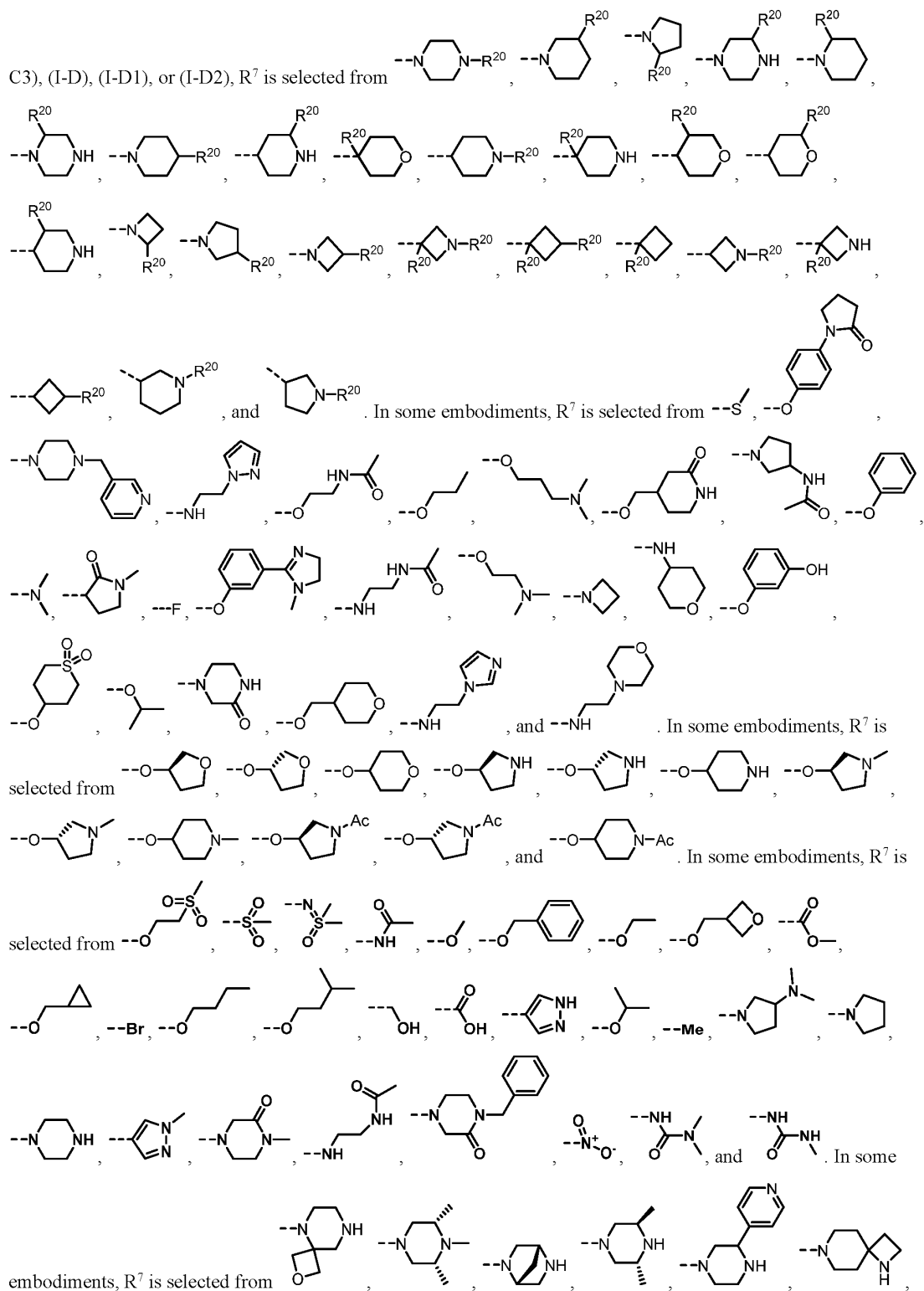
For example, R^7 may be selected from $(R^{20})_{n4}$, $(R^{20})_{n4}$, $(R^{20})_{n4}$, $(R^{20})_{n4}$, $(R^{20})_{n4}$, $(R^{20})_{n4}$,

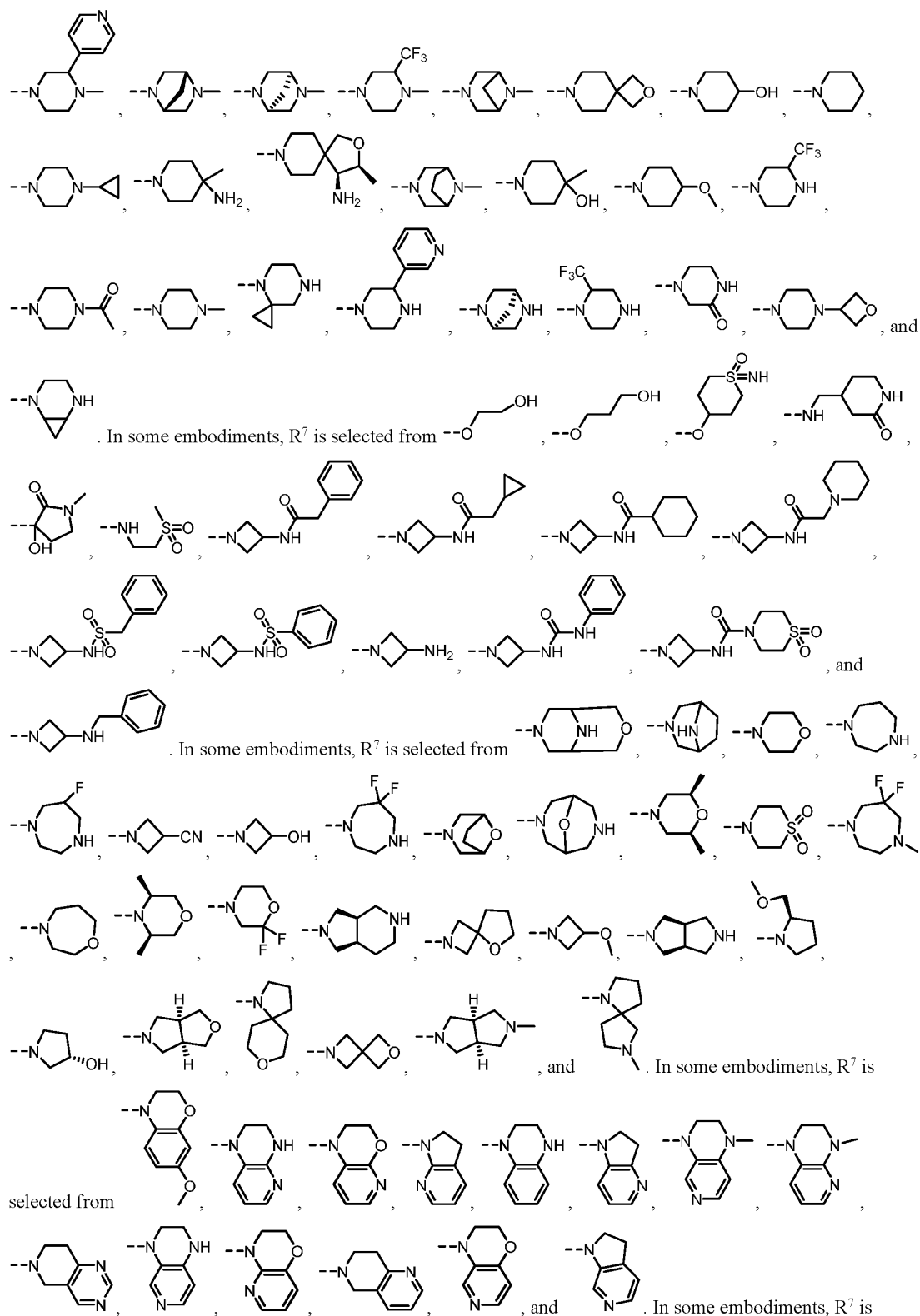


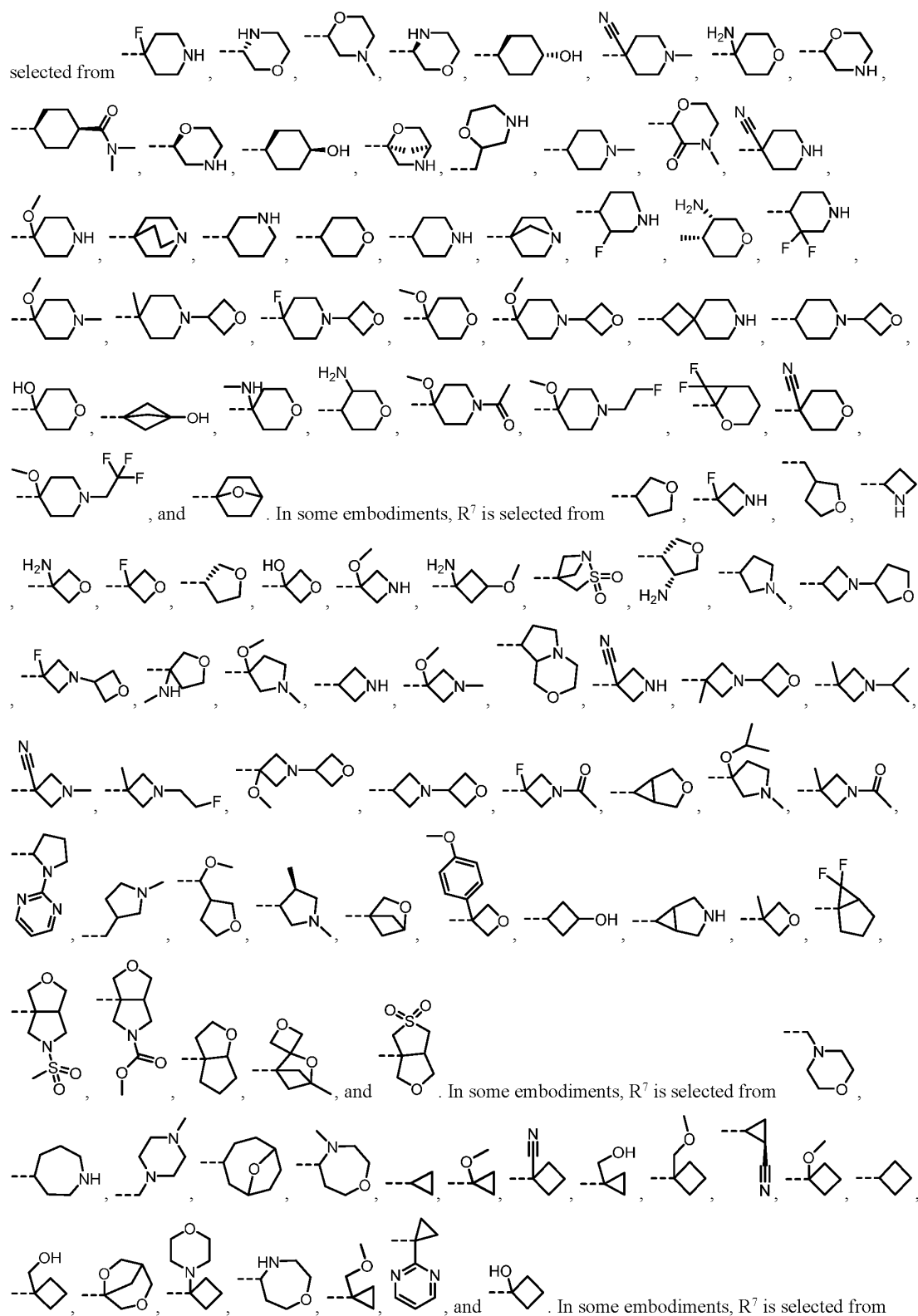
and $(R^{20})_{n4}$. In some embodiments, X is selected from $-O-$, $-S(O)_2-$, $-S(O)(NR^{12})-$, $-P(O)-$, $-CH_2-$, $-CH(OH)-$, $-CH(OR^{12})-$, $-CH(R^{20})-$, $-C(R^{20})_2-$, $-NR^{12}-$, $-CH(N(R^{12})(R^{13}))-$, -

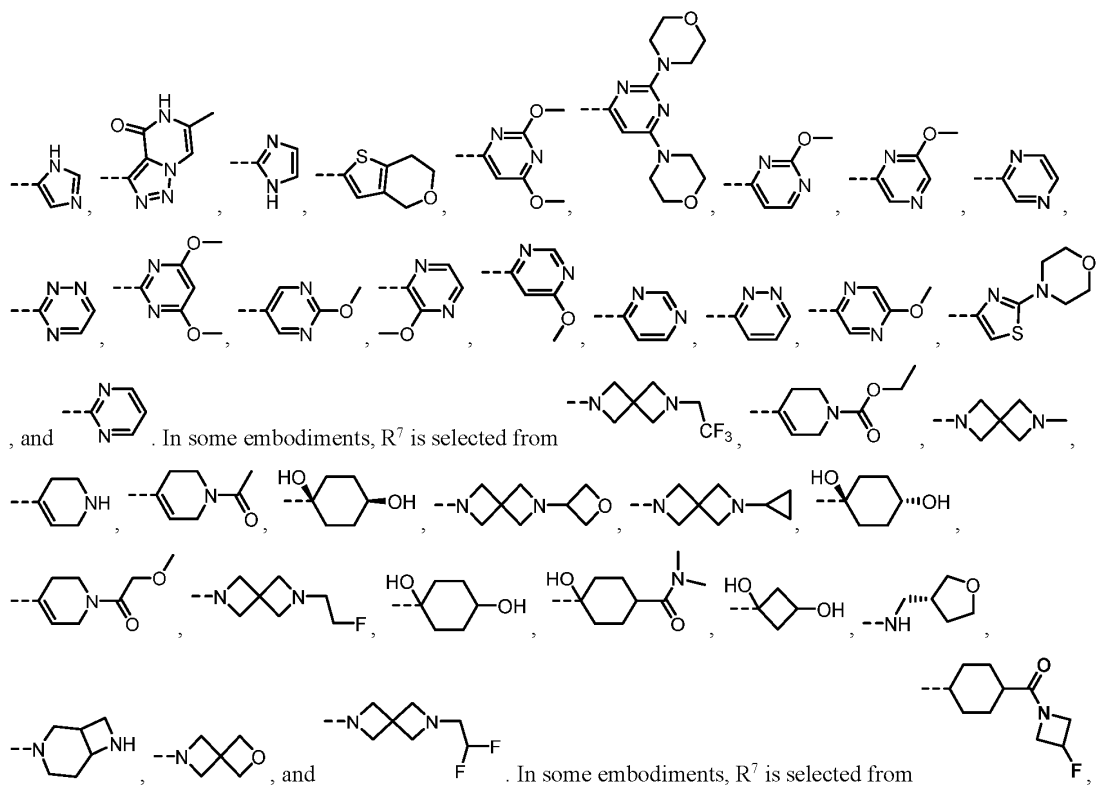
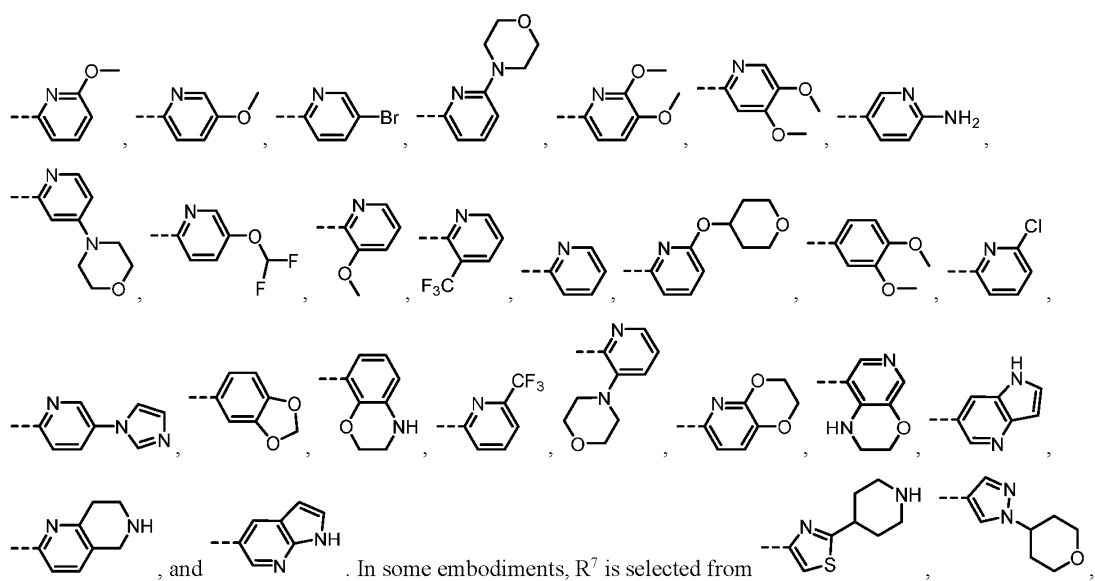
$\text{CH}(\text{C}(\text{O})\text{N}(\text{R}^{12})(\text{R}^{13}))$ -, and $-\text{CH}(\text{S}(\text{O})_2\text{N}(\text{R}^{12})(\text{R}^{13}))$ -.

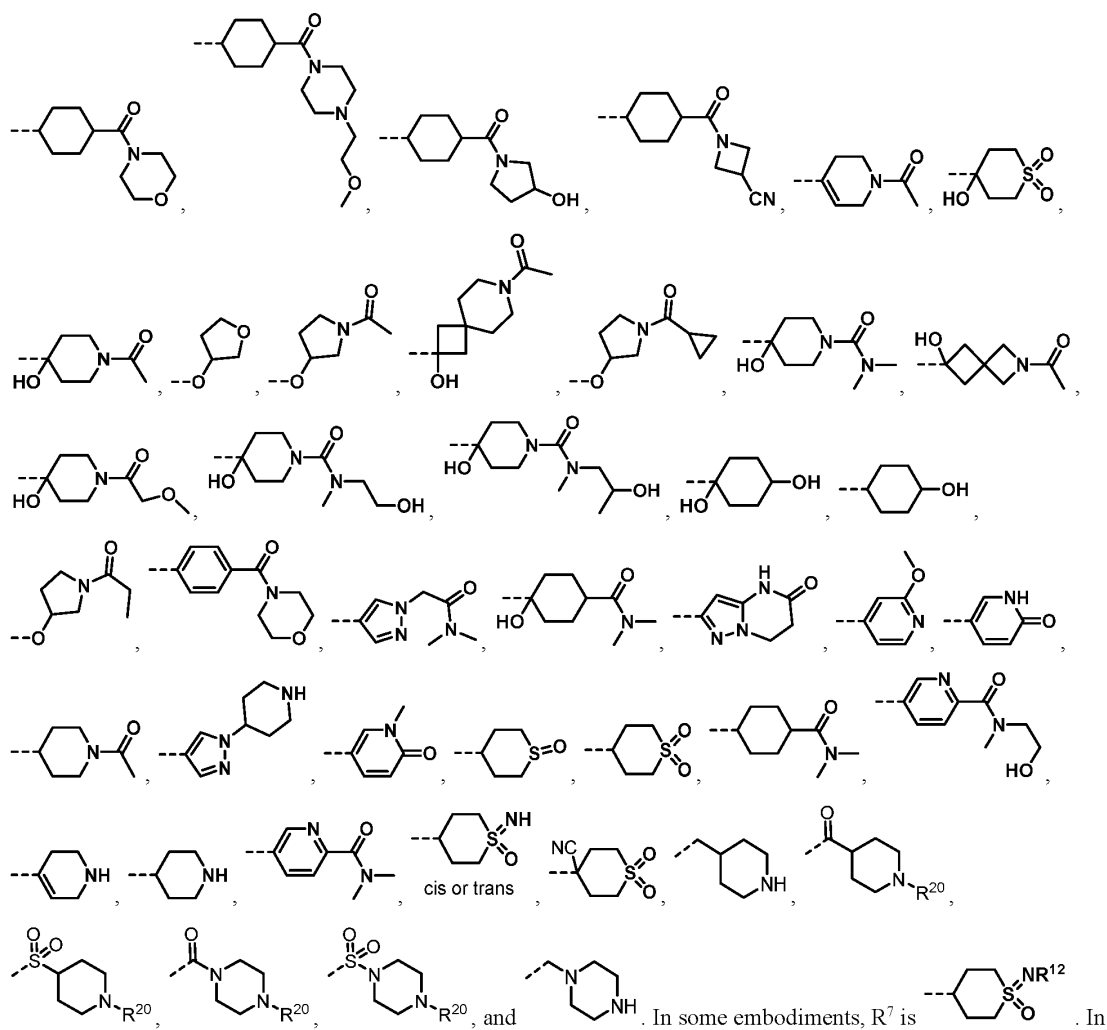
[171] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-



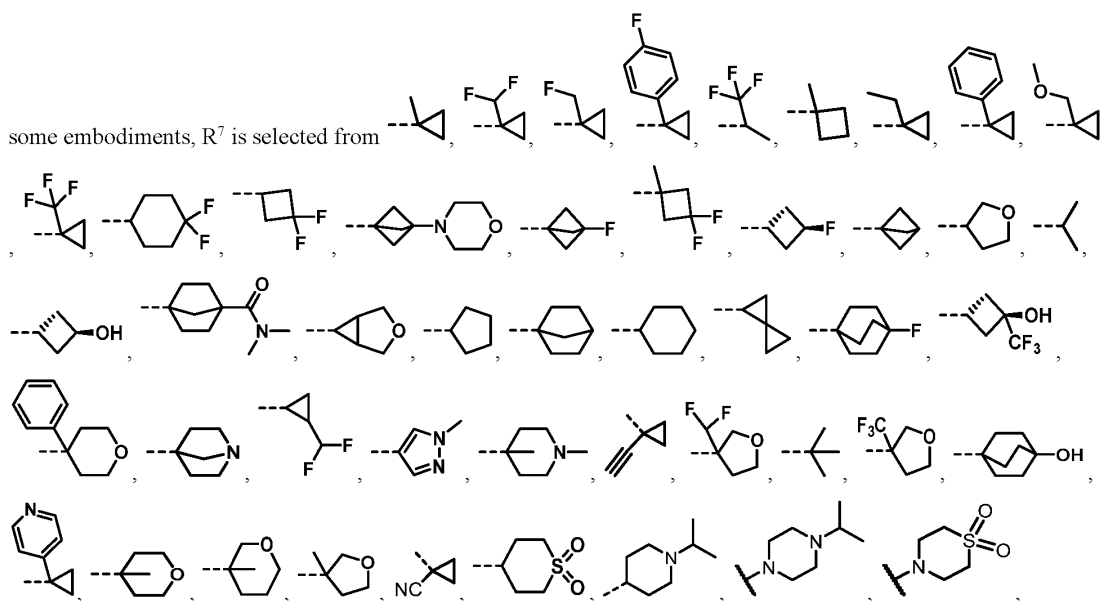


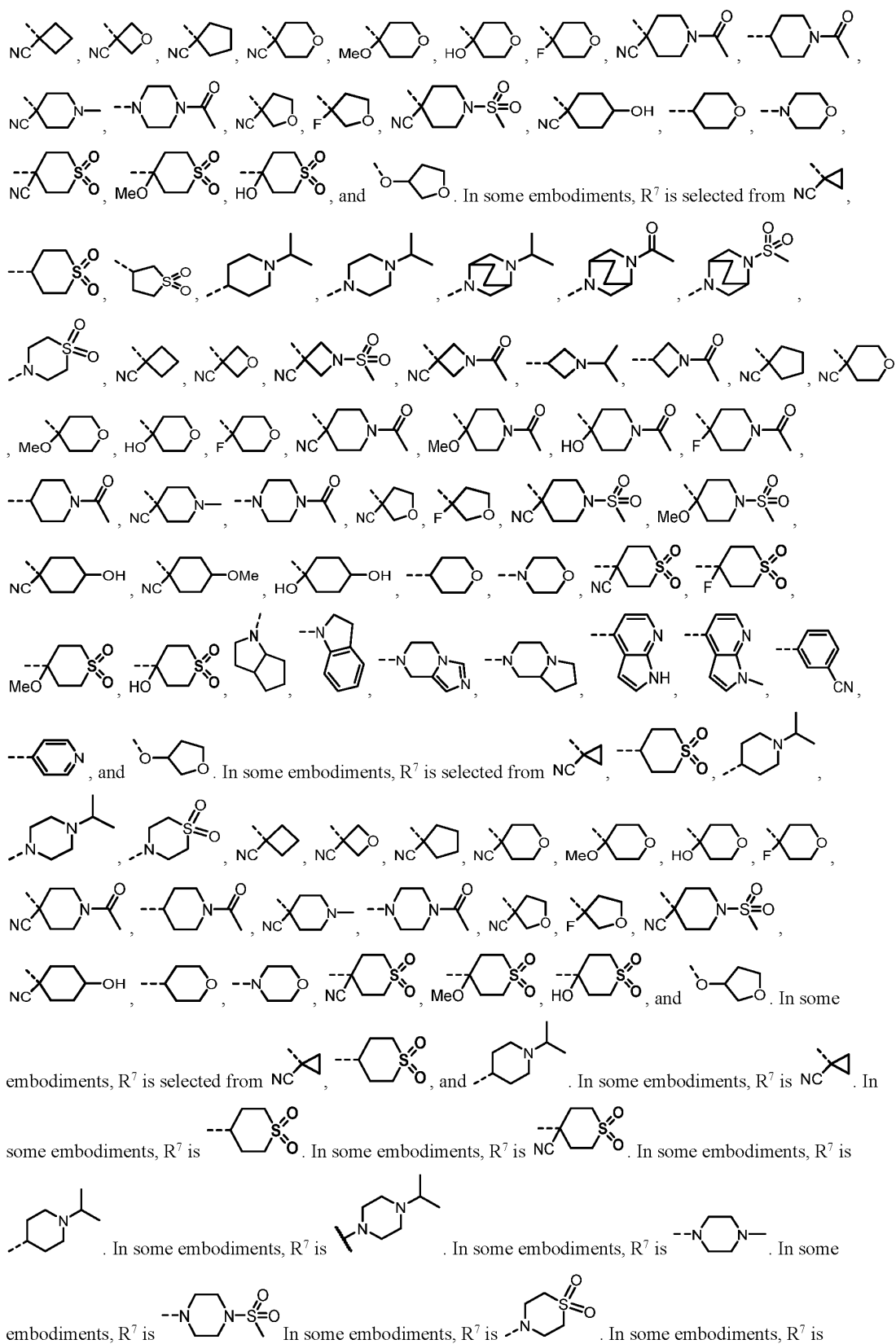


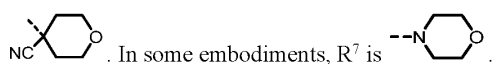




some embodiments, R^7 is selected from







[172] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1), R⁸ is selected from hydrogen, halogen, and C₁₋₆ alkyl optionally substituted with one, two, or three R²⁰. In some embodiments, R⁸ is hydrogen.

[173] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-

C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1),  is selected from C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, such as C₅₋₇ carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with

one or more R¹¹. In some embodiments,  is selected from C₅₋₇ cycloalkyl, 5- to 7-membered heterocycloalkyl, 5- to 7-membered heteroaryl, and phenyl, each of which is optionally substituted with one or more

R¹¹. In some embodiments,  is selected from phenyl, pyridyl, and thiophenyl, each of which is optionally

substituted with one or more R¹¹. In some embodiments,  is selected from , , ,

, and , such as , , , and . In some embodiments, R¹¹, when

present, is independently selected at each occurrence from fluorine and -CH₃. In some embodiments,  is

selected from  and , such as  and . In some embodiments,  is

, In some embodiments,  is . In some embodiments,  is .

[174] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1), L¹ is selected from C₁₋₆ alkylene and C₁₋₆ haloalkylene, such as C₁₋₃ alkylene and C₁₋₃ haloalkylene. In some embodiments, L¹ is selected from a bond and C₁₋₃ haloalkylene. In some embodiments, L¹ is C₁₋₃ haloalkylene, such as -CF₂-, -CF₂CH₂-, or -CF₂CH₂CH₂-. In some embodiments, L¹ is C₁₋₂ haloalkylene, such as -CF₂- or -CF₂CH₂-. In some embodiments, L¹ is -CF₂-. In some embodiments, L¹ is -CF₂CH₂-. In some embodiments, L¹ is -CF₂CH₂CH₂-. In some embodiments, L¹ is a bond. In some embodiments, L¹ is selected from a bond, -O-, -NR¹²-, -S-, C₁₋₆ alkylene, C₁₋₆ haloalkylene, and 2- to 6-membered heteroalkylene, wherein C₁₋₆ alkylene, C₁₋₆ haloalkylene, and 2- to 6-membered heteroalkylene are optionally substituted with one or more R^{11b}. In some embodiments, L¹ is selected from -O-, -NR¹²-, -S-, and 2- to 6-membered heteroalkylene, wherein 2- to 6-membered heteroalkylene is optionally substituted with one or more R^{11b}. In some embodiments, L¹ is C₁₋₆ alkylene optionally substituted with one or more R^{11b}, such as one, two, or three R^{11b}. In some embodiments, L¹ is selected from a bond, -O-, -NR¹²-, -S-, C₁₋₃ alkylene, C₁₋₃ haloalkylene, and 2- to 3-membered heteroalkylene, wherein C₁₋₃ alkylene, C₁₋₃ haloalkylene, and 2- to 3-membered heteroalkylene are optionally substituted with one or

more R^{11b} . In some embodiments, L^1 is selected from -O-, -NR¹²-, -S-, and 2- to 3-membered heteroalkylene, wherein 2- to 3-membered heteroalkylene is optionally substituted with one or more R^{11b} . In some embodiments, L^1 is C₁₋₃ alkylene substituted with one or more R^{11b} , such as one, two, or three R^{11b} .

[175] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-

C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1),  is absent or selected from C₄₋₈ carbocycle and 4- to 8-membered

heterocycle, each of which is optionally substituted with one or more R^{11a} . 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^{11a} . In some embodiments,  is selected from phenyl and 4- to 8-membered heterocycle, each of which is

optionally substituted with one or more R^{11a} . In some embodiments,  is absent or selected from phenyl, azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more R^{11a} . In some

embodiments,  is selected from phenyl, azetidine, pyrrolidine, and piperidine, each of which is optionally

substituted with one or more R^{11a} . In some embodiments,  is selected from azetidine, pyrrolidine, and

piperidine, each of which is optionally substituted with one or more -CH₃. In some embodiments,  is

phenyl, optionally substituted with one or more R^{11a} . In some embodiments,  is , optionally

substituted with one or more R^{11a} . In some embodiments,  is . In some embodiments,  is

azetidine, optionally substituted with one or more R^{11a} . In some embodiments,  is , optionally

substituted with one or more R^{11a} . In some embodiments,  is . In some embodiments,  is

pyrrolidine, optionally substituted with one or more R^{11a} . In some embodiments,  is piperidine, optionally

substituted with one or more R^{11a} . In some embodiments,  is , optionally substituted with one or

more R^{11a} . In some embodiments,  is . In some embodiments,  is unsubstituted. In some



embodiments, B is substituted with one or more R^{11a} , such as one, two or three R^{11a} . In some embodiments, R^{11a} is independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{3-6} carbocycle, 3- to 6-membered heterocycle, -OR¹², -N(R¹²)(R¹³), -N(R¹⁴)S(O)₂R¹⁵, -C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, and -S(O)₂N(R¹²)(R¹³), wherein C_{1-6} alkyl, C_{3-6} carbocycle, and 3- to 6-membered heterocycle are optionally substituted with one, two, or three R^{20} . In some embodiments, R^{11a} is independently selected at each occurrence from halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments, R^{11a} is independently selected at each occurrence from C_{1-6} alkyl. In some embodiments, R^{11a} is -CH₃.

[176] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1), L^2 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^{11b} . In some embodiments, L^2 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^{11b} . In some embodiments, L^2 , 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^2 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^{11b} . In some embodiments, L^2 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^{11b} . In some embodiments, an alkylene or heteroalkylene of L^2 comprises one carbon-carbon double bond. In some embodiments, a heteroalkylene or heteroalkenylene of L^2 comprises at least one oxygen or nitrogen atom. In some embodiments, a heteroalkylene or heteroalkenylene of L^2 comprises at least one basic nitrogen. In some embodiments, L^2 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^{11b} . In some embodiments, L^2 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^{11b} . In some embodiments, L^2 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^{11b} . In some embodiments, L^2 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^{11b} . In some embodiments, L^2 is selected from C_{6-8} alkylene and C_{6-8} alkenylene, each of which is optionally substituted with one or more R^{11b} . In some embodiments, L^2 is selected from C_6 alkylene and C_6 alkenylene, each of which is optionally substituted with one or more R^{11b} . In some embodiments, L^2 is selected from C_7 alkylene and C_7 alkenylene, each of which is optionally substituted with one or more R^{11b} . In some embodiments, L^2 is selected from C_8 alkylene and C_8 alkenylene, each of which is optionally substituted with one or more R^{11b} . In some embodiments, L^2 is -CH₂CHCH(CH₂)₄-. In some embodiments, L^2 is 6- to 8-membered heteroalkylene, optionally substituted with one or more R^{11b} . In some embodiments, L^2 is 6-membered heteroalkylene, optionally substituted with one or more R^{11b} . In some embodiments, L^2 is 7-membered heteroalkylene, optionally substituted with one or more R^{11b} . In some embodiments, L^2 is 8-membered heteroalkylene, optionally substituted with one or more R^{11b} . In some embodiments, L^2 is 8-membered heteroalkylene, wherein the heteroalkylene comprises one oxygen atom. In some embodiments, L^2 is -(CH₂)₂₋₅O(CH₂)₀₋₅-, such as L^2 is -(CH₂)₂₋₅O(CH₂)₂₋₅-. In some embodiments, L^2 is -(CH₂)₄O(CH₂)₃-. In some embodiments, R^{11b} 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^{11b} is independently selected at each

occurrence from -F, =O, -CH₃, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂OH, and -OH. In some embodiments, R^{11b} is independently selected at each occurrence from -CH₃, -CH₂OH, -CH₂F, -CHF₂, and -CF₃, or two R^{11b} join to form =O or C₃₋₆ cycloalkyl, such as cyclopropyl. In some embodiments, R^{11b} is independently selected at each occurrence from -CH₃, -CH₂OH, -CH₂F, -CHF₂, and -CF₃, or two R^{11b} join to form C₃₋₆ cycloalkyl, such as cyclopropyl. In some embodiments, R^{11b} is independently selected at each occurrence from -CH₃, -F, -CN, and -OH. In some embodiments, L² comprises -C(O)N(R¹⁴)- or -N(R¹⁴)C(O)-. In some embodiments, L² comprises -O-. In some embodiments, L² is substituted with at least one -CH₃, -CH₂OH, -CH₂F, -CHF₂, or -CF₃, or two substituents join to form cyclopropyl. In some embodiments, L² is substituted with at least one -CH₃, -F, -CN, or -OH. In some embodiments, L² is unsubstituted.

[177] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1), L² is -(C₁₋₅ alkylene)-C(O)N(R¹⁴)-(C₁₋₅ alkylene)-, such as -(C₁₋₅ alkylene)-C(O)N(CH₃)-(C₁₋₅ alkylene)- or -(C₁₋₅ alkylene)-C(O)NH-(C₁₋₅ alkylene)-, wherein C₁₋₅ alkylene is optionally substituted with one or more R^{11b}. In some embodiments, L² is -(C₁₋₂ alkylene)-C(O)N(R¹⁴)-(C₃₋₄ alkylene)-, such as -(C₁₋₂ alkylene)-C(O)N(CH₃)-(C₃₋₄ alkylene)- or -(C₁₋₂ alkylene)-C(O)NH-(C₃₋₄ alkylene)-, wherein C₁₋₂ alkylene and C₃₋₄ alkylene are each independently optionally substituted with one or more R^{11b}. In some embodiments, R^{11b} is independently selected at each occurrence from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ alkyl)-OH, and -OH. In some embodiments, R^{11b} is independently selected at each occurrence from -F, -CH₃, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂OH, and -OH. In some embodiments, R^{11b} is independently selected at each occurrence from -CH₃, -CH₂OH, -CH₂F, -CHF₂, and -CF₃, or two R^{11b} join to form C₃₋₆ cycloalkyl, such as cyclopropyl. In some embodiments, R^{11b} is independently selected at each occurrence from -CH₃, -F, -CN, and -OH. In some embodiments, L² is substituted with at least one -CH₃, -F, -CN, or -OH.

[178] In some embodiments, L² is selected from -C(R^{11b})(R^{11b})-(C₃₋₁₀ alkylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(C₃₋₁₀ alkylene)-C(R^{11b})(R^{11b})-, -CH₂-(C₃₋₁₀ alkylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(C₃₋₁₀ alkylene)-CH(R^{11b})-, -CH₂-(C₃₋₁₀ alkylene)-CH(R^{11b})-, -C(R^{11b})(R^{11b})-(C₃₋₁₀ alkenylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(C₃₋₁₀ alkenylene)-C(R^{11b})(R^{11b})-, -CH₂-(C₃₋₁₀ alkenylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(C₃₋₁₀ alkenylene)-CH(R^{11b})-, -CH₂-(C₃₋₁₀ alkenylene)-CH(R^{11b})-, -C(R^{11b})(R^{11b})-(3- to 10-membered heteroalkylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(3- to 10-membered heteroalkylene)-C(R^{11b})(R^{11b})-, -CH₂-(3- to 10-membered heteroalkylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(3- to 10-membered heteroalkylene)-CH(R^{11b})-, -CH₂-(3- to 10-membered heteroalkylene)-CH(R^{11b})-, -C(R^{11b})(R^{11b})-(3- to 10-membered heteroalkenylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(3- to 10-membered heteroalkenylene)-C(R^{11b})(R^{11b})-, -CH₂-(3- to 10-membered heteroalkenylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(3- to 10-membered heteroalkenylene)-CH(R^{11b})-, and -CH₂-(3- to 10-membered heteroalkenylene)-CH(R^{11b})-. In some embodiments, L² is selected from -C(R^{11b})(R^{11b})-(C₃₋₁₀ alkylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(C₃₋₁₀ alkylene)-C(R^{11b})(R^{11b})-, -CH₂-(C₃₋₁₀ alkylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(C₃₋₁₀ alkylene)-CH(R^{11b})-, and -CH₂-(C₃₋₁₀ alkylene)-CH(R^{11b})-. In some embodiments, L² is selected from -C(R^{11b})(R^{11b})-(C₃₋₁₀ alkenylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(C₃₋₁₀ alkenylene)-C(R^{11b})(R^{11b})-, -CH₂-(C₃₋₁₀ alkenylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(C₃₋₁₀ alkenylene)-CH(R^{11b})-, and -CH₂-(C₃₋₁₀ alkenylene)-CH(R^{11b})-. In some embodiments, L² is selected from -C(R^{11b})(R^{11b})-(3- to 10-membered heteroalkylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(3- to 10-membered heteroalkylene)-C(R^{11b})(R^{11b})-, -CH₂-(3- to 10-membered heteroalkylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(3- to 10-membered heteroalkylene)-CH(R^{11b})-, and -CH₂-(3- to 10-membered heteroalkylene)-CH(R^{11b})-. In some embodiments, L² is selected from -C(R^{11b})(R^{11b})-(3- to 10-membered heteroalkenylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(3- to 10-membered heteroalkenylene)-C(R^{11b})(R^{11b})-, -CH₂-(3- to 10-membered heteroalkenylene)-C(R^{11b})(R^{11b})-, -CH(R^{11b})-(3- to 10-membered heteroalkenylene)-CH(R^{11b})-, and -CH₂-(3- to 10-membered heteroalkenylene)-CH(R^{11b})-.

heteroalkenylene)-CH(R^{11b})-. Any C₃₋₁₀ alkylene, C₃₋₁₀ alkenylene, 3- to 10-membered heteroalkylene, or 3- to 10-membered heteroalkenylene in this paragraph may optionally be substituted with one or more R^{11b}. In some embodiments, R^{11b} is independently selected at each occurrence from halogen, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ alkyl)-OH, and -OH. In some embodiments, R^{11b} is independently selected at each occurrence from -F, -CH₃, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂OH, and -OH. In some embodiments, R^{11b} is independently selected at each occurrence from -CH₃, -CH₂OH, -CH₂F, -CHF₂, and -CF₃, or two R^{11b} join to form =O or C₃₋₆ cycloalkyl, such as cyclopropyl.

[179] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1), L² is -L³-D-L⁴-, wherein L³ is selected from C₁₋₁₀ alkylene, C₂₋₁₀ alkenylene, C₂₋₁₀ alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}; D is absent or selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{11d}; and L⁴ is selected from C₁₋₁₀ alkylene, C₂₋₁₀ alkenylene, C₂₋₁₀ alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}. 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 C₂₋₁₀ alkenylene, C₂₋₁₀ alkynylene, C₂₋₈ alkenylene, C₂₋₈ alkynylene, C₅₋₂₅ alkenylene, C₅₋₂₅ alkynylene, C₆₋₁₅ alkenylene, C₆₋₁₅ alkynylene, C₅₋₁₀ alkenylene, and C₅₋₁₀ 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, L² is -L³-D-L⁴-, wherein L³ is selected from C₁₋₁₀ alkylene, C₂₋₁₀ alkenylene, C₂₋₁₀ alkynylene, 2- to 10-membered heteroalkylene, and 3- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}; D is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{11d}; and L⁴ is absent. In some embodiments, L² is -L³-D-L⁴-, wherein L³ is selected from C₁₋₈ alkylene, C₂₋₈ alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}; D is absent or selected from C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{11d}; and L⁴ is selected from C₁₋₈ alkylene, C₂₋₈ alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}. In some embodiments, L² is -L³-D-L⁴-, wherein L³ is selected from C₁₋₈ alkylene, C₂₋₈ alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}; D is selected from C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{11d}; and L⁴ is selected from C₁₋₈ alkylene, C₂₋₈ alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}. In some embodiments, R^{11b} is independently selected at each occurrence from halogen, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ alkyl)-OH, and -OH. In some embodiments, R^{11b} is independently selected at each occurrence from -F, -CH₃, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂OH, and -OH. In some embodiments, R^{11b} is independently selected at each occurrence from -CH₃, -CH₂OH, -CH₂F, -CHF₂, and -CF₃, or two R^{11b} join to form =O or C₃₋₆ 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^{11d}, such as one, two, or three R^{11d}.

[180] In some embodiments, for a compound of Formula (I), L^2 is covalently bound to one of W^3 , W^4 , W^5 , W^6 , or W^7 ; or L^2 is $-L^3-D-L^4-$, wherein L^4 is covalently bound to one of W^3 , W^4 , W^5 , W^6 , or W^7 . For example, L^2 may be covalently bound to W^3 —wherein R^{3b} or R^3 is a bond to L^2 —as depicted in Formula (I-A). In some embodiments, L^2 is covalently bound to W^4 —wherein R^{4b} or R^4 is a bond to L^2 —as depicted in Formula (I-B). In some embodiments, L^2 is covalently bound to W^5 —wherein R^{5b} or R^5 is a bond to L^2 —as depicted in Formula (I-C). In some embodiments, L^2 is covalently bound to W^6 —wherein R^{6b} or R^6 is a bond to L^2 —as depicted in Formula (I-D). In some embodiments, L^2 is covalently bound to W^7 —wherein R^{7b} or R^7 is a bond to L^2 —as depicted in Formula (I-E).

[181] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-I), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1):

R^{20} 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, $-CH_2-(C_{3-10} \text{ carbocycle})$, 3- to 10-membered heterocycle, $-CH_2-(3\text{- to } 10\text{-membered heterocycle})$, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10} \text{ carbocycle})$, 3- to 10-membered heterocycle, and $-CH_2-(3\text{- to } 10\text{-membered heterocycle})$ 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.

[182] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-I), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1), R^{20} is independently selected at each occurrence from halogen, oxo, $=NR^{22}$, $-CN$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10} \text{ carbocycle})$, 3- to 10-membered heterocycle, $-CH_2-(3\text{- to } 10\text{-membered heterocycle})$, $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, and $-OC(O)R^{25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, $-CH_2-(C_{3-10} \text{ carbocycle})$, 3- to 10-membered heterocycle, and $-CH_2-(3\text{- to } 10\text{-membered heterocycle})$ are optionally substituted with one, two, or three groups independently selected from halogen, oxo, $=NR^{22}$, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -

OR²¹, -SR²¹, and -N(R²²)(R²³).

[183] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-1), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1), R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, -NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OH, -OCH₃, -OCH₂CH₃, -NH₂, -NHCH₃, and -NHCH₂CH₃, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, -NO₂, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -C(CH₃)₃, -OH, -OCH₃, -OCH₂CH₃, -NH₂, -NHCH₃, and -NHCH₂CH₃.

[184] In some embodiments, for a compound of Formula (I-B1), R^{5b} is -CH₃; R⁷ is selected from C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰; and R⁸ is hydrogen. In some embodiments, for a compound of Formula (I-B2), R⁵ is hydrogen; R⁶ is selected from hydrogen and -OCH₃; R⁷ is selected from C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰; and R⁸ is hydrogen.

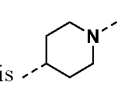
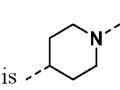
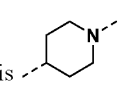
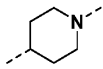
[185] In some embodiments, for a compound of Formula (I-C1), R³ is hydrogen or -CH₃; R⁷ is selected from C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰; and R⁸ is hydrogen. In some embodiments, for a compound of Formula (I-C2), R^{3b} is -CH₃; R⁷ is selected from C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰; and R⁸ is hydrogen. In some embodiments, for a compound of Formula (I-C3), R³ is hydrogen or -CH₃; R⁶ is selected from hydrogen and -OCH₃; R⁷ is selected from C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰; and R⁸ is hydrogen.

[186] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-

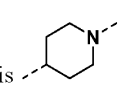
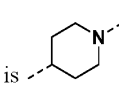
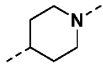
C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1): R¹ is -CH₃;  is selected from phenyl and 5- to 7-membered heteroaryl, each of which is optionally substituted with one or more R¹¹; L¹ is selected from a bond and C₁₋₃

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^{11a}; and L² is selected from C₅₋₁₀ alkylene, C₅₋₁₀ alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}. In some embodiments, R¹¹, when present, is fluorine; R^{11a}, when present, is -CH₃; and R^{11b}, when present, is selected from halogen, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ alkyl)-OH, and -OH.

[187] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-

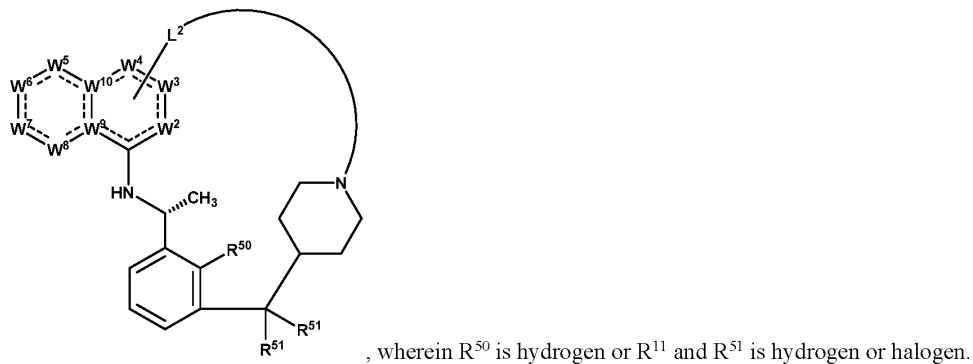
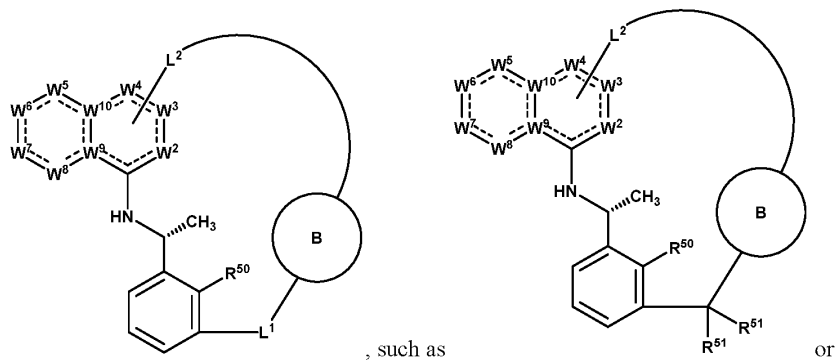
C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1): R¹ is -CH₃;  is selected from  and ; L¹ is C₁₋₂ haloalkylene;  is , optionally substituted with one or more R^{11a}; and L² is selected from C₆₋₈ alkylene, C₆₋₈ alkenylene, and 6- to 8-membered heteroalkylene, each of which is optionally substituted with one or more R^{11b}. In some embodiments, R¹ is -CH₃;  is ; L¹ is C₁₋₂ haloalkylene;  is ; and L² is 6- to 8-membered heteroalkylene, optionally substituted with one or more R^{11b}. In some embodiments, R¹ is -CH₃;  is selected from  and ; L¹ is C₁₋₂ haloalkylene;  is , optionally substituted with one or more R^{11a}; and L² is selected from C₆₋₈ alkylene and C₆₋₈ alkenylene, each of which is optionally substituted with one or more R^{11b}. In some embodiments, R¹ is -CH₃;  is ; L¹ is C₁₋₂ haloalkylene;  is ; and L² is C₆₋₈ alkenylene, optionally substituted with one or more R^{11b}. In some embodiments, R¹ is -CH₃;  is selected from  and ; L¹ is C₁₋₂ haloalkylene;  is , optionally substituted with one or more R^{11a}; and L² is -(C₁₋₂ alkylene)-C(O)N(CH₃)-(C₃₋₄ alkylene)- or -(C₁₋₂ alkylene)-C(O)NH-(C₃₋₄ alkylene)-, wherein C₁₋₂ alkylene and C₃₋₄ alkylene are each independently optionally substituted with one or more R^{11b}. In some embodiments, R^{11a}, when present, is -CH₃; and R^{11b}, when present, is selected from halogen, -CN, oxo, C₁₋₃ alkyl, C₁₋₃ haloalkyl, (C₁₋₃ alkyl)-OH, and -OH.

[188] In some embodiments, for a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-

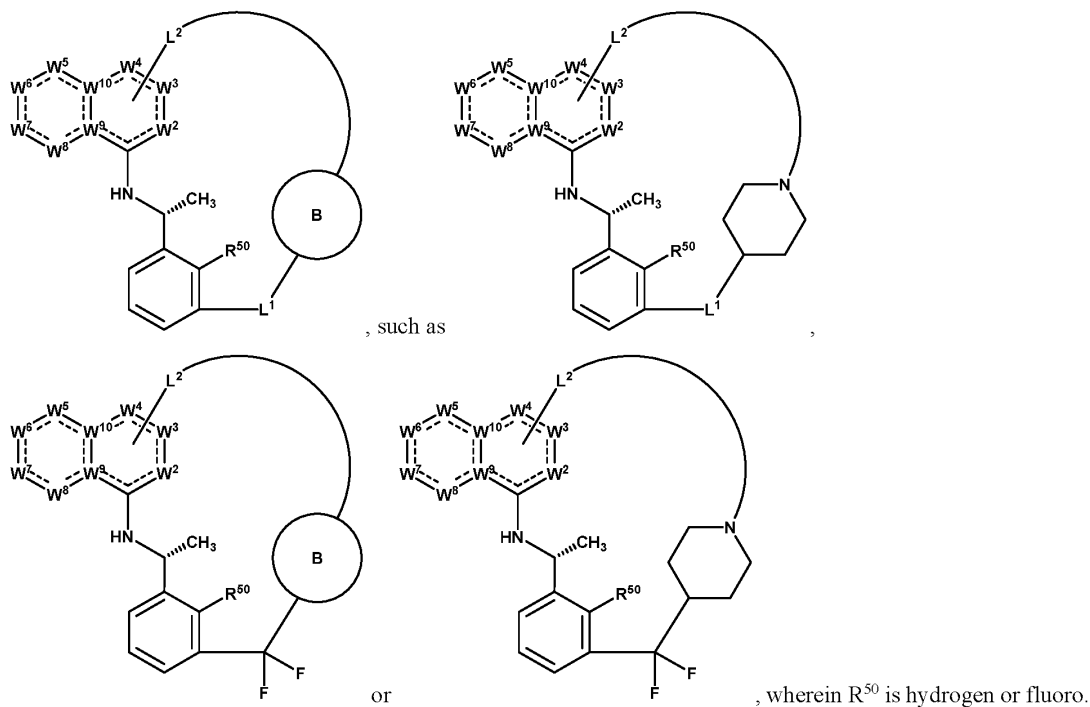
C3), (I-D), (I-D1), (I-D2), (I-E), or (I-E1): R¹ is -CH₃;  is selected from  and ; L¹ is C₁₋₂ haloalkylene;  is ; and L² is selected from C₆₋₈ alkylene, C₆₋₈ alkenylene, and 6- to 8-membered heteroalkylene, each of which is optionally substituted with one or more R^{11b}. In some embodiments, R¹ is -CH₃;  is selected from  and ; L¹ is C₁₋₂ haloalkylene;  is ; and L² is selected from C₆₋₈ alkylene and C₆₋₈ alkenylene, each of which is optionally substituted with one or more R^{11b}. In some embodiments, R¹ is -CH₃;  is selected from  and ; L¹ is C₁₋₂ haloalkylene;  is ; and L² is -(C₁₋₂ alkylene)-C(O)N(CH₃)-(C₃₋₄ alkylene)- or -(C₁₋₂ alkylene)-C(O)NH-(C₃₋₄ alkylene)-,

wherein C₁₋₂ alkylene and C₃₋₄ alkylene are each independently optionally substituted with one or more R^{11b}. In some embodiments, R^{11b}, when present, is selected from halogen, -CN, oxo, C₁₋₃ alkyl, C₁₋₃ haloalkyl, (C₁₋₃ alkyl)-OH, and -OH.

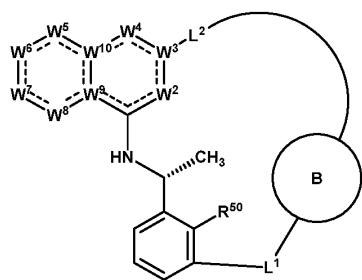
[189] In some embodiments, a compound of Formula (I) is a compound of the formula:



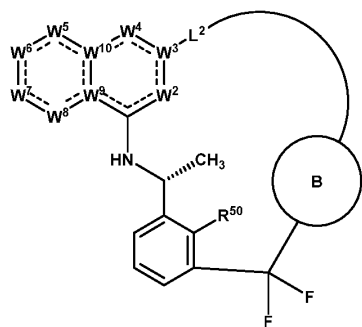
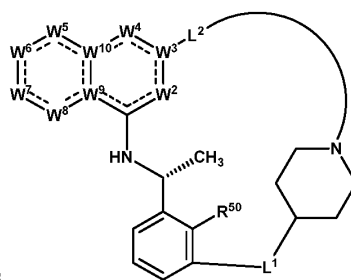
[190] In some embodiments, a compound of Formula (I) is a compound of the formula:



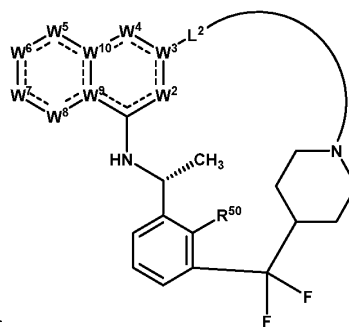
In some embodiments, a compound of Formula (I-A) is a compound of the formula:



, such as

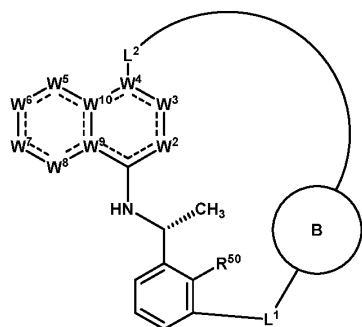


or

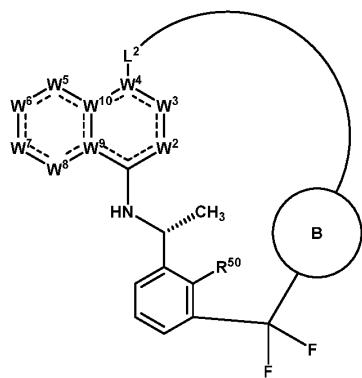
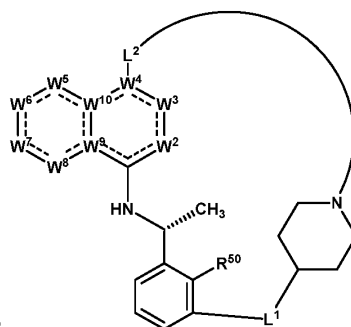


, wherein R⁵⁰ is hydrogen or fluoro.

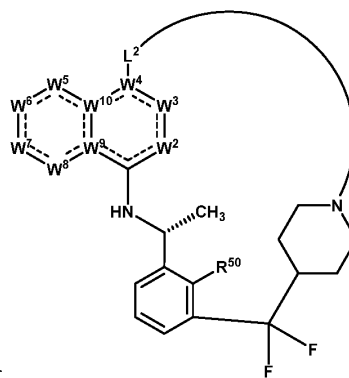
In some embodiments, a compound of Formula (I-B) is a compound of the formula:



, such as

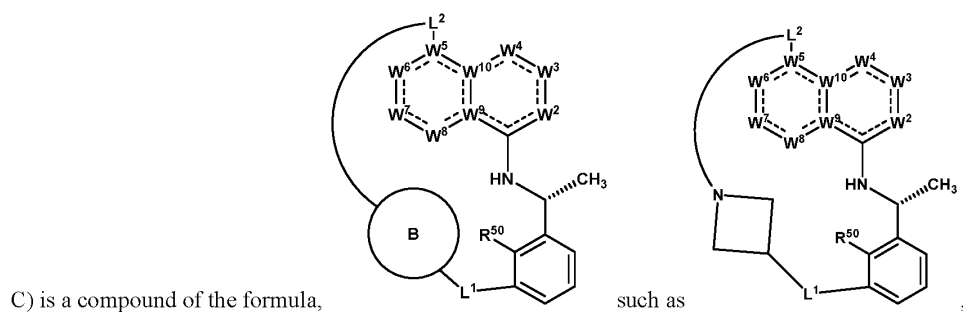
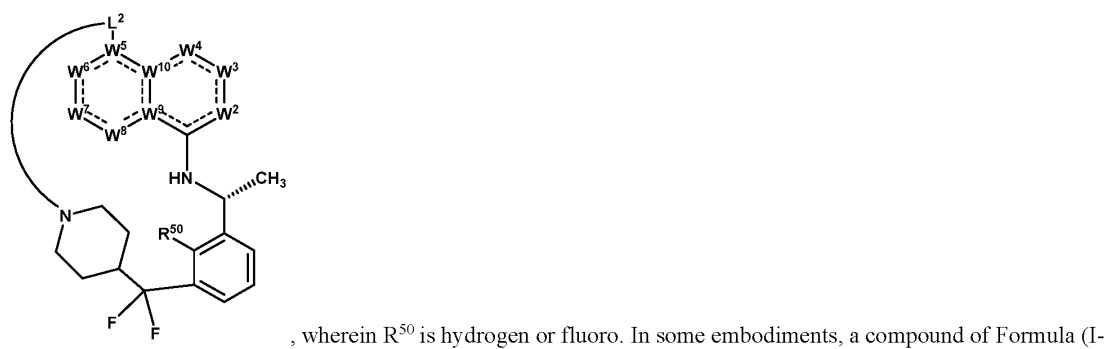
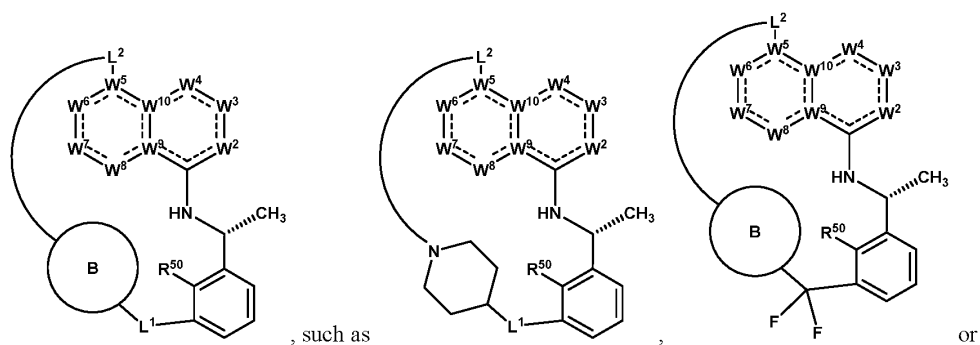


or

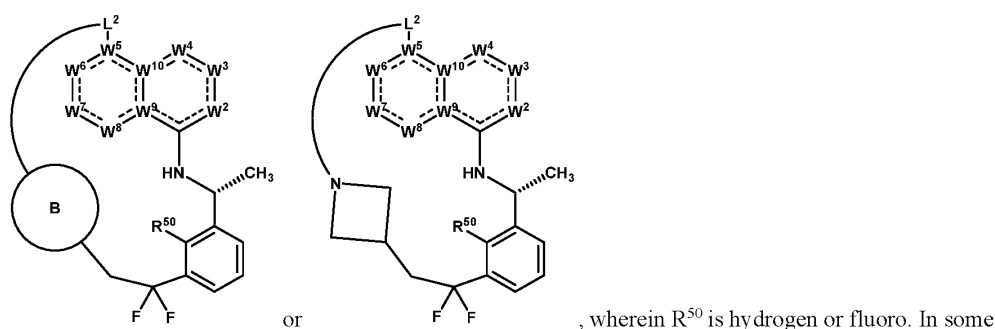


, wherein R⁵⁰ is hydrogen or fluoro.

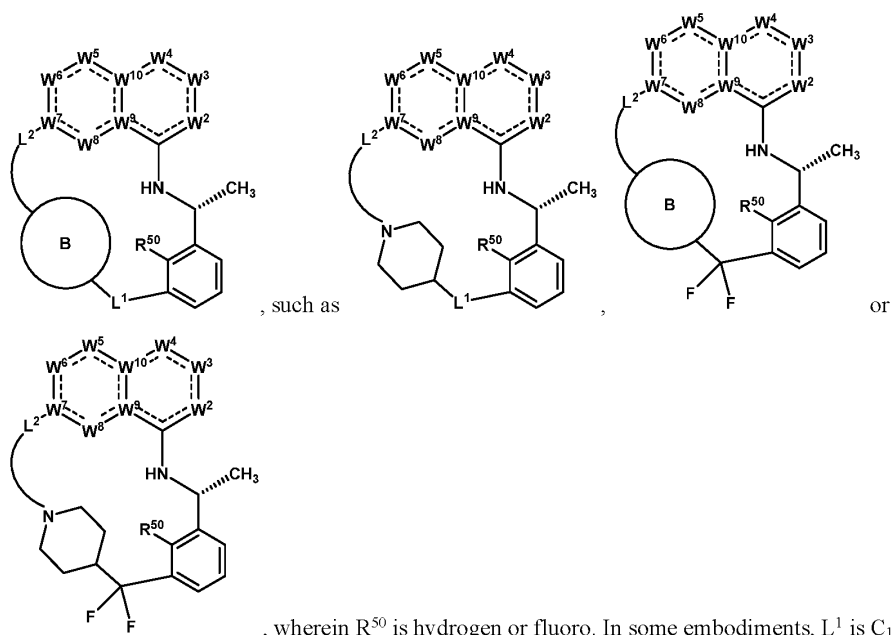
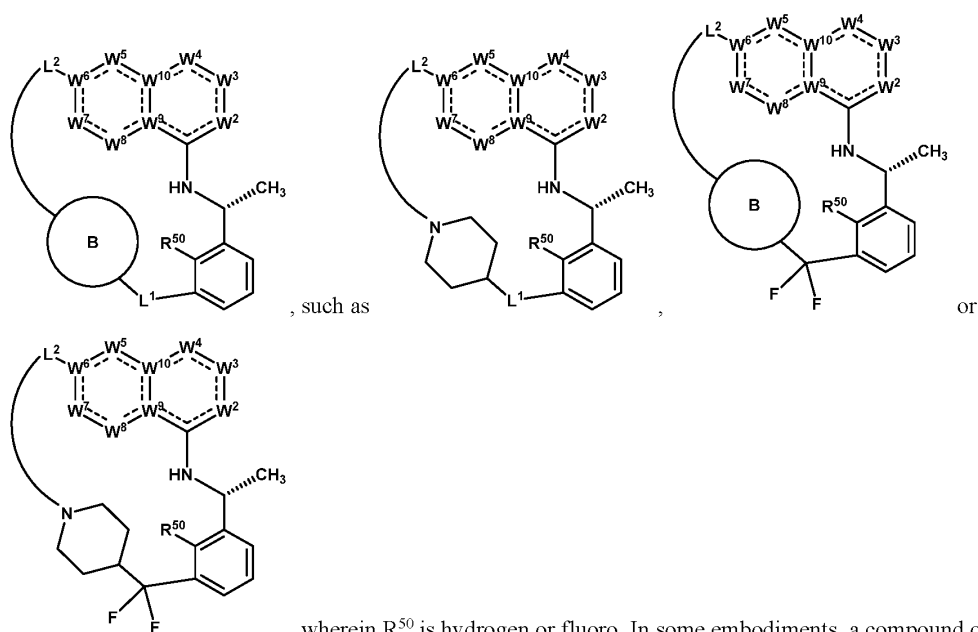
In some embodiments, a compound of Formula (I-C) is a compound of the formula:



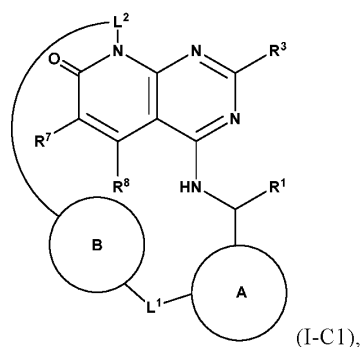
C) is a compound of the formula,



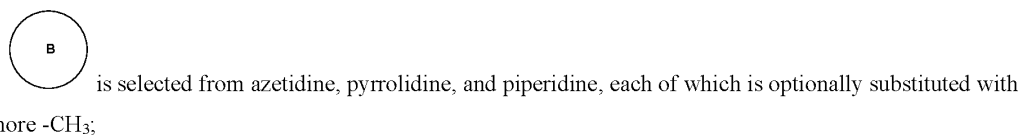
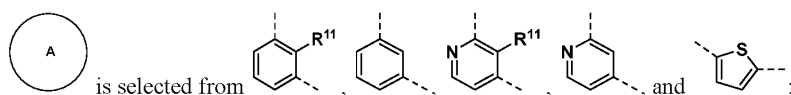
embodiments, a compound of Formula (I-D) is a compound of the formula:



[191] In certain aspects, the present disclosure provides a compound of Formula (I-C1):



or a pharmaceutically acceptable salt or solvate thereof, wherein:

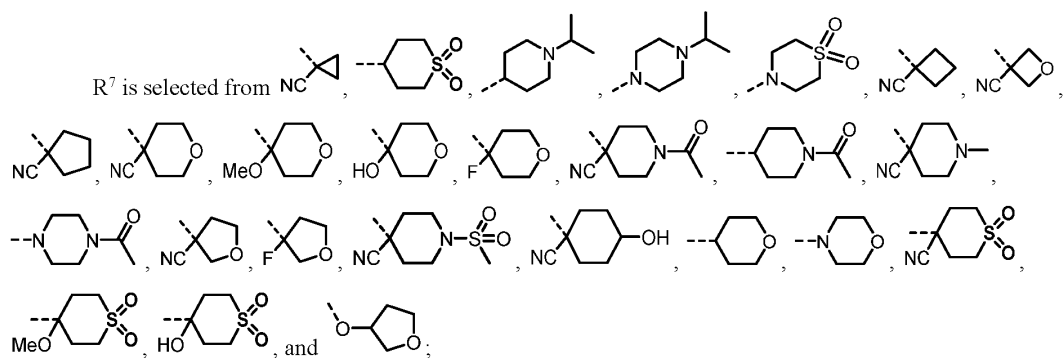


L¹ is C₁₋₃ haloalkylene;

L² is selected from C₅₋₁₀ alkylene, C₅₋₁₀ alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b},

R¹ is -CH₃;

R³ is hydrogen or -CH₃;

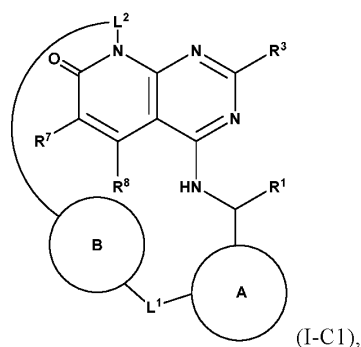


R⁸ is hydrogen;

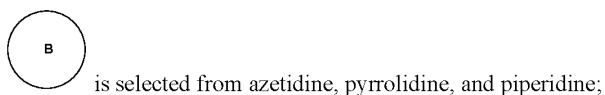
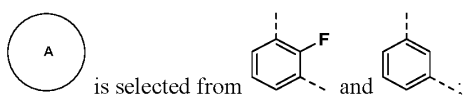
R¹¹ is selected from fluorine and -CH₃; and

R^{11b} is selected from halogen, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ alkyl)-OH, and -OH.

[192] In certain aspects, the present disclosure provides a compound of Formula (I-C1):



or a pharmaceutically acceptable salt or solvate thereof, wherein:

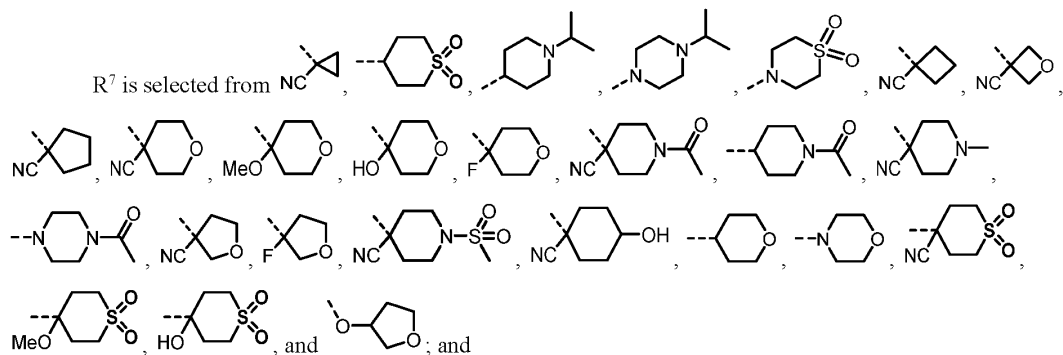


L¹ is selected from -CF₂-, -CF₂CH₂-, and -CF₂CH₂CH₂-;

L² is selected from C₅₋₁₀ alkylene, C₅₋₁₀ alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene;

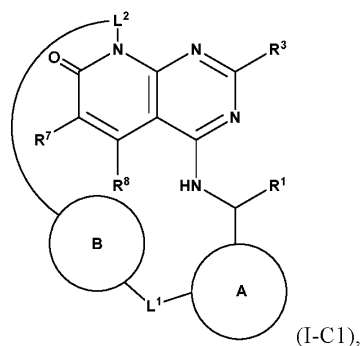
R¹ is -CH₃;

R³ is hydrogen or -CH₃;

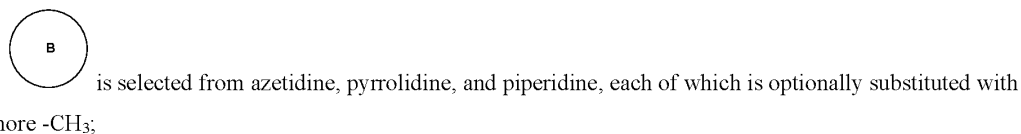
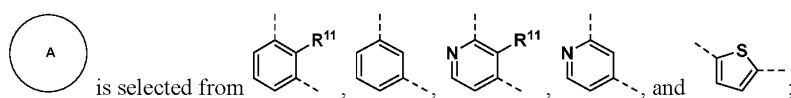


R⁸ is hydrogen.

[193] In certain aspects, the present disclosure provides a compound of Formula (I-C1):



or a pharmaceutically acceptable salt or solvate thereof, wherein:

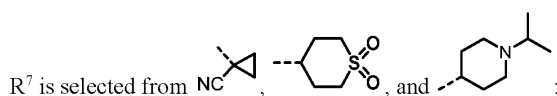


L¹ is C₁₋₃ haloalkylene;

L² is C₅₋₁₀ alkenylene optionally substituted with one or more R^{11b};

R¹ is -CH₃;

R³ is -CH₃;

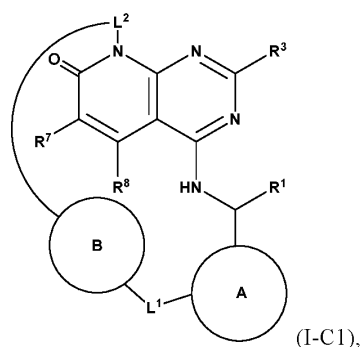


R⁸ is hydrogen;

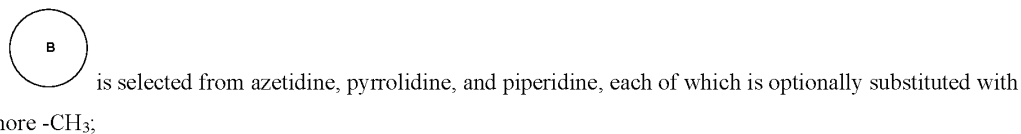
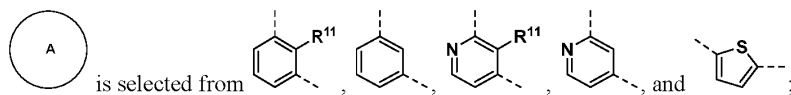
R¹¹ is selected from fluorine and -CH₃; and

R^{11b} is selected from halogen, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ alkyl)-OH, and -OH.

[194] In certain aspects, the present disclosure provides a compound of Formula (I-C1):



or a pharmaceutically acceptable salt or solvate thereof, wherein:

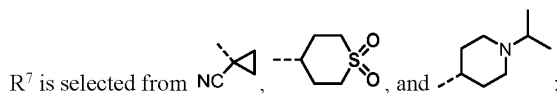


L¹ is C₁₋₃ haloalkylene;

L² is selected from 5- to 10-membered heteroalkylene optionally substituted with one or more R^{11b};

R¹ is -CH₃;

R³ is hydrogen or -CH₃;

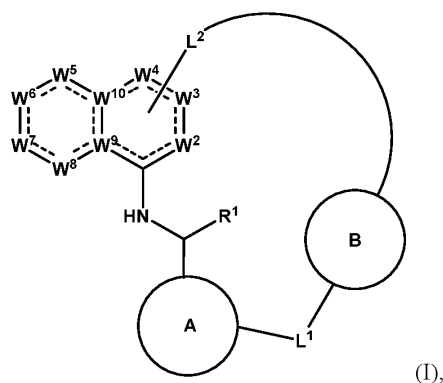


R⁸ is hydrogen;

R¹¹ is selected from fluorine and -CH₃; and

R^{11b} is selected from halogen, oxo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, (C₁₋₆ alkyl)-OH, and -OH.

[195] In certain aspects, the present disclosure provides a compound of Formula (I):



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 R¹¹;



is absent or selected from phenyl and 4- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{11a};

L¹ is selected from a bond and C₁₋₃ haloalkylene;

L² is selected from C₅₋₁₀ alkylene, C₅₋₁₀ alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}, wherein L² is covalently bound to one of W³, W⁴, W⁵, W⁶, or W⁷; or L² is -L³-D-L⁴-, wherein L⁴ is covalently bound to one of W³, W⁴, W⁵, W⁶, or W⁷;

L³ is selected from C₁₋₈ alkylene, C₂₋₈ alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b};

D is selected from C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{11d};

L⁴ is selected from C₁₋₈ alkylene, C₂₋₈ alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}

W² is N;

W³ is selected from N(R^{3b}), N, C(R³), and C(O);

W⁴ is selected from N(R^{4b}), N, C(R⁴), and C(O);

W⁵ is selected from N(R^{5b}), N, and C(R⁵);

W⁶ is selected from C(R⁶) and C(O);

W⁷ is C(R⁷);

W⁸ is C(R⁸);

W⁹ and W¹⁰ are each C;

R¹ is -CH₃;

R², R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R⁸, and R^{8a} are each independently selected from hydrogen and -CH₃;

R³, R⁴, R⁵, and R⁶ are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₃ alkyl,

C₁₋₃ haloalkyl, -OH, -OCH₃, -NH₂, -NHCH₃, -N(CH₃)₂;

R⁷ is selected from a bond to L², C₁₋₆ alkyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -N(R¹²)(R¹³), -C(O)R¹⁵, -C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, and -SO₂N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R^{3b}, R^{4b}, and R^{5b} are each independently selected from a bond to L², hydrogen, and C₁₋₃ alkyl;

R¹¹, R^{11a}, and R^{11d} are each independently selected at each occurrence from halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹² is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹³ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; or R¹² and R¹³, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R²⁰;

R¹⁴ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R¹⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹⁷ and R^{17a} are each independently selected at each occurrence from C₁₋₆ alkyl and C₃₋₆ cycloalkyl, wherein C₁₋₆ alkyl and C₃₋₆ cycloalkyl are optionally substituted with one, two or three R²⁰; or R¹⁷ and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -

$N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, 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;

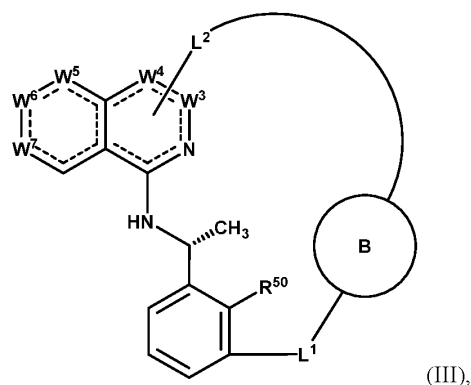
R^{23} is independently selected at each occurrence from H and C_{1-6} alkyl;

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

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; and

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

[196] In certain aspects, the present disclosure provides a compound of Formula (III):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



is selected from 3- to 8-membered heterocycle, optionally substituted with one or more R^{11a} ;

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

L^2 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^{11b} , wherein L^2 is covalently bound to one of W^3 , W^4 , W^5 , W^6 , or W^7 ; or L^2 is $-L^3-D-L^4$, wherein L^4 is covalently bound to one of W^3 , W^4 , W^5 , W^6 , or W^7 ;

L^3 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^{11b} ;

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^{11d} ;

L^4 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^{11b} ;

W³ is selected from N(R^{3b}) and N and W⁴ is selected from C(R⁴) and C(O); or W³ is selected from C(R³) and C(O), and W⁴ is selected from N(R^{4b}) and N;

W⁵ is selected from N(R^{5b}), N, and C(R⁵);

W⁶ is selected from N, C(R⁶), and C(O);

W⁷ is selected from N, C(R⁷), and C(O);

R⁵⁰ is hydrogen or halogen;

R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰;

R^{3b}, R^{4b}, and R^{5b} are each independently selected from a bond to L², hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰;

R^{11a} and R^{11d} are each independently selected at each occurrence from halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹² is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹³ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; or R¹² and R¹³, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R²⁰;

R¹⁴ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R¹⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀

carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R¹⁷ and R^{17a} are each independently selected at each occurrence from C₁₋₆ alkyl and C₃₋₆ cycloalkyl, wherein C₁₋₆ alkyl and C₃₋₆ cycloalkyl are optionally substituted with one, two or three R²⁰; or R¹⁷ and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), and -OC(O)R²⁵;

R²¹ is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

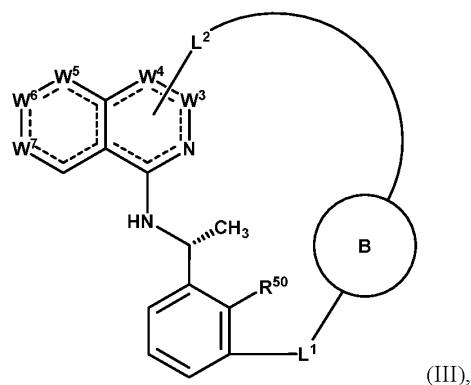
R²³ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁴ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

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

[197] In certain aspects, the present disclosure provides a compound of Formula (III):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



is selected from 3- to 8-membered heterocycle, optionally substituted with one or more R^{11a} ;

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

L^2 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^{11b} , wherein L^2 is covalently bound to one of W^3 , W^4 , W^5 , W^6 , or W^7 ;

W^3 is selected from $N(R^{3b})$ and N and W^4 is selected from $C(R^4)$ and $C(O)$; or W^3 is selected from $C(R^3)$ and $C(O)$, and W^4 is selected from $N(R^{4b})$ and N;

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

W^6 is selected from N, $C(R^6)$, and $C(O)$;

W^7 is selected from N, $C(R^7)$, and $C(O)$;

R^{50} is hydrogen or halogen;

R^3 , R^4 , R^5 , R^6 , and R^7 are each independently selected from a bond to L^2 , hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), 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^{20} ;

R^{3b} , R^{4b} , and R^{5b} are each independently selected from a bond to L^2 , hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), 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^{20} ;

R^{11a} 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, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), 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^{20} ;

R^{11b} 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, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), 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^{20} ;

R^{12} 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 R²⁰,

R¹³ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; or R¹² and R¹³, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R²⁰;

R¹⁴ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R¹⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹⁷ and R^{17a} are each independently selected at each occurrence from C₁₋₆ alkyl and C₃₋₆ cycloalkyl, wherein C₁₋₆ alkyl and C₃₋₆ cycloalkyl are optionally substituted with one, two or three R²⁰; or R¹⁷ and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), and -OC(O)R²⁵;

R²¹ is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

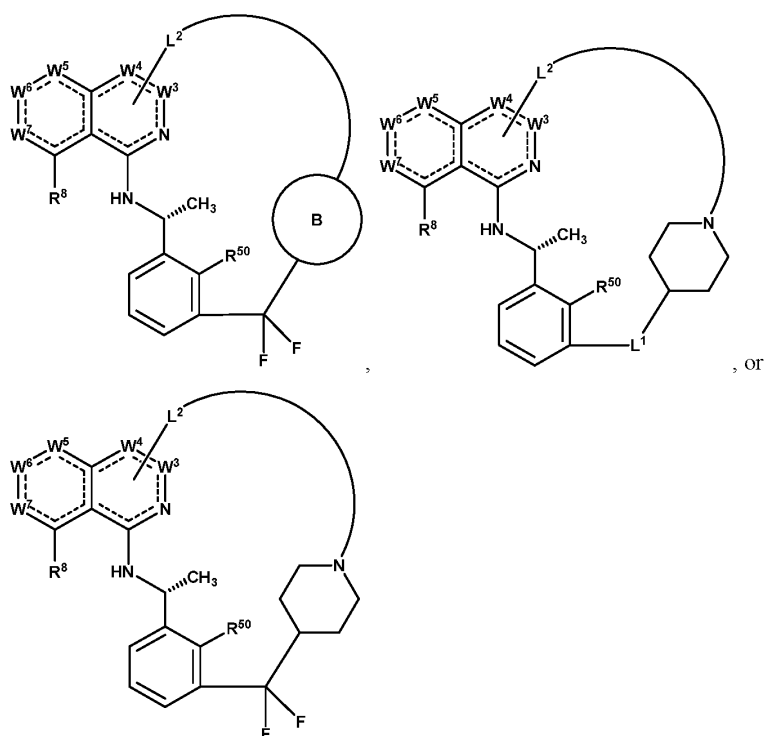
R²³ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁴ is independently selected at each occurrence from H and C₁₋₆ alkyl;

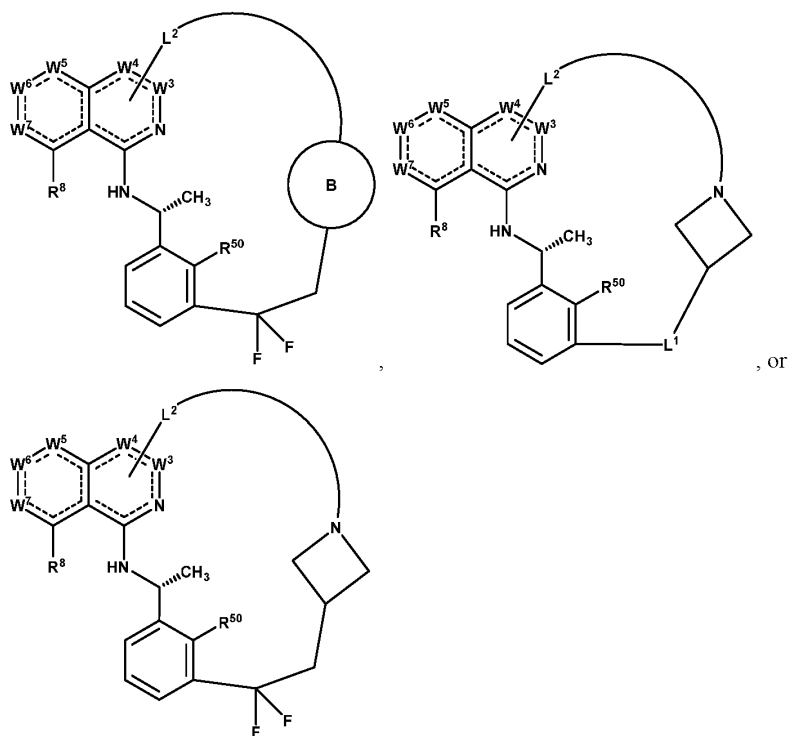
R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

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

[198] In some embodiments, a compound of Formula (III) is a compound of the formula:



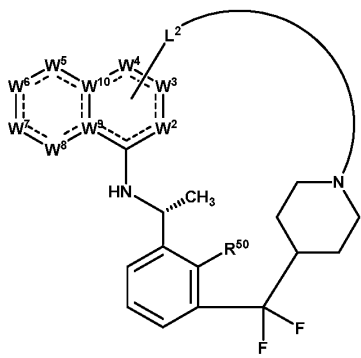
[199] In some embodiments, a compound of Formula (III) is a compound of the formula:



[200] In some embodiments, for a compound of Formula (III),  is selected from azetidine, pyrrolidine,

and piperidine, each of which is optionally substituted with one or more R^{11a} . In some embodiments,  is , each of which is optionally substituted with one or more R^{11a} . In some embodiments,  is , each of which is optionally substituted with one or more R^{11a} . In some embodiments, L^1 is C_{1-3} haloalkylene. In some embodiments, L^2 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^{11b} , wherein L^2 is covalently bound to one of W^3 , W^4 , W^5 , W^6 , or W^7 ; or L^2 is $-L^3-D-L^4-$, wherein L^4 is covalently bound to one of W^3 , W^4 , W^5 , W^6 , or W^7 ; L^3 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^{11b} ; 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^{11d} ; and L^4 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^{11b} .

[201] In certain aspects, the present disclosure provides a compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

L^2 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^{11b} , wherein L^2 is covalently bound to one of W^3 , W^4 , W^5 , W^6 , or W^7 ; or L^2 is $-L^3-D-L^4-$, wherein L^4 is covalently bound to one of W^3 , W^4 , W^5 , W^6 , or W^7 ;

L^3 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^{11b} ;

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^{11d} ;

L^4 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^{11b} ;

W^2 is selected from $N(R^{2b})$, N , $C(R^2)$, $C(R^2)(R^{2a})$, and $C(O)$;

W^3 is selected from $N(R^{3b})$, N , $C(R^3)$, $C(R^3)(R^{3a})$, and $C(O)$;

W^4 is selected from $N(R^{4b})$, N , $C(R^4)$, $C(R^4)(R^{4a})$, and $C(O)$;

W^5 is selected from $N(R^{5b})$, N , $C(R^5)$, $C(R^5)(R^{5a})$, and $C(O)$;

W^6 is selected from $N(R^{6b})$, N , $C(R^6)$, $C(R^6)(R^{6a})$, and $C(O)$;

W^7 is selected from $N(R^{7b})$, N , $C(R^7)$, $C(R^7)(R^{7a})$, and $C(O)$;

W⁸ is selected from N(R^{8b}), N, C(R⁸), C(R⁸)(R^{8a}), and C(O);

W⁹ is selected from N, C(R⁹), and C;

W¹⁰ is selected from N, C(R¹⁰), and C;

R², R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R⁸, and R^{8a} are each independently selected from hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R^{2b} and R^{8b} are each independently selected from hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R^{3b}, R^{4b}, R^{5b}, R^{6b}, and R^{7b} are each independently selected from a bond to L², hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) is independently optionally substituted with one, two, or three R²⁰,

R^{11d} is independently selected at each occurrence from halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹² is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹³ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; or R¹² and R¹³, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R²⁰;

R¹⁴ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R¹⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹⁷ and R^{17a} are each independently selected at each occurrence from C₁₋₆ alkyl and C₃₋₆ cycloalkyl, wherein C₁₋₆ alkyl and C₃₋₆ cycloalkyl are optionally substituted with one, two or three R²⁰; or R¹⁷ and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), and -OC(O)R²⁵;

R²¹ is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²³ is independently selected at each occurrence from H and C₁₋₆ alkyl;

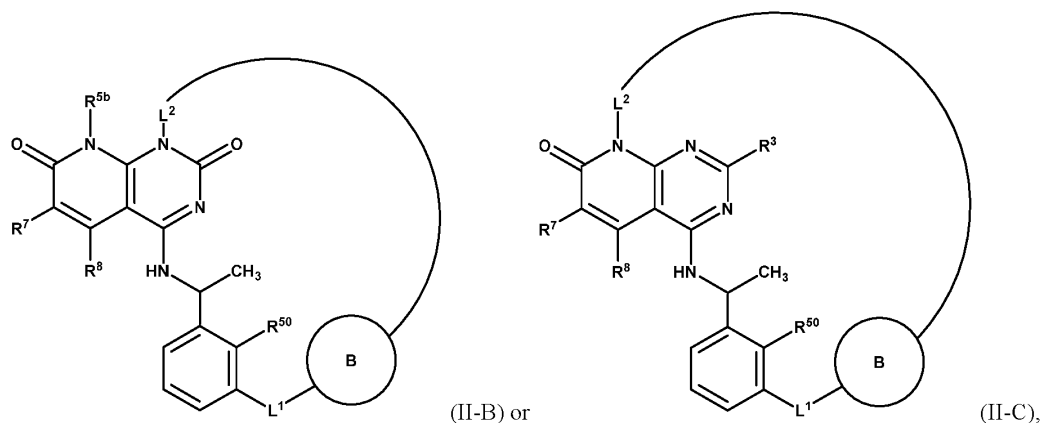
R²⁴ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3-

to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

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

[202] In certain aspects, the present disclosure provides a compound of Formula (II-B) or (II-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^{11a};

L¹ is C₁₋₃ haloalkylene;

L² is selected from C₅₋₁₀ alkylene, C₅₋₁₀ alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}, or L² is -L³-D-L⁴;

L³ is selected from C₁₋₈ alkylene, C₂₋₈ alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b};

D is selected from C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more R^{11d};

L⁴ is selected from C₁₋₈ alkylene, C₂₋₈ alkenylene, 2- to 8-membered heteroalkylene, and 3- to 8-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b};

R³ and R⁸ are each independently selected from hydrogen and -CH₃;

R⁷ is selected from C₃₋₈ carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one, two, or three R²⁰;

R^{5b} is selected from hydrogen and C₁₋₃ alkyl;

R⁵⁰ is selected from hydrogen and halogen;

R^{11a} and R^{11d} are each independently selected at each occurrence from halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆

alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹² is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹³ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; or R¹² and R¹³, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R²⁰;

R¹⁴ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R¹⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹⁷ and R^{17a} are each independently selected at each occurrence from C₁₋₆ alkyl and C₃₋₆ cycloalkyl, wherein C₁₋₆ alkyl and C₃₋₆ cycloalkyl are optionally substituted with one, two or three R²⁰; or R¹⁷ and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), and -OC(O)R²⁵;

R²¹ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

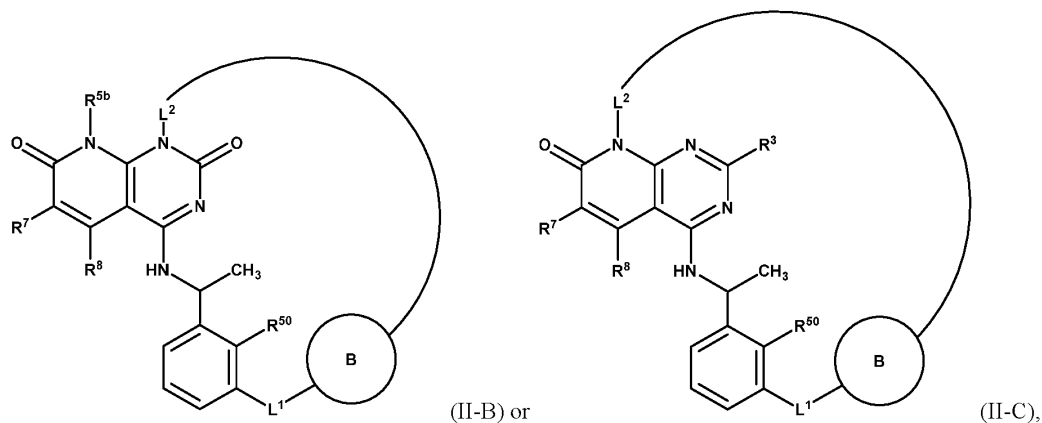
R²³ is independently selected at each occurrence from hydrogen and C₁₋₆ alkyl;

R²⁴ is independently selected at each occurrence from hydrogen and C₁₋₆ alkyl; and

R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered

heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle.

[203] In some embodiments, the present disclosure provides a compound of Formula (II-B) or (II-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^{11a};

L¹ is C₁₋₃ haloalkylene;

L² is selected from C₅₋₁₀ alkylene, C₅₋₁₀ alkenylene, 5- to 10-membered heteroalkylene, and 5- to 10-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b};

R³, R^{5b}, and R⁸ are each independently selected from hydrogen and -CH₃;

R⁷ is selected from C₃₋₈ carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one, two, or three R²⁰;

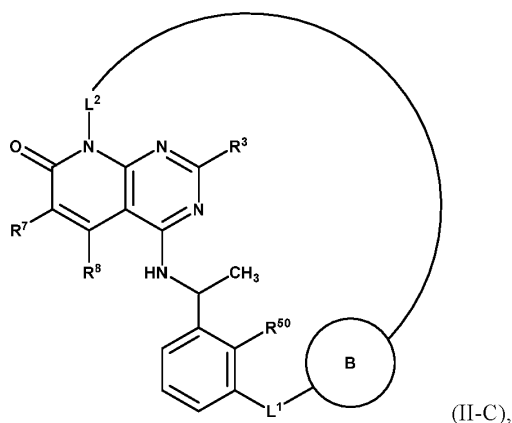
R⁵⁰ is selected from hydrogen and halogen;

R^{11a} is independently selected at each occurrence from halogen, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₃ alkyl, and -OH; and

R²⁰ is independently selected at each occurrence from halogen, oxo, -CN, and C₁₋₆ alkyl.

[204] In some embodiments, the present disclosure provides a compound of Formula (II-C):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



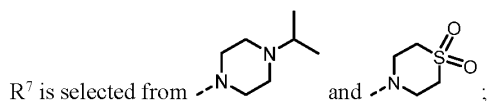
is absent or 4- to 8-membered heterocycle optionally substituted with one or more R^{11a} ;

L^1 is C_{1-3} haloalkylene;

L^2 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^{11b} ;

R^3 is hydrogen;

R^8 is selected from hydrogen and $-CH_3$;



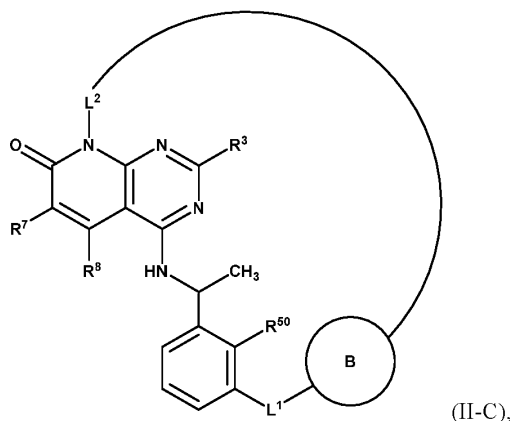
R^{50} is selected from hydrogen and halogen;

R^{11a} is independently selected at each occurrence from halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^{11b} is independently selected at each occurrence from halogen, oxo, $-CN$, C_{1-3} alkyl, and $-OH$; and

R^{20} is independently selected at each occurrence from halogen, oxo, $-CN$, and C_{1-6} alkyl.

[205] In some embodiments, the present disclosure provides a compound of Formula (II-C):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



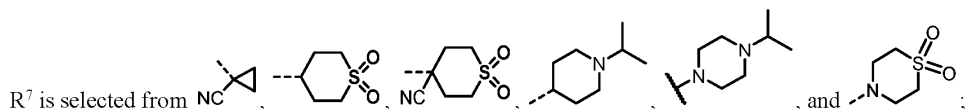
is 4- to 8-membered heterocycle optionally substituted with one or more R^{11a} ;

L^1 is C_{1-3} haloalkylene;

L^2 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^{11b} ;

R^3 is selected from hydrogen and $-CH_3$;

R^8 is selected from hydrogen and $-CH_3$;

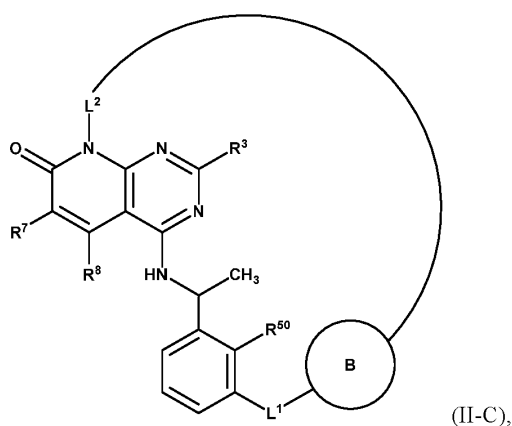


R^{50} is selected from hydrogen and halogen;

R^{11a} is independently selected at each occurrence from halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; and

R^{11b} is independently selected at each occurrence from halogen, oxo, $-CN$, C_{1-3} alkyl, and $-OH$.

[206] In some embodiments, the present disclosure provides a compound of Formula (II-C):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



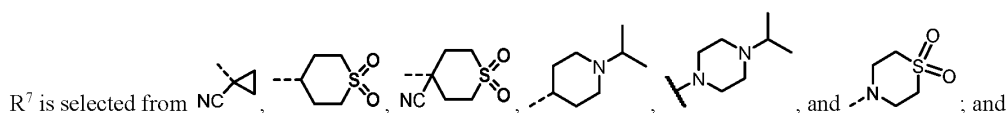
is 4- to 6-membered heterocycle;

L¹ is C₁₋₃ haloalkylene;

L² is selected from C₅₋₁₀ alkylene, C₅₋₁₀ alkenylene, and 5- to 10-membered heteroalkylene;

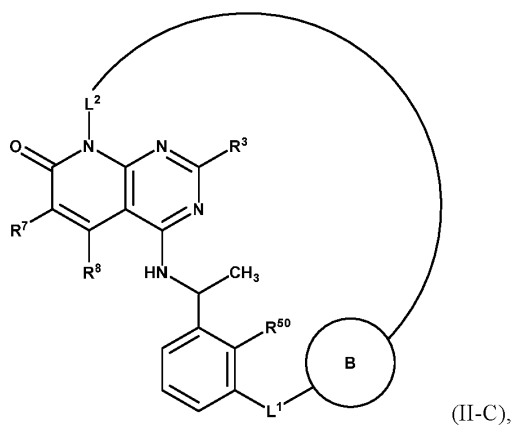
R³ is selected from hydrogen and -CH₃;

R⁸ is hydrogen;

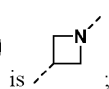


R⁵⁰ is selected from hydrogen and halogen.

[207] In some embodiments, the present disclosure provides a compound of Formula (II-C):



or a pharmaceutically acceptable salt or solvate thereof, wherein:

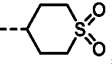
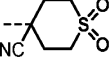
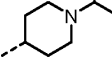
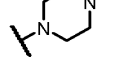
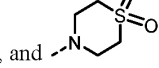


L¹ is -CF₂CH₂-;

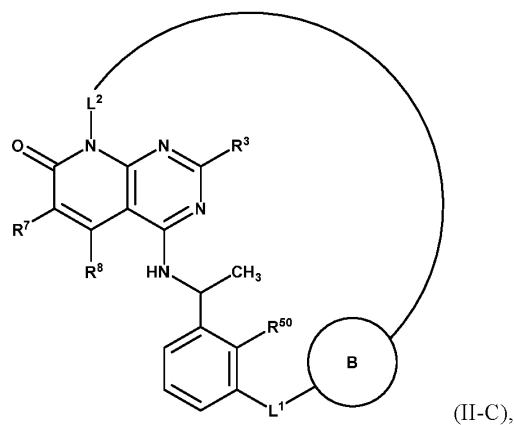
L² is 5- to 10-membered heteroalkylene, wherein the heteroalkylene comprises one oxygen atom;

R³ is selected from hydrogen and -CH₃;

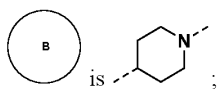
R⁸ is hydrogen;

R^7 is selected from , , , , , and ; and R^{50} is selected from hydrogen and halogen.

[208] In some embodiments, the present disclosure provides a compound of Formula (II-C):



or a pharmaceutically acceptable salt or solvate thereof, wherein:

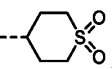
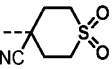
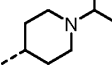
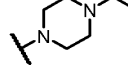
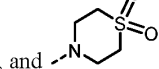


L^1 is $-\text{CF}_2-$;

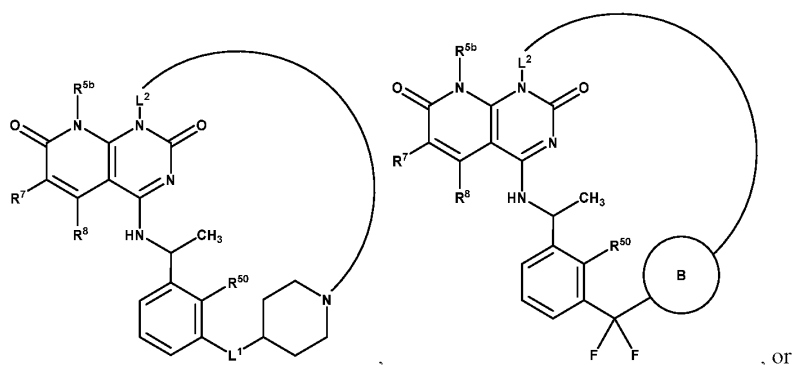
L^2 is selected from C_{5-10} alkenylene;

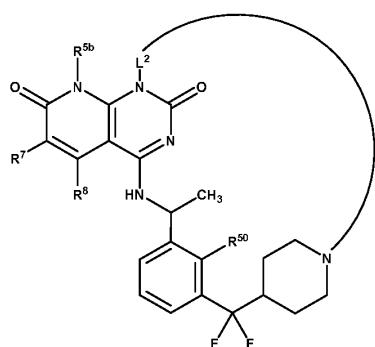
R^3 is selected from hydrogen and $-\text{CH}_3$;

R^8 is hydrogen;

R^7 is selected from , , , , , and ; and R^{50} is selected from hydrogen and halogen.

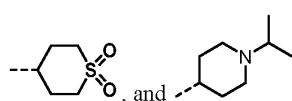
[209] In some embodiments, a compound of Formula (II-B) is a compound of the formula:



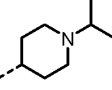


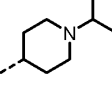
. In some embodiments, R^{5b} is $-\text{CH}_3$; R^8 is hydrogen; and R^{50} is selected from hydrogen and fluoro. In some embodiments, R^{5b} is $-\text{CH}_3$; R^8 is hydrogen; and R^{50} is hydrogen. In some

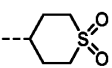
embodiments, R^{5b} is $-\text{CH}_3$; R^8 is hydrogen; and R^{50} is fluoro. In some embodiments, R^7 is selected from NC ,



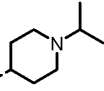
. In some embodiments, R^{5b} is $-\text{CH}_3$; R^8 is hydrogen; R^{50} is hydrogen; and R^7 is

selected from NC , , and . In some embodiments, R^{5b} is $-\text{CH}_3$; R^8 is hydrogen; R^{50} is

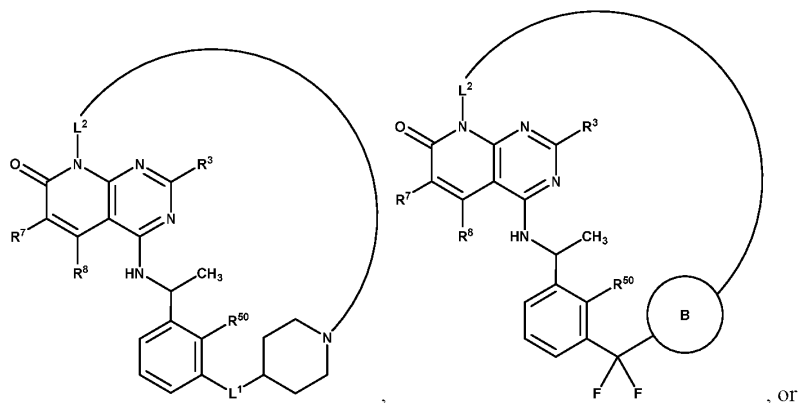
fluoro; and R^7 is selected from NC , , and . In some embodiments, R^{5b} is $-\text{CH}_3$; R^8 is

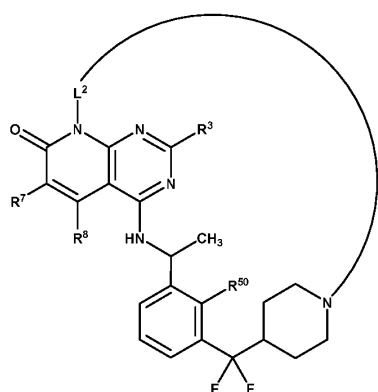
hydrogen; R^{50} is selected from hydrogen and fluoro; and R^7 is . In some embodiments, R^{5b} is $-\text{CH}_3$; R^8 is

hydrogen; R^{50} is selected from hydrogen and fluoro; and R^7 is NC . In some embodiments, R^{5b} is $-\text{CH}_3$; R^8 is

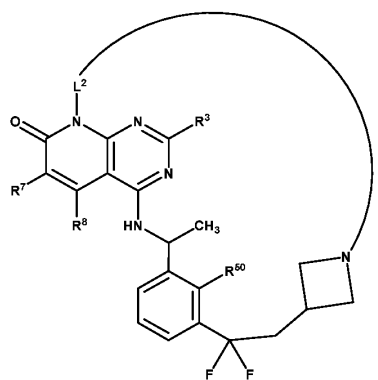
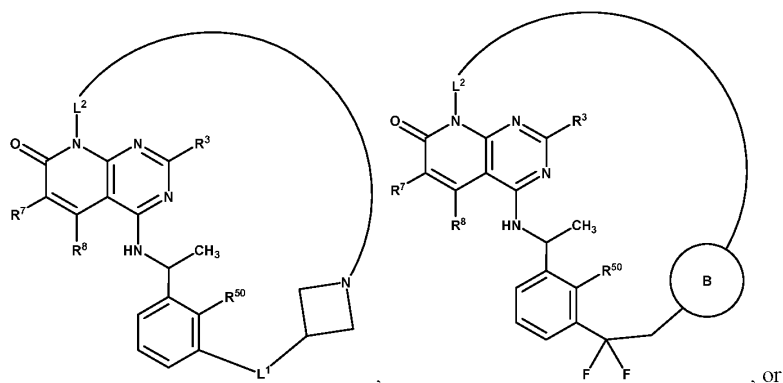
hydrogen; R^{50} is selected from hydrogen and fluoro; and R^7 is .

[210] In some embodiments, a compound of Formula (II-C) is a compound of the formula:

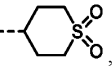
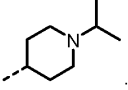


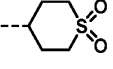
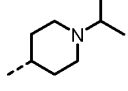


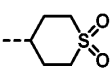
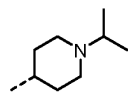
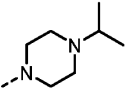
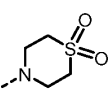
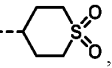
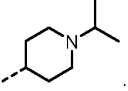
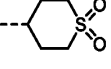
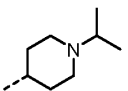
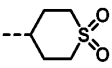
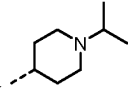
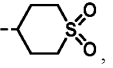
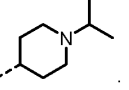
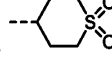
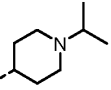
. In some embodiments, a compound of Formula (II-C) is a compound of the formula:



. In some embodiments, R^3 is selected from hydrogen and $-CH_3$; R^8 is hydrogen; and R^{50} is selected from hydrogen and fluoro. In some embodiments, R^3 is selected from hydrogen and $-CH_3$; R^8 is hydrogen; and R^{50} is hydrogen. In some embodiments, R^3 is selected from hydrogen and $-CH_3$; R^8 is hydrogen; and R^{50} is fluoro. In some embodiments, R^3 is hydrogen; R^8 is hydrogen; and R^{50} is hydrogen. In some embodiments, R^3 is hydrogen; R^8 is hydrogen; and R^{50} is fluoro. In some embodiments, R^3 is $-CH_3$; R^8 is hydrogen; and R^{50} is hydrogen. In some embodiments, R^3 is $-CH_3$; R^8 is hydrogen; and R^{50} is fluoro. In some embodiments, R^7

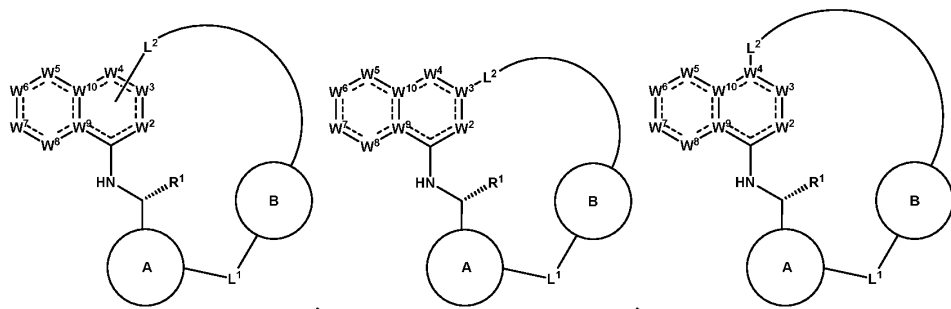
is selected from , , and . In some embodiments, R^3 is selected from hydrogen and $-$

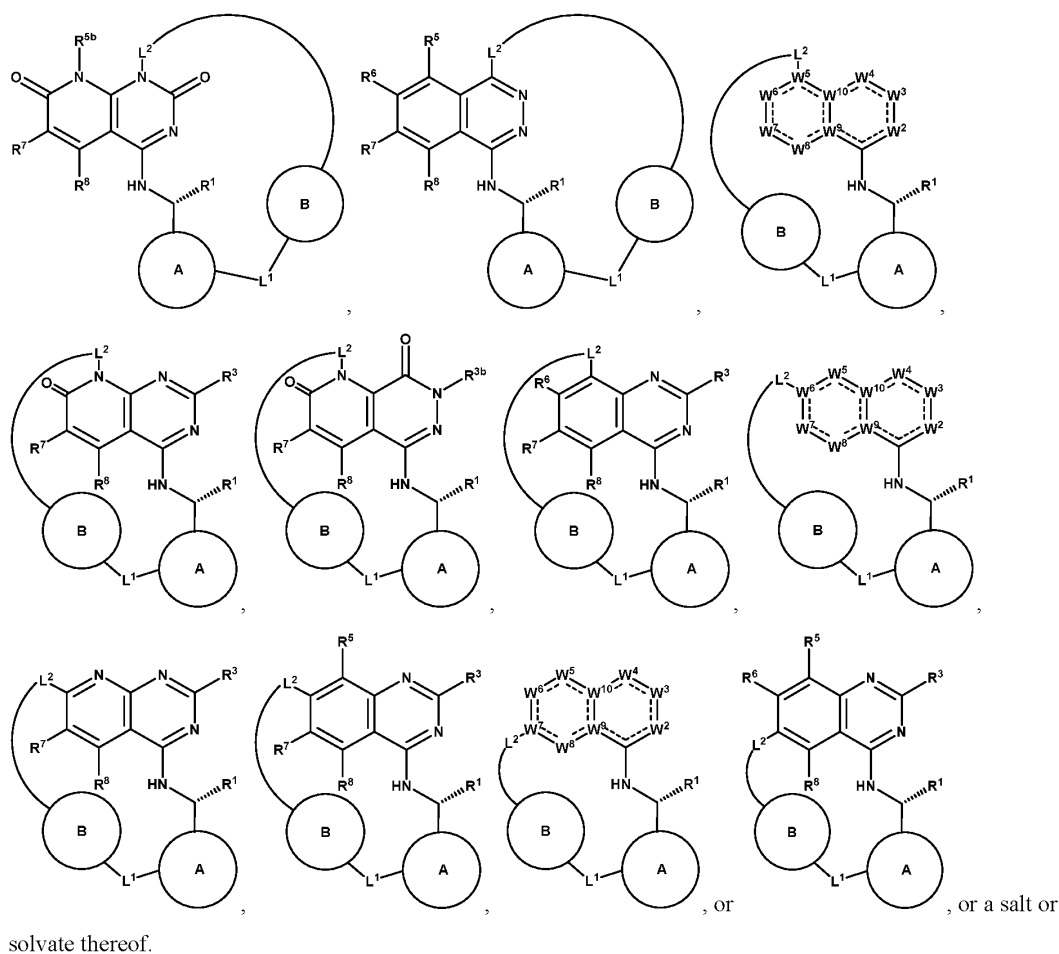
CH_3 ; R^8 is hydrogen; R^{50} is hydrogen; and R^7 is selected from , , and . In some

embodiments, R^3 is selected from hydrogen and $-\text{CH}_3$; R^8 is hydrogen; R^{50} is fluoro; and R^7 is selected from NC , , and . In some embodiments, R^3 is hydrogen; R^8 is hydrogen; R^{50} is selected from hydrogen and fluoro; and R^7 is selected from  and . In some embodiments, R^3 is hydrogen; R^8 is hydrogen; R^{50} is hydrogen; and R^7 is selected from NC , , and . In some embodiments, R^3 is hydrogen; R^8 is hydrogen; R^{50} is fluoro; and R^7 is selected from NC , , and . In some embodiments, R^3 is $-\text{CH}_3$; R^8 is hydrogen; R^{50} is hydrogen; and R^7 is selected from NC , , and . In some embodiments, R^3 is $-\text{CH}_3$; R^8 is hydrogen; R^{50} is fluoro; and R^7 is selected from NC , , and . In some embodiments, R^3 is selected from hydrogen and $-\text{CH}_3$; R^8 is hydrogen; R^{50} is selected from hydrogen and fluoro; and R^7 is NC . In some embodiments, R^3 is selected from hydrogen and $-\text{CH}_3$; R^8 is hydrogen; R^{50} is selected from hydrogen and fluoro; and R^7 is . In some embodiments, R^3 is selected from hydrogen and $-\text{CH}_3$; R^8 is hydrogen; R^{50} is selected from hydrogen and fluoro; and R^7 is .

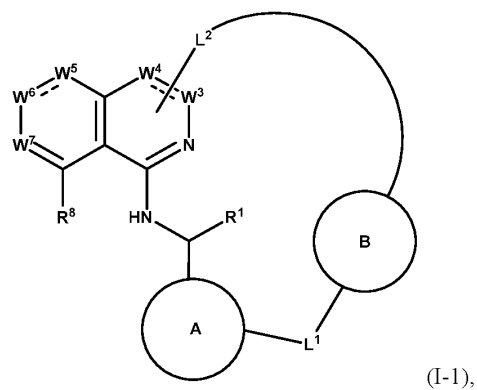
[211] Embodiments disclosed herein that refer to a compound of Formula (I), (I-A), (I-B), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), and/or (I-E1) are also intended to apply to a compound of Formula (I-1), (II-B), (II-C), and (III) unless the context of the embodiment clearly dictates otherwise (e.g., the embodiment refers solely to a variable not present in the compound of Formula (I-1), (II-B), (II-C), or (III), such as R^1).

[212] In some embodiments, a compound of Formula (I) is a compound of the formula:





[213] In certain aspects, the present disclosure provides a compound of Formula (I-1):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



is selected from C₅₋₇ carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R¹¹;



is absent or selected from C₃₋₈ carbocycle and 3- to 8-membered heterocycle, each of which is

optionally substituted with one or more R^{11a},

L¹ is selected from a bond, C₁₋₆ alkylene, and C₁₋₆ haloalkylene;

L² is selected from C₅₋₂₅ alkylene, C₅₋₂₅ alkenylene, C₅₋₂₅ alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}, wherein L² is covalently bound to one of W³, W⁴, W⁵, W⁶, or W⁷;

W³ is selected from N(R^{3b}), N, C(R³), and C(O);

W⁴ is selected from N(R^{4b}), N, C(R⁴), and C(O);

W⁵ is selected from N(R^{5b}), N, and C(R⁵);

W⁶ is selected from C(R⁶) and C(O);

W⁷ is C(R⁷);

R¹ is C₁₋₃ alkyl optionally substituted with one or more R^{11c};

R⁸ is selected from hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R^{3b}, R^{4b}, and R^{5b} are each independently selected from a bond to L², hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰,

R¹¹ and R^{11a} are each independently selected at each occurrence from halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰,

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -

$C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-CH_2N(R^{12})S(O)_2(R^{13})$, and $-P(O)(R^{17})(R^{17a})$, 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^{20} ;

R^{11c} is independently selected at each occurrence from halogen, $-OR^{12}$, and $-N(R^{12})(R^{13})$;

R^{12} 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^{20} ;

R^{13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{12} and R^{13} , 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^{20} ;

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

R^{15} 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^{20} ;

R^{17} and R^{17a} 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^{20} ; or R^{17} and R^{17a} , together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{20} 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), $-OR^{21}$, $-SR^{21}$, $-N(R^{22})(R^{23})$, $-C(O)OR^{22}$, $-C(O)N(R^{22})(R^{23})$, $-C(O)C(O)N(R^{22})(R^{23})$, $-OC(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)N(R^{22})(R^{23})$, $-N(R^{24})C(O)OR^{25}$, $-N(R^{24})C(O)R^{25}$, $-N(R^{24})S(O)_2R^{25}$, $-C(O)R^{25}$, $-S(O)_2R^{25}$, $-S(O)_2N(R^{22})(R^{23})$, $-OCH_2C(O)OR^{22}$, 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;

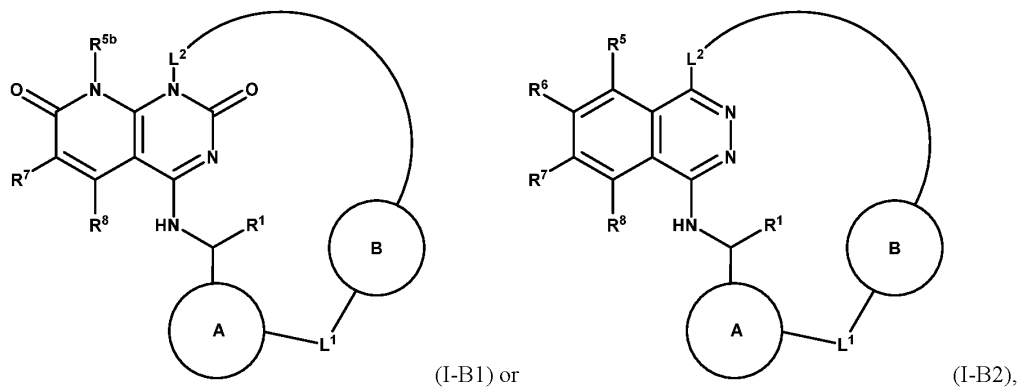
R^{24} is independently selected at each occurrence from H and C_{1-6} alkyl;

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,

C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

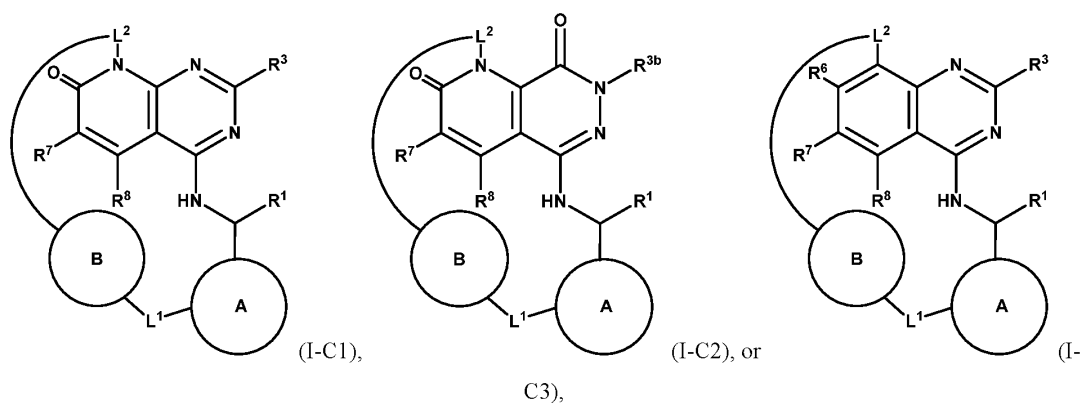
----- indicates a single or double bond such that all valences are satisfied.

[214] In some embodiments, the compound of Formula (I-1) is a compound of Formula (I-B1) or (I-B2):



or a pharmaceutically acceptable salt or solvate thereof.

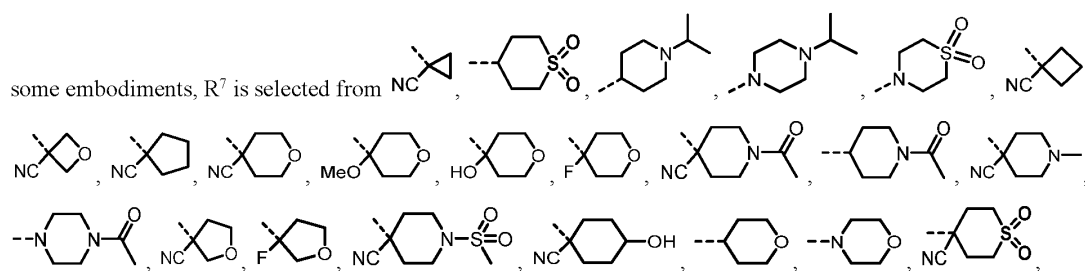
[215] In some embodiments, the compound of Formula (I-1) is a compound of Formula (I-C1), (I-C2), or (I-C3):

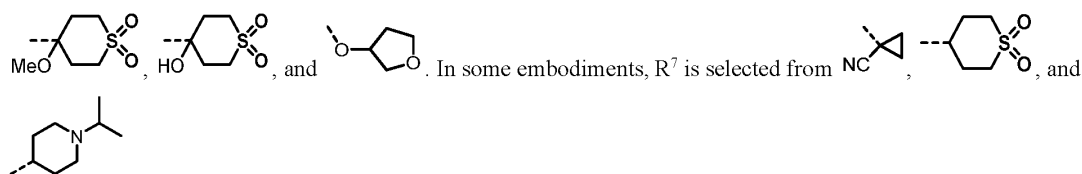


or a pharmaceutically acceptable salt or solvate thereof.

[216] In some embodiments, for a compound of Formula (I-1), (I-B1), (I-B2), (I-C1), (I-C2), or (I-C3), R¹ is -CH₃. In some embodiments, for a compound of Formula (I-1), (I-C1), or (I-C3), R³ is selected from hydrogen, -CN, -OR¹², and -CH₃. In some embodiments, for a compound of Formula (I-1), (I-B2), or (I-C3), R⁶ is selected from hydrogen, -OR¹², and C₁₋₆ alkyl optionally substituted with one, two, or three R²⁰, and wherein R¹² is selected from C₁₋₆ alkyl. In some embodiments, for a compound of Formula (I-1), (I-B1), (I-B2), (I-C1), (I-C2), or (I-C3), R⁸ is hydrogen.

[217] In some embodiments, for a compound of Formula (I-1), (I-B1), (I-B2), (I-C1), (I-C2), or (I-C3), R⁷ is selected from C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocycloalkyl, and -N(R¹²)(R¹³), wherein C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocycloalkyl are optionally substituted with one, two, or three R²⁰. In





[218] In some embodiments, for a compound of Formula (I-1), (I-B1), (I-B2), (I-C1), (I-C2), or (I-C3),  is selected from phenyl and 5- to 7-membered heteroaryl, each of which is optionally substituted with one or more

R^{11} . In some embodiments,  is selected from , , , , and . In some embodiments, R^{11} is independently selected from fluorine and $-\text{CH}_3$.

[219] In some embodiments, for a compound of Formula (I-1), (I-B1), (I-B2), (I-C1), (I-C2), or (I-C3), L^1 is C_{1-3} haloalkylene. In some embodiments, L^1 is selected from $-\text{CF}_2-$, $-\text{CF}_2\text{CH}_2-$, and $-\text{CF}_2\text{CH}_2\text{CH}_2-$.

[220] In some embodiments, for a compound of Formula (I-1), (I-B1), (I-B2), (I-C1), (I-C2), or (I-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^{11a} . In some embodiments,  is selected from azetidine, pyrrolidine, and piperidine, each of which is optionally substituted with one or more $-\text{CH}_3$.

[221] In some embodiments, for a compound of Formula (I-1), (I-B1), (I-B2), (I-C1), (I-C2), or (I-C3), L^2 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^{11b} . In some embodiments, L^2 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^{11b} . 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.

[222] In some embodiments, for a compound of Formula (I-1), (I-B1), or (I-B2), R^5 is hydrogen; R^{5b} is $-\text{CH}_3$; R^6 is selected from hydrogen and $-\text{OCH}_3$; R^7 is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-\text{N}(\text{R}^{12})(\text{R}^{13})$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})(\text{R}^{13})$, $-\text{S}(\text{O})_2\text{R}^{15}$, and $-\text{SO}_2\text{N}(\text{R}^{12})(\text{R}^{13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{20} ; and R^8 is hydrogen.

[223] In some embodiments, for a compound of Formula (I-1), (I-C1), (I-C2), or (I-C3), R^3 is hydrogen or $-\text{CH}_3$; R^{3b} is $-\text{CH}_3$; R^6 is selected from hydrogen and $-\text{OCH}_3$; R^7 is selected from C_{1-6} alkyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-\text{N}(\text{R}^{12})(\text{R}^{13})$, $-\text{C}(\text{O})\text{R}^{15}$, $-\text{C}(\text{O})\text{N}(\text{R}^{12})(\text{R}^{13})$, $-\text{S}(\text{O})_2\text{R}^{15}$, and $-\text{SO}_2\text{N}(\text{R}^{12})(\text{R}^{13})$, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{20} ; and R^8 is hydrogen.

[224] Small molecule SOS1 inhibitors suitable for use in the subject methods—including the synergistic inhibition of proliferation of EGFR-mediated cancer cells in combination with osimertinib—include compounds of Formula (I); Formula (I-A); Formula (I-B); Formula (I-1), encompassing Compound A; Formula (I-B1); Formula (I-

B2); Formula (I-C); Formula (I-C1); Formula (I-C2); Formula (I-C3); Formula (I-D); Formula (I-D1); Formula (I-D2); Formula (I-E); Formula (I-E1); Formula (II-B); Formula (II-C); and Formula (III). Exemplary small molecule SOS1 inhibitors include, but are not limited to, compounds selected from Table 1 (including Compound A), or a salt or solvate thereof.

[225] In some embodiments, a compound disclosed herein, such as a compound of Formula (I), (I-A), (I-B), (I-1), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), (I-E1), (II-B), (II-C), or (III), 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.

[226] 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.

[227] 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.

[228] 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.

[229] 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.

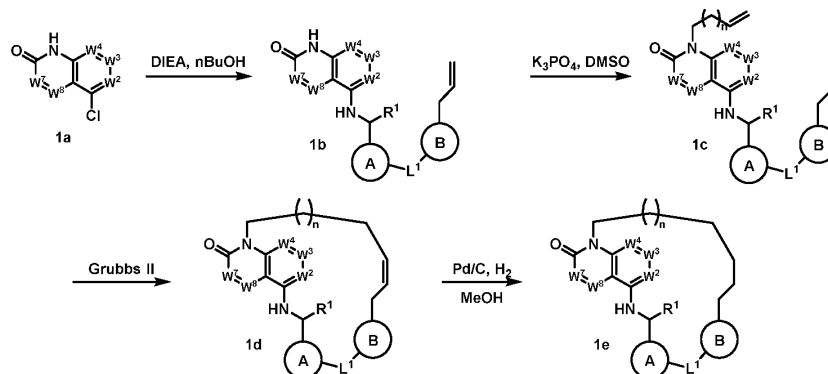
[230] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques known in the art. Materials used herein are either commercially available or prepared by synthetic methods generally known in the art. These schemes are not limited to 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 1-8**, the steps in some cases may be performed in a different order than the order shown in **Schemes 1-8**. 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.

[231] 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.

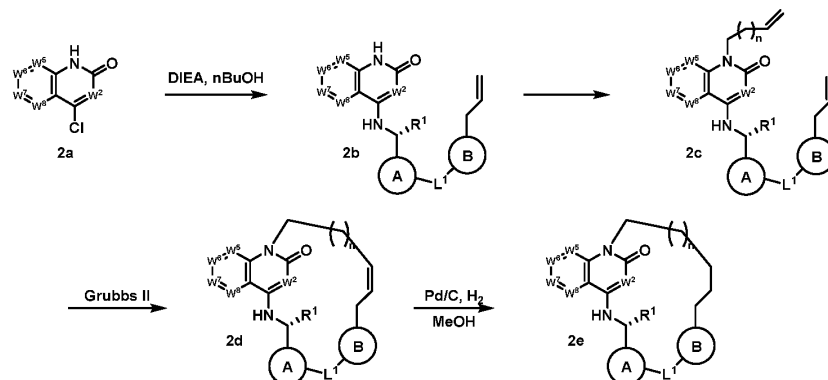
[232] In general, compounds of the disclosure may be prepared by the following reaction schemes:

Scheme 1



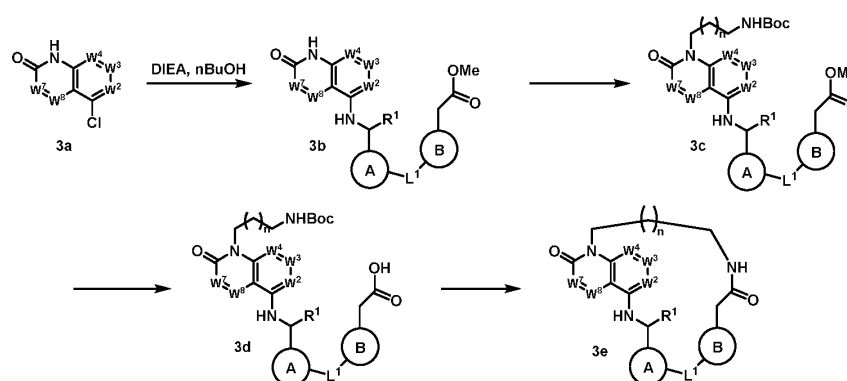
[233] In some embodiments, a compound of Formula 1e may be prepared according to Scheme 1. For example, heteroaryl amine 1b can be formed from chloride 1a via a nucleophilic aromatic substitution reaction. Substitution of the lactam can proceed under basic conditions to give diene 1c, which can undergo 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



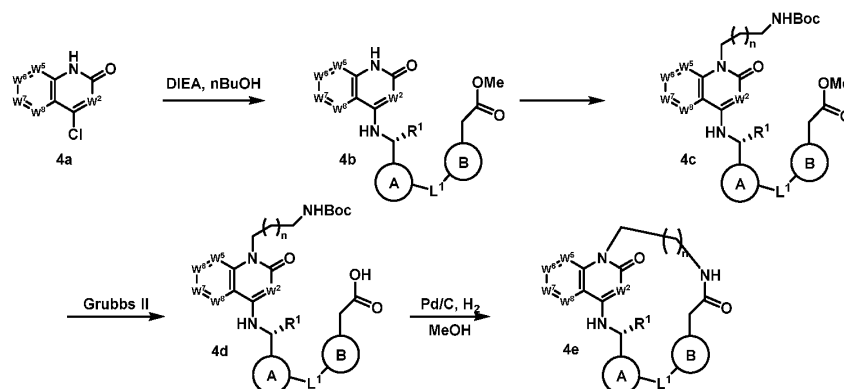
[234] Similarly, in some embodiments, a compound of Formula 2e may be prepared according to Scheme 2. For example, heteroaryl amine 2b can be formed from chloride 2a via a nucleophilic aromatic substitution reaction. Substitution of the lactam can proceed under basic conditions to give diene 2c, which 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



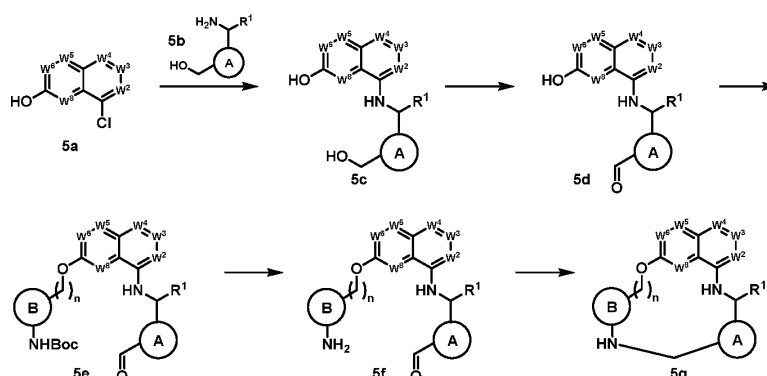
[235] In some embodiments, a compound of Formula **3e** may be prepared according to **Scheme 3**. For example, heteroaryl amine **3b** can be formed from chloride **3a** via a substitution reaction. Substitution of the lactam can give protected amine **3c**. Hydrolysis of the ester can form carboxylic acid **3d**, which can undergo deprotection and peptide coupling reactions to afford macrocycle of Formula **3e**.

Scheme 4



[236] 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**.

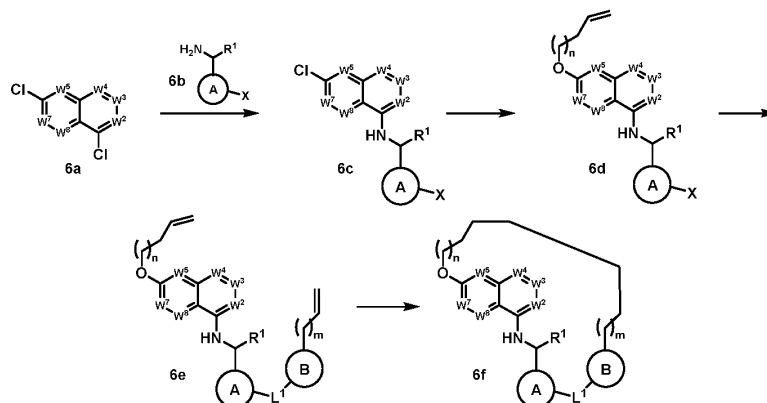
Scheme 5



[237] 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

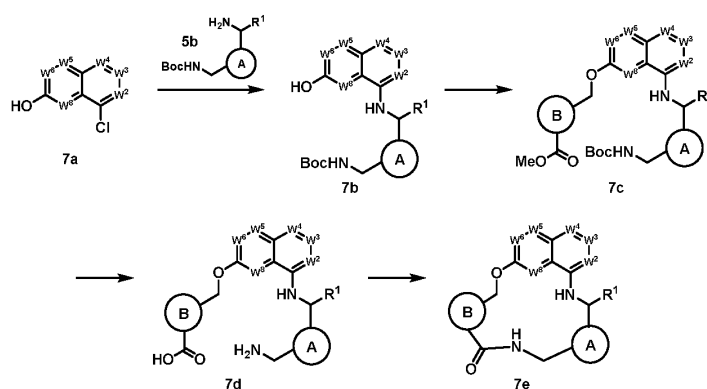
aldehyde **5d**, which can be followed with substitution of the phenol to give **5e**. Removal of the amine protecting group can afford **5f**, which can undergo a reductive amination to form a macrocycle of Formula **5g**.

Scheme 6



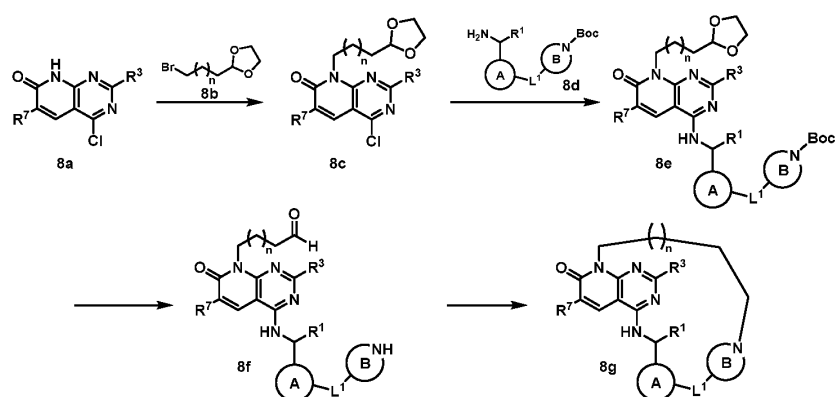
[238] In some embodiments, a compound of Formula **6f** may be prepared according to **Scheme 6**. For example, heteroaryl amine **6c** can be formed by coupling chloride **1a** with amine **6b**. Substitution of the phenol to olefin **6d** can be followed by installation of a second olefin to give diene **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



[239] 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



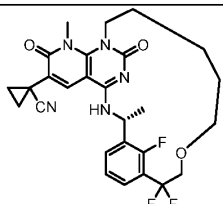
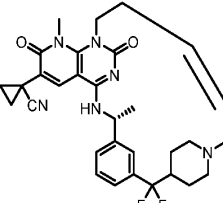
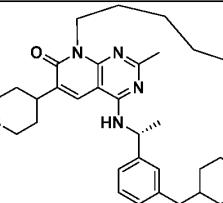
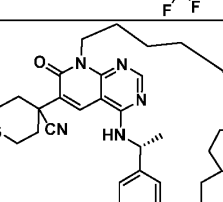
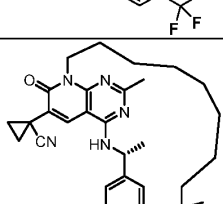
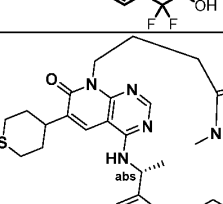
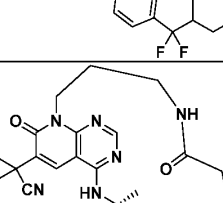
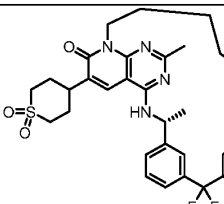
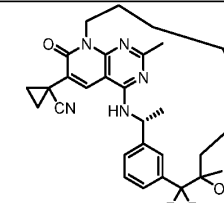
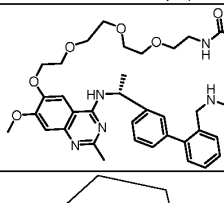
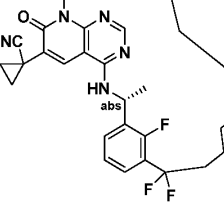
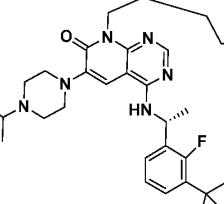
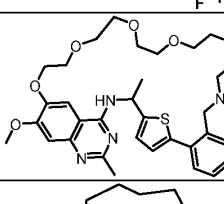
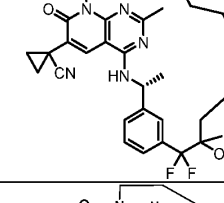
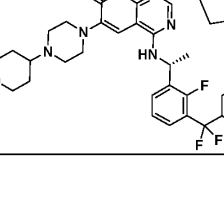
[240] In some embodiments, a compound of Formula **8g** may be prepared according to **Scheme 8**. For example, substitution of lactam **8a** with a suitable bromo dioxolane (**8b**) can give acetal **8c**. Nucleophilic aromatic substitution with amine **8d** can provide heteroaryl amine **8e**, which 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**.

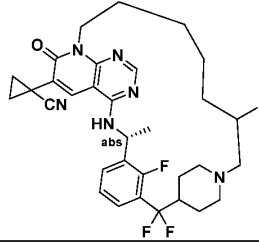
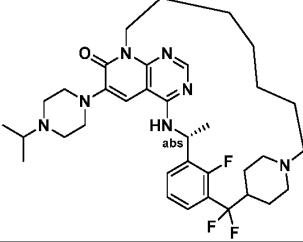
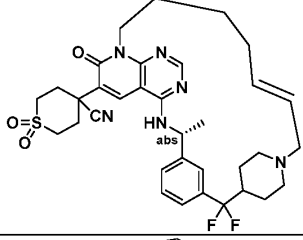
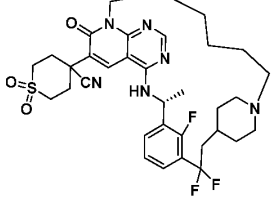
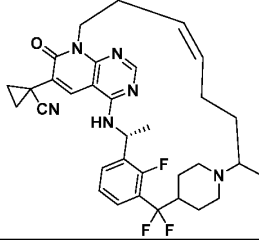
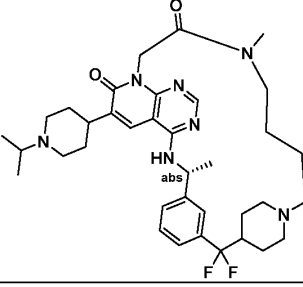
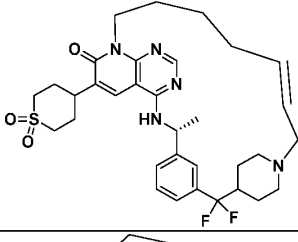
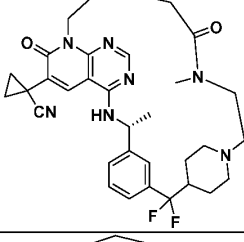
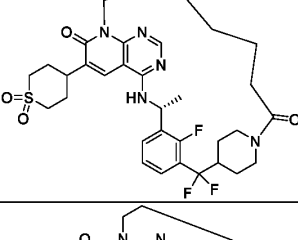
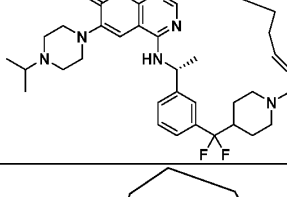
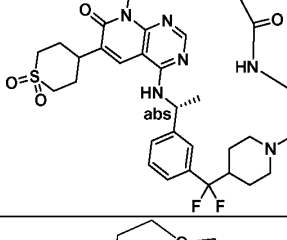
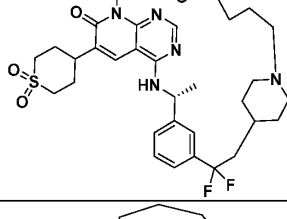
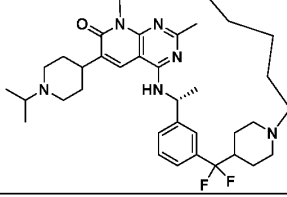
[241] Synthetic procedures for certain compounds may be found in PCT/US2022/018584, U.S. Pat. No. 11,648,254, PCT/US2023/065963, and U.S. App. No. 18/328,109, each of which is incorporated by reference in its entirety, including any compounds, formulas, recitations of compound variables, and synthetic 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. In some embodiments, a SOS1 inhibitor of the present disclosure is a compound described in U.S. Pat. No. 11,912,708, which is incorporated herein by reference in its entirety.

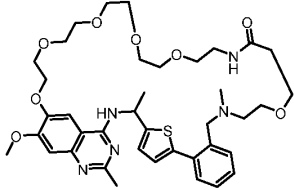
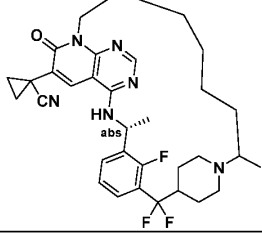
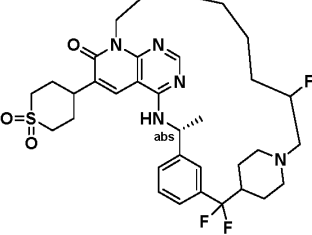
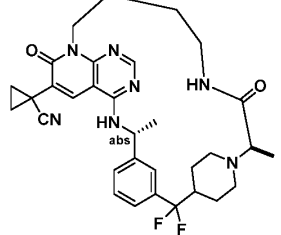
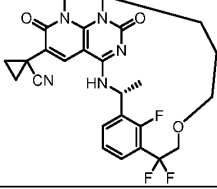
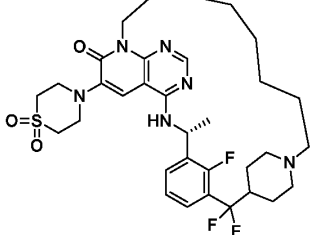
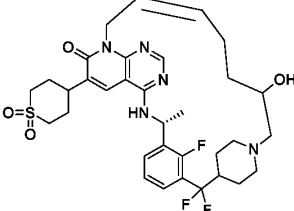
[242] In some embodiments, a compound of the present disclosure, for example, a compound of a formula given in **Table 1**, was synthesized according to one of the general routes outlined in **Schemes 1-8** or by methods generally known in the art. In some embodiments, exemplary compounds may include, but are not limited to, a compound selected from **Table 1**, or a salt or solvate thereof.

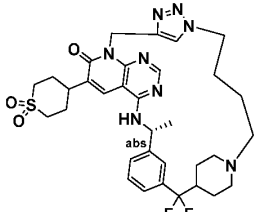
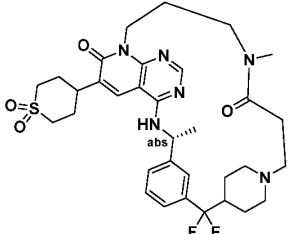
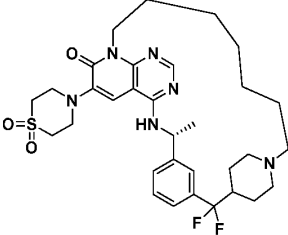
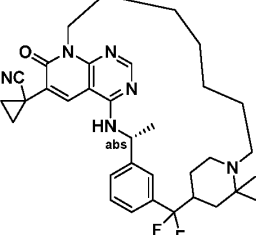
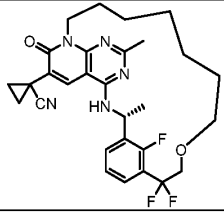
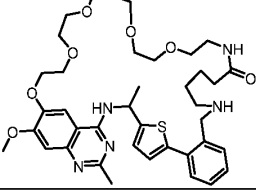
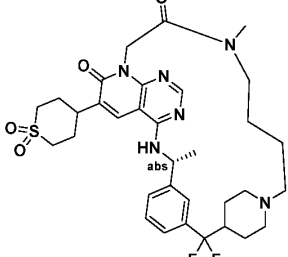
Table 1

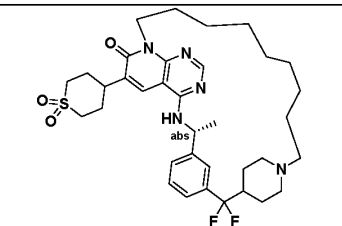
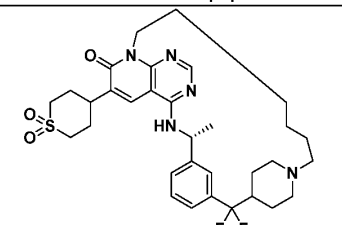
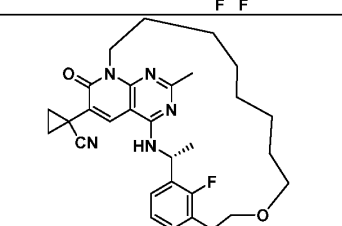
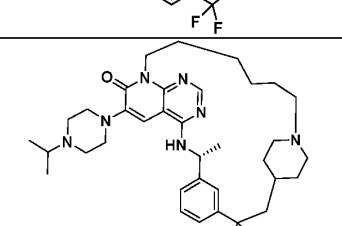
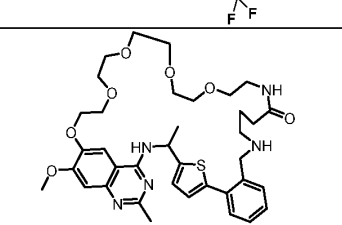
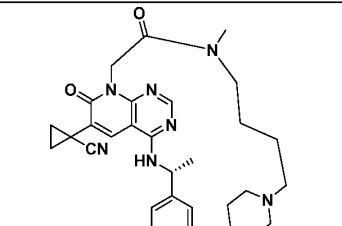
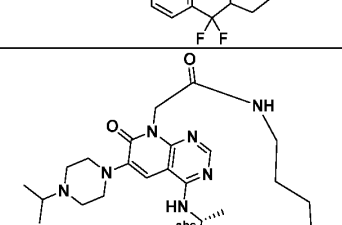
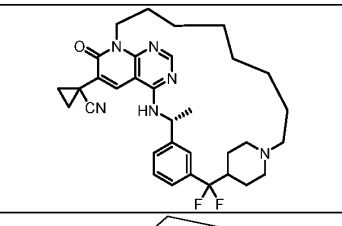
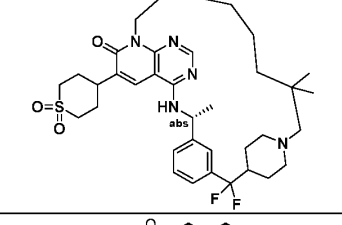
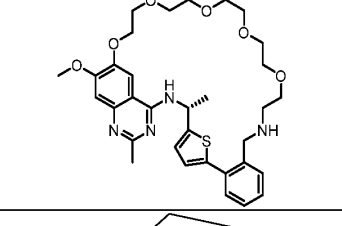
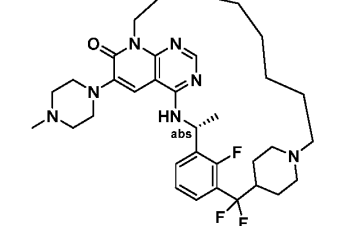
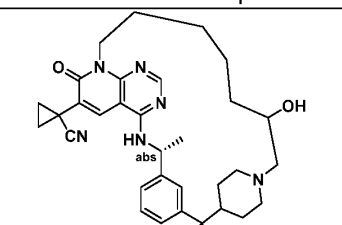
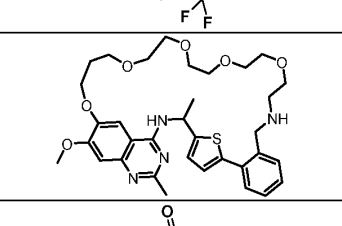
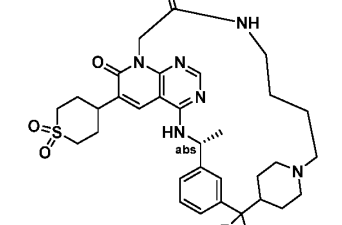
No.	Structure	[M+H] ⁺
A1		524.4
A2		540.4
A3		510.4
A4		548.3

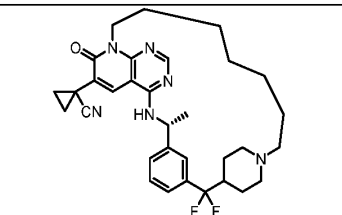
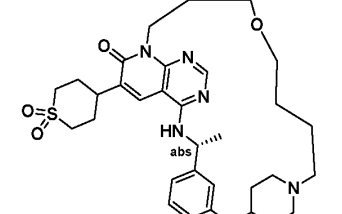
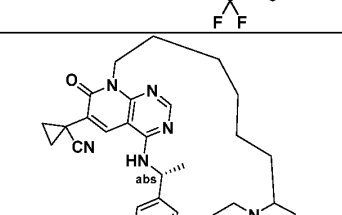
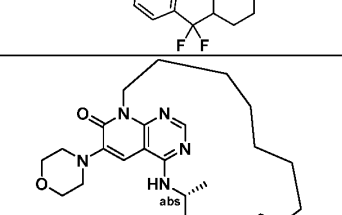
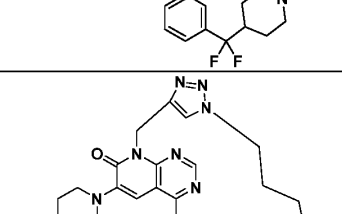
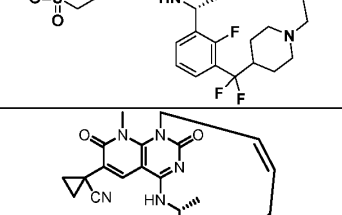
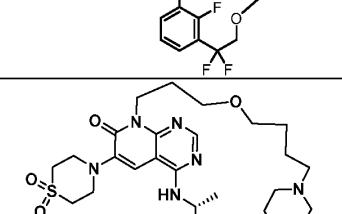
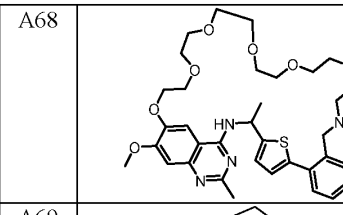
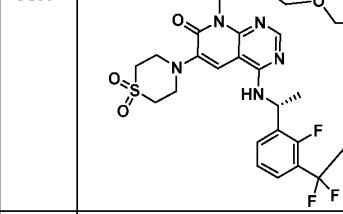
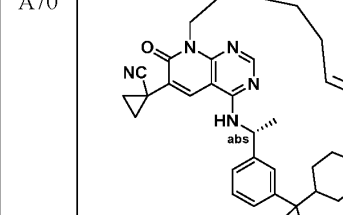
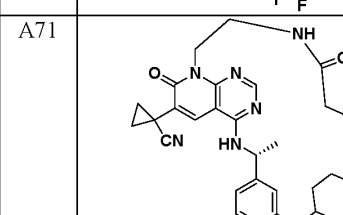
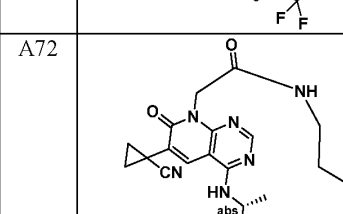
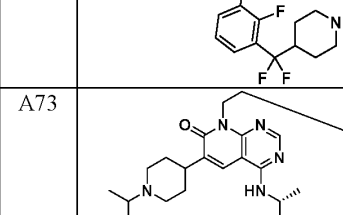
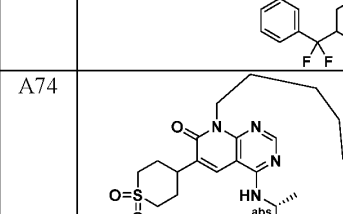
A5		528.4
A6		561.4
A7		644.5
A8		653.3
A9		550.4
A10		657.4
A11		594.5
A12		601.4
A13		534.4
A14		688.4
A15		579.4
A16		640.8
A17		650.3
A18		562.4
A19		682.5

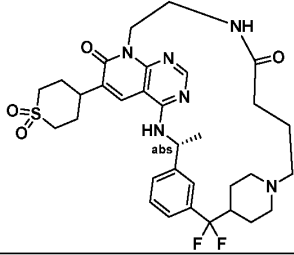
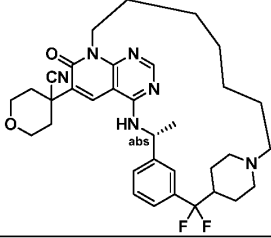
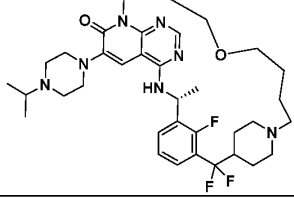
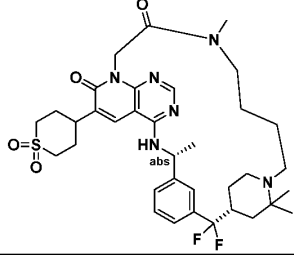
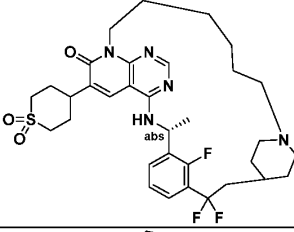
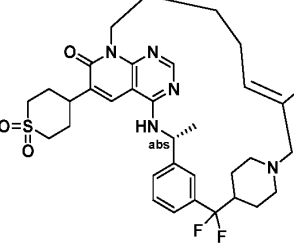
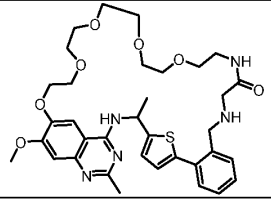
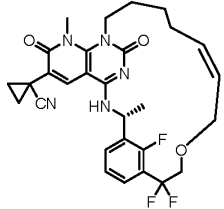
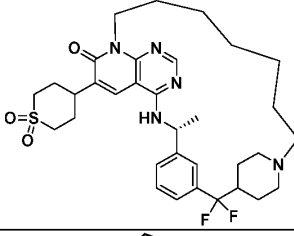
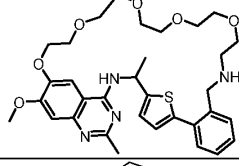
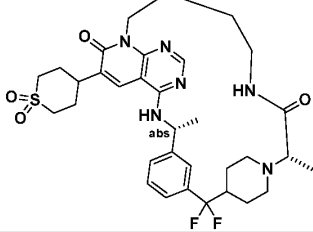
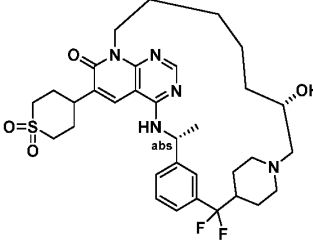
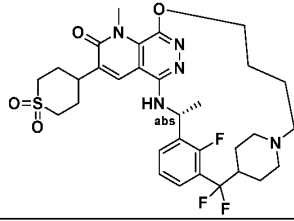
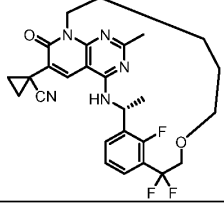
A20		593.4
A21		640.3
A22		651.3
A23		671.3
A24		591.5
A25		650.3
A26		626.4
A27		590.3
A28		660.2
A29		620.3
A30		643.4
A31		664.5
A32		635.6

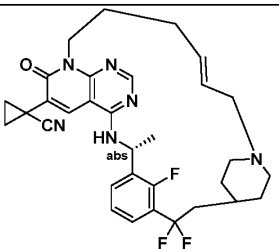
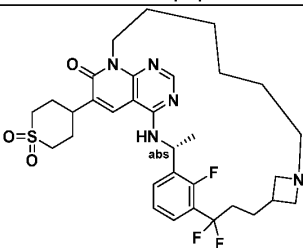
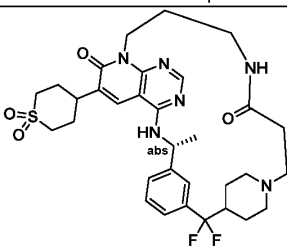
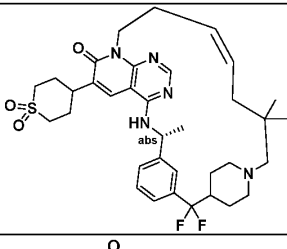
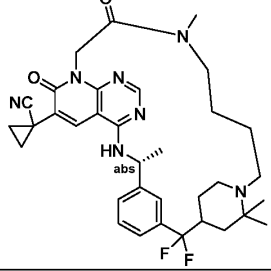
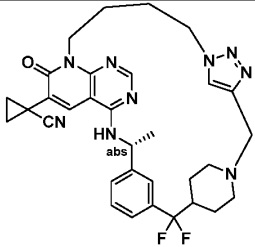
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A34		593.4
A35		646.4
A36		590.3
A37		514.3
A38		647.6
A39		660.4

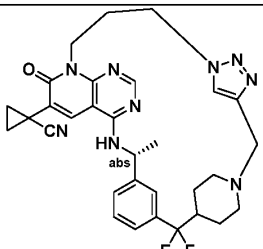
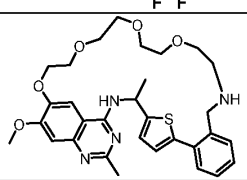
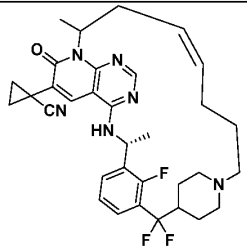
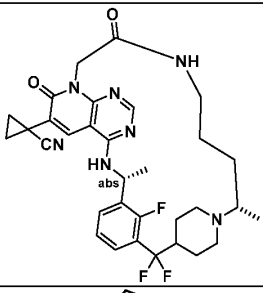
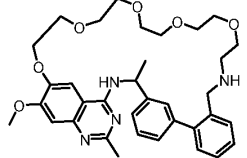
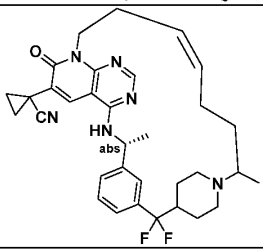
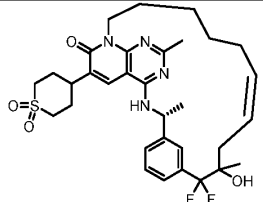
A40		667.3
A41		657.4
A42		629.3
A43		589.3
A44		540.4
A45		722.4
A46		657.3

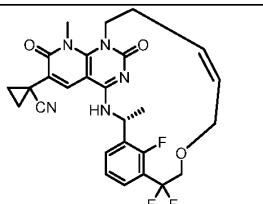
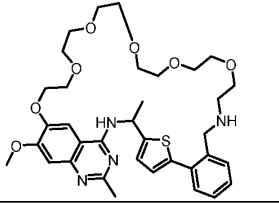
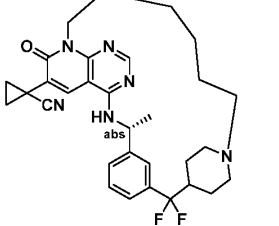
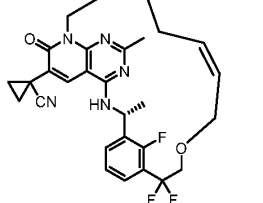
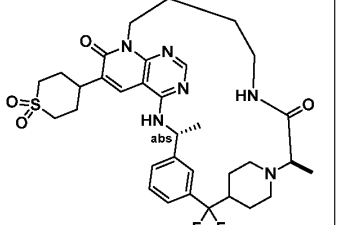
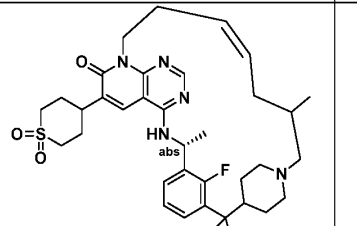
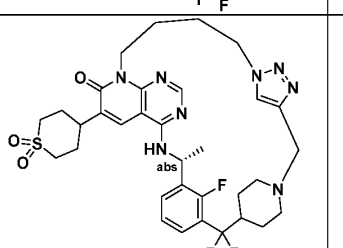
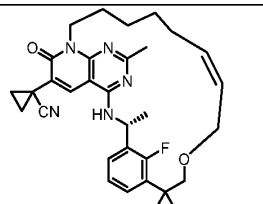
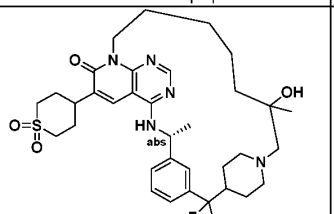
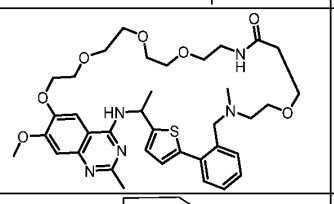
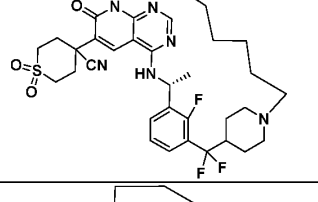
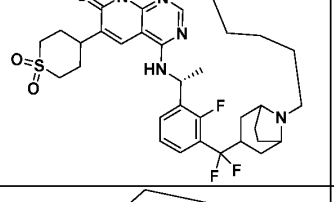
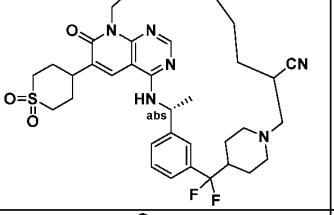
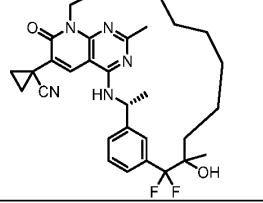
A47		656.3
A48		614.4
A49		554.3
A50		622.4
A51		708.3
A52		590.3
A53		637.2
A54		575.4
A55		656.6
A56		623.2
A57		612.3
A58		577.3
A59		637.3
A60		643.3

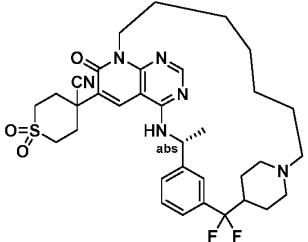
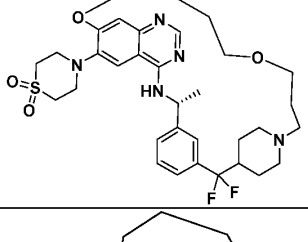
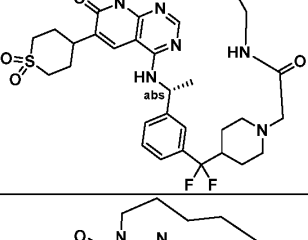
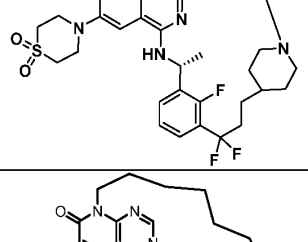
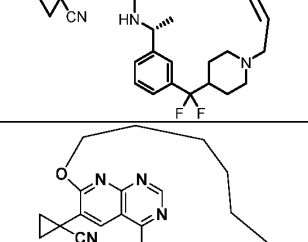
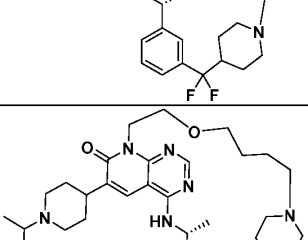
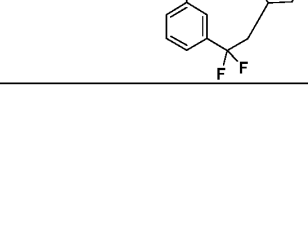
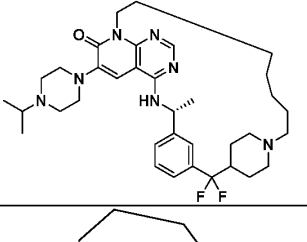
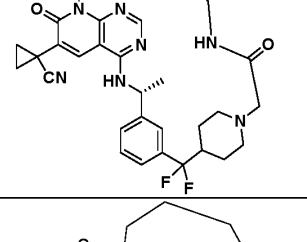
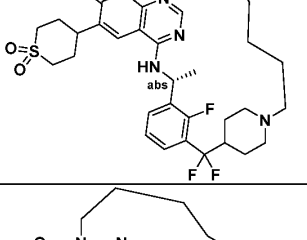
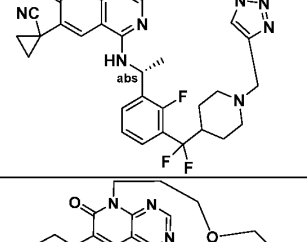
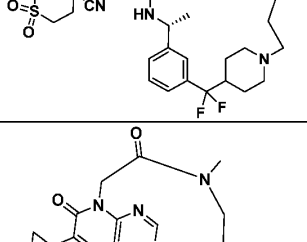
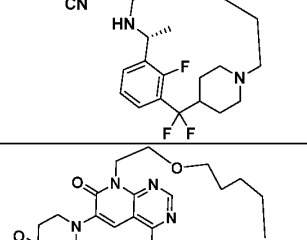
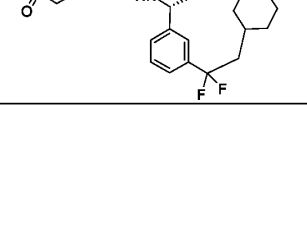
A61		561.5
A62		644.5
A63		575.3
A64		581.3
A65		686.2
A66		512.3
A67		640.4
A68		694.3
A69		663.3
A70		587.4
A71		576.3
A72		608.3
A73		621.6
A74		654.3

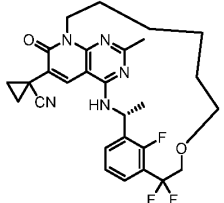
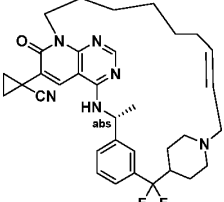
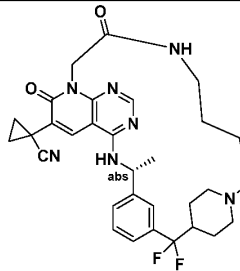
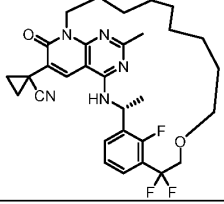
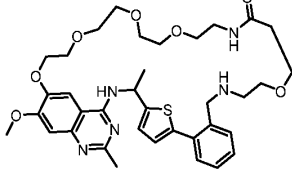
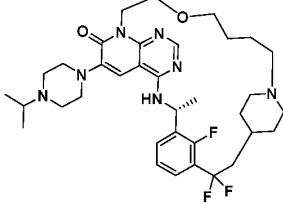
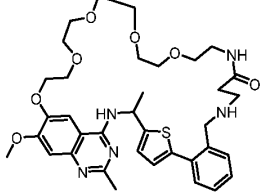
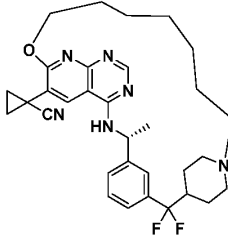
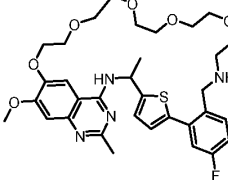
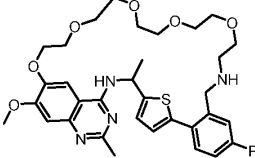
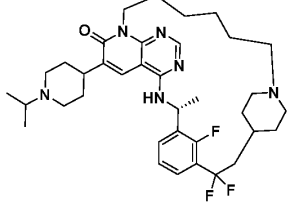
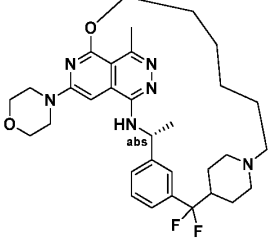
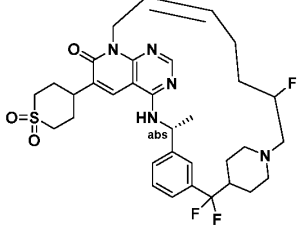
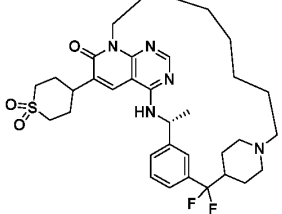
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A76		605.2
A77		656.6
A78		685.3
A79		646.1
A80		640.3
A81		680.3
A82		554.4
A83		628.3
A84		623.3
A85		657.3
A86		644.3
A87		634.2
A88		512.4

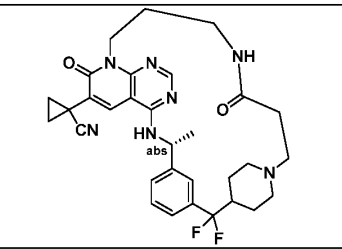
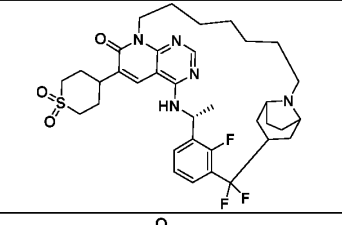
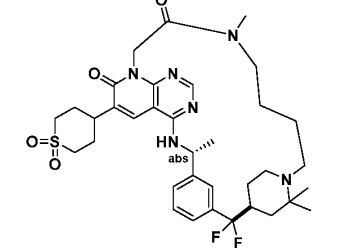
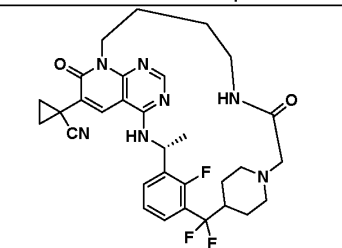
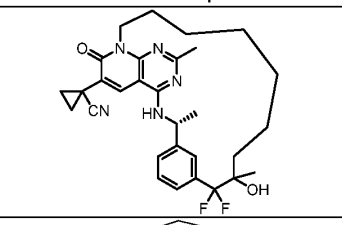
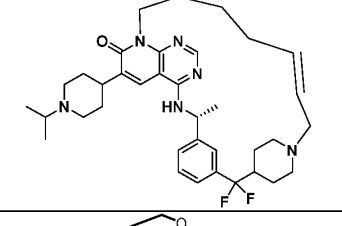
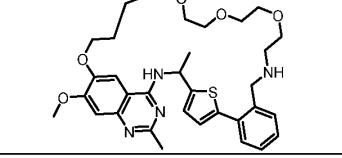
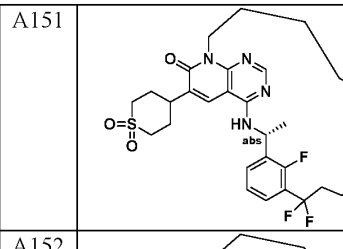
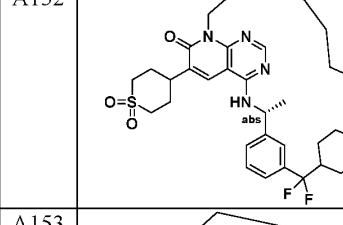
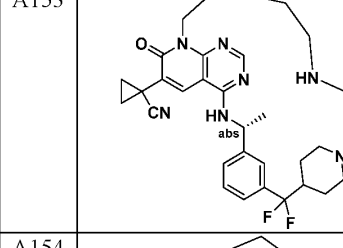
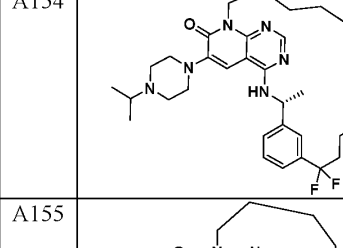
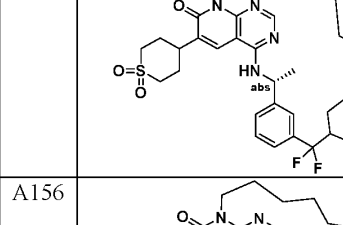
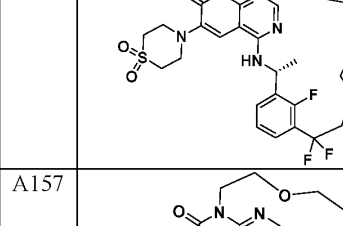
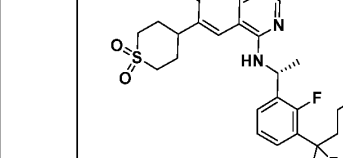
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A91		643.2
A92		654.4
A93		618.3
A94		600.3

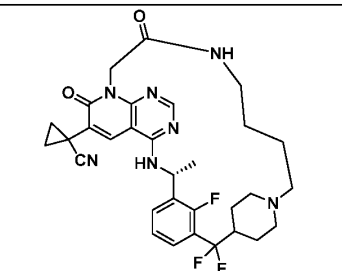
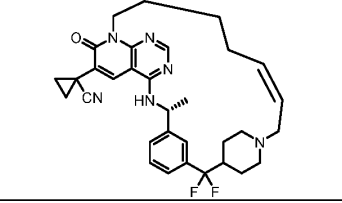
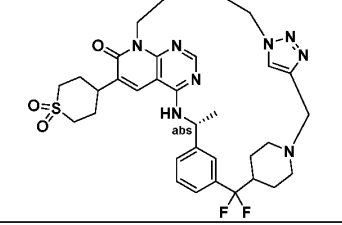
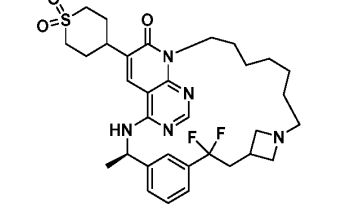
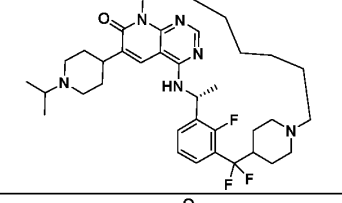
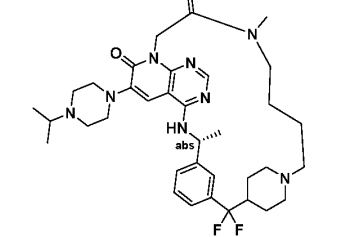
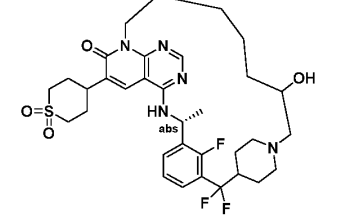
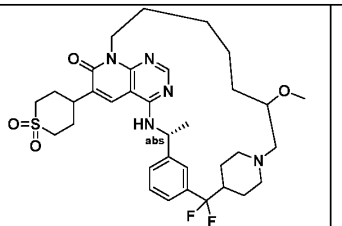
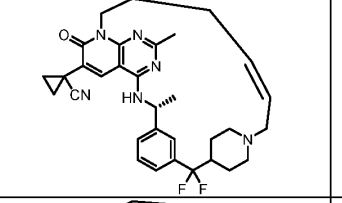
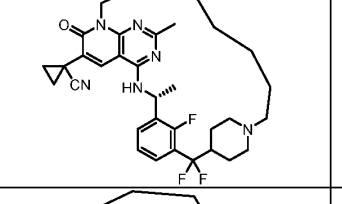
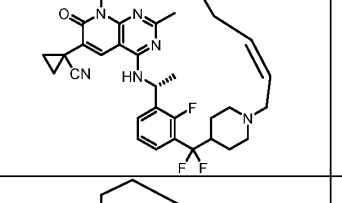
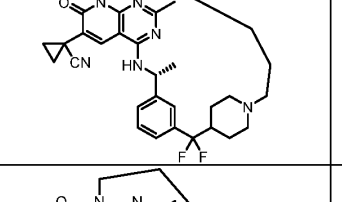
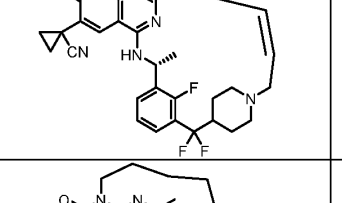
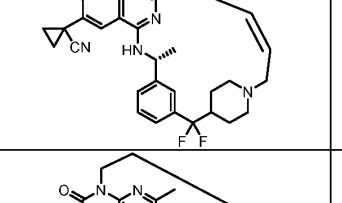
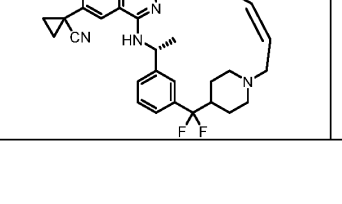
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A98		608.3
A99		617.4
A100		573.3
A101		615.4

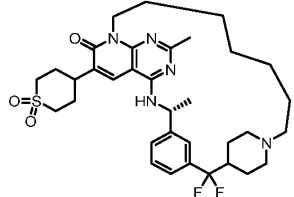
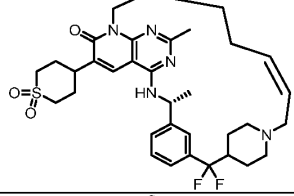
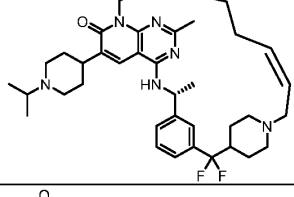
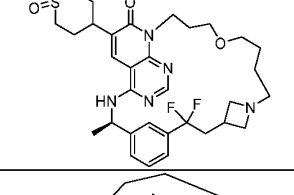
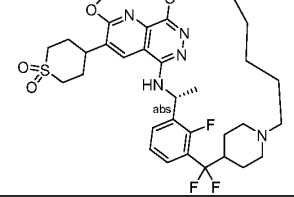
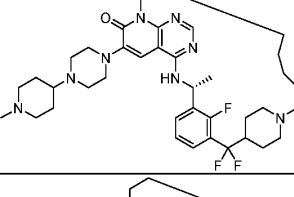
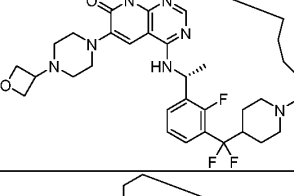
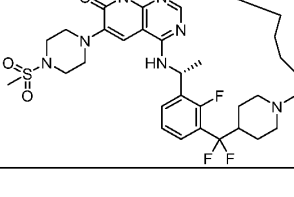
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A104		547.3
A105		538.4
A106		657.3
A107		658.2
A108		685.2
A109		552.4
A110		658.3
A111		708.3
A112		671.5
A113		672.3
A114		653.2
A115		564.4

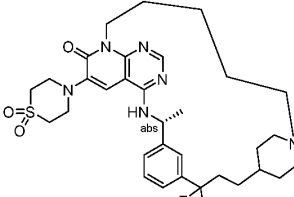
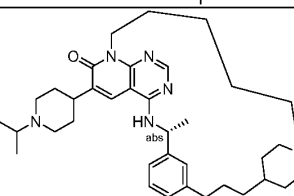
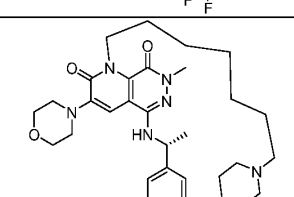
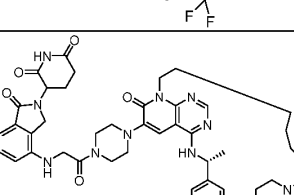
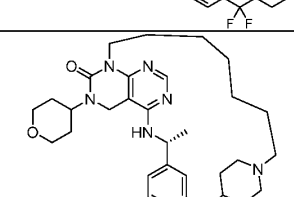
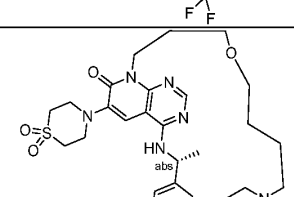
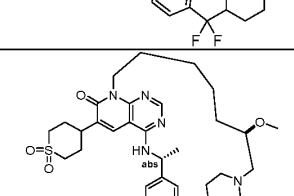
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A117		644.4
A118		643.3
A119		647.3
A120		573.4
A121		547.3
A122		637.5
A123		622.3
A124		576.3
A125		646.3
A126		618.4
A127		669.3
A128		608.4
A129		645.4

A130		526.4
A131		587.3
A132		576.7
A133		568.5
A134		694.3
A135		656.7
A136		694.3
A137		561.4
A138		641.3
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A140		639.3
A141		581.2
A142		644.2
A143		642.4

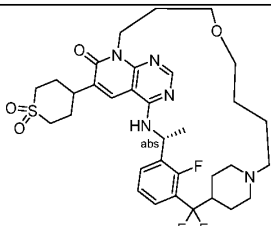
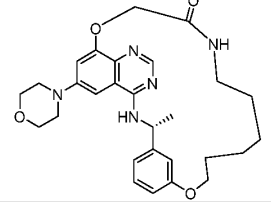
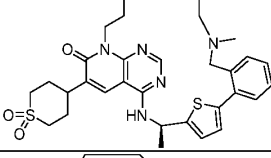
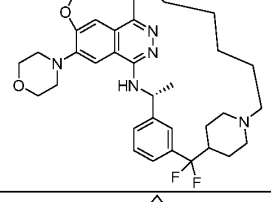
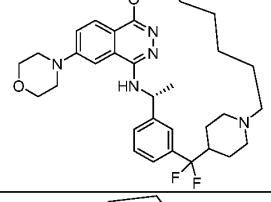
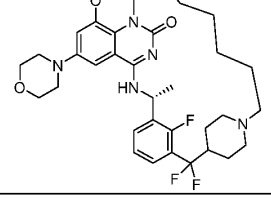
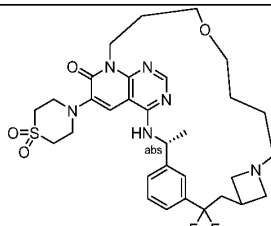
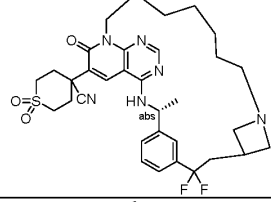
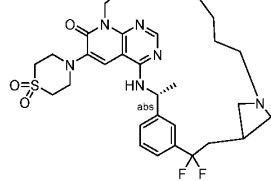
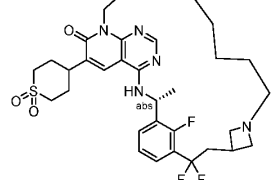
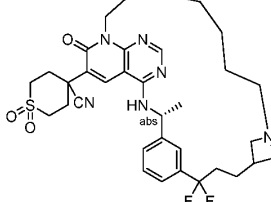
A144		576.3
A145		672.3
A146		685.3
A147		594.3
A148		536.4
A149		619.4
A150		607.3
A151		646.2
A152		644.2
A153		590.3
A154		622.4
A155		656.3
A156		646.8
A157		648.6

A158		594.7
A159		559.4
A160		667.3
A161		614.3
A162		639.7
A163		651.3
A164		662.4
A165		658.3
A166		559.5
A167		593.5
A168		591.5
A169		547.4
A170		577.5
A171		587.5
A172		545.4

A173		642.5
A174		640.5
A175		633.5
A176		630.4
A177		676.3
A178		695.5
A179		654.3
A180		676.4

A181		629.3
A182		621.4
A183		611.5
A184		879.7
A185		583.5
A186		645.3
A187		658.3

A188		658.6
A189		669.3
A190		638.4
A191		662.3
A192		644.4
A193		614.6
A194		644.3
A195		607.5
A196		580.5
A197		659.3
A198		
A200		
A201		
A202		687.3

A203		662.3
A204		506.4
A205		634.5
A206		594.5
A207		566.2
A208		628.4
A209		631.6
A210		639.5
A211		615.3
A212		632.0
A213		639.2

[243] 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. In some embodiments, the IC₅₀ of a subject compound (including those shown in Table 1) for a SOS protein is less than about 5 μ M, less than about 1 μ M, less than about 50 nM, less than about 10 nM, less than about 1 nM, less than about 0.5 nM, less than about 100 pM, or less than about 50 pM, as measured in an in vitro

assay known in the art or exemplified herein.

[244] 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.

[245] 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.

Kits

[246] Another aspect of the present disclosure provides a kit for use in reducing proliferation of cancer cells comprising an EGFR mutation, such as an EGFR exon 20 insertion. Typically, the kit comprises: (1) a composition comprising a SOS1 inhibitor of Formula (I), (I-A), (I-B), (I-1), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), (I-E1), (II-B), (II-C), or (III); (2) a composition comprising osimertinib; and (3) instructions for using the composition(s) of (1) and (2). In some embodiments, the small molecule SOS1 inhibitor is a compound described in Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, instructions for contacting the cells in vitro, ex vivo, or in vivo are provided. In some embodiments, the SOS1 inhibitor and osimertinib are formulated in the same unit dosage form. In some embodiments, the SOS1 inhibitor and osimertinib are formulated in different unit dosage forms. In some embodiments, the kit can comprise a multi-day supply, including instructions directing the multi-day administration.

Pharmaceutical compositions and methods of administration

[247] In certain aspects, the present disclosure provides a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[248] A compound of Formula (I), (I-A), (I-B), (I-1), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), (I-E1), (II-B), (II-C), or (III), or a pharmaceutically acceptable salt or solvate thereof, may be administered to a subject in a biologically compatible form suitable for administration to treat or prevent a disease, disorder or condition. A compound described herein may be administered in any pharmacological form including a therapeutically effective amount of a compound of Formula (I), (I-A), (I-B), (I-1), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), (I-E1), (II-B), (II-C), or (III), or a pharmaceutically acceptable salt or solvate thereof, alone or in combination with a pharmaceutically acceptable carrier. In some embodiments, the present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (I), (I-A), (I-B), (I-1), (I-B1), (I-B2), (I-C), (I-C1), (I-C2), (I-C3), (I-D), (I-D1), (I-D2), (I-E), (I-E1), (II-B), (II-C), or (III), or a pharmaceutically acceptable salt or solvate thereof.

[249] 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)).

[250] Accordingly, provided herein is a pharmaceutical composition comprising at least one compound described herein, or a pharmaceutically acceptable salt, 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.

[251] 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 effected 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.

[252] 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.

[253] 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.

[254] 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.

[255] 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.

[256] 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.

EXAMPLES

[257] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

[258] Example 1: Sequences

[259] Human K-Ras4b (SEQ ID NO. 1):

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1 MTEYKLVVVG AGGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHHYREQI
101 KRVKDSSEVP MVLVGNKCDL PSRTVDTKQA QDLARSYGIP FIETSAKTRQ
151 GVDDAFYTLV REIRKHKEKM SKDGKKKKKK SKTKCVIM
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[260] Human SOS1 (SEQ ID NO. 2):

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1 MQAQQLPYEF FSEENAPKWR GLLVPALKKV QGQVHPTLES NDDALQYVEE
51 LILQLLNMLC QAQPRSASDV EERVQKSFPH PIDKWAIADA QSAIEKRKRR
101 NPLSLPVEKI HPLLKEVLGY KIDHQVSVYI VAVLEYISAD ILKLVGNVYR
151 NIRHYEITKQ DIKVAMCADK VLMDMFHQDV EDINILSLTD EEPSTSGEQT
201 YYDLVKAFMA EIRQYIRELN LIIKVFREPF VSNSKLFSDN DVENIFSRIV
251 DIHLSVKLL GHIEDTVEMT DEGSPHPL VG SCFEDLAEEL AFDPYESYAR
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301 DILRPGFHDR FLSQLSKPGA ALYLSIGEG FKEAVQYVLP RLLLAPVYHC
 351 LHYFELLKQL EEKSEDQEDK ECLKQAITAL LNVQSGMEKI CSKSLAKRRL
 401 SESACRFYSQ QMKGKQLAIK KMNEIQKNID GWEGKDIGQC CNEFIMEGTL
 451 TRVGAKHERH IFLFDGLMIC CKSNHGQPRL PGASNAEYRL KEKFFMRKVQ
 501 INDKDDTNEY KHAFEILKD ENSVIFSAKS AEEKNNWMAA LISLQYRSTL
 551 ERMLDVTMLQ EEKEEQMRLP SADVYRFAEP DSEENIIFEE NMQPKAGIPI
 601 IKAGTVIKLI ERLTYHMYAD PNFVRTFLT T YRSFCKPQEL LSLIIFERFI
 651 PEPEPTEADR IAIENGDQPL SAEKLRFRKE YIQPVQLRVL NVCRHWVEHH
 701 FYDFERDAYL LQRMEEFIGT VRGKAMKKWV ESITKIIQRK KIARDNGPGH
 751 NITFQSSPPT VEWHISRPGH IETFDLL TLH PIEIARQL TL LESDLYRAVQ
 801 PSEL VGSVWT KEDKEINSPN LLKMIRHTTN LTLWFEK CIV ETENLEERVA
 851 VVSRIIEILQ VFQELNNFNG VLEVVSAMNS SPVYRLDHTF EQIPSRQKKI
 901 LEEAHELSED HYKKYLAKLR SINPPCVPFF GIYLTNLIK T EEGNPEVLKR
 951 HGKELINFSK RRKVAEITGE IQQYQNQPYC LRVESDIKRF FENLNPMGNS
 1001 MEKEFTDYLF NKSLEIEPRN PKPLPRFPKK YSYPLKSPGV RPSNRPGMT
 1051 RHPTPLQEP RKISYSRIPE SETESTASAP NSPRTPPTPP PASGASSTTD
 1101 VCSVFSDHS SPFHSSNDTV FIQVTLPHGP RSASVSSISL TKGTDVPPVP
 1151 PPVPPRRRPE SAPAESSPSK IMSKHLDSP AIPPRQPTSK AYSPRYSISD
 1201 RTSISDPPEP PLLPPREP RPTDVFSSSP LHLQPPPLGK KSDHGNAFFP
 1251 NSPSPFTPPP PQTPSPHGTR RHLPSPLTQ EVDLHSIAGP PVPPRQSTSQ
 1301 HIPKLPPKTY KREHTHPSMH RDGPPLLENA HSS

[261] Example 2: SOS purification

[262] 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.

[263] Example 3: Ras-SOS interaction assay

[264] 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.

[265] 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.

[266] 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 μ M, 2.5 μ M, 0.63 μ M, 0.16 μ M, 0.04 μ M, 0.01 μ M 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).

[267] Example 4: Ras-SOS cellular growth inhibition assay

[268] 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.

[269] Growth of cells with K-Ras G12C mutation: MIA PaCa-2 (ATCC CRL-1420) and NCI-H1792 (ATCC CRL-5895) cell lines comprise a G12C mutation and 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, e.g., more potent inhibition against Kras G12D relative to Kras G12C mutant, by using MIA PaCa-2 (G12C driven tumor cell line) as a comparison. Cell culture medium (comprising, for example, MIA PaCa-2 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 9 point 3-fold dilution series) of the compounds herein (e.g., approximately 125 μ L 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 μ L), 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.

[270] Example 5: Inhibition of cell proliferation using SOS1 inhibitors in combination with osimertinib

[271] A variety of EGFR mutant cell lines are available commercially, including Ba/F3-EGFR_Ex20_ASV insertion cells, Ba/F3 EGFR L858R/T790M cells, PC9-EGFR Ex19 E746_A750 cells, and H1975-EGFR L858R/T790M cells. These exemplary cells can be maintained in a humidified incubator at 37 °C with 5% CO₂ and grown in RPMI 1640 with 10% FBS (Gibco) and 50 IU mL⁻¹ penicillin/streptomycin (Gibco). 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, 3-fold dilution series of indicated compounds (40 μ L final volume per well) and growth inhibition is monitored ~72 hours later (for BaF/3 EGFR mutant lines) or 5 days later for other cell lines according to the manufacturer's recommended instructions, where 20 μ L 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 osimertinib are monitored as stated above. FIG. 1A and FIG. 1B show that a SOS1 inhibitor of the present disclosure (Compound A) in combination with osimertinib synergistically inhibits cell growth of EGFR exon 20 insertion cells. FIG. 2A and FIG. 2B show that a SOS1 inhibitor of the present disclosure (Compound A) in combination with osimertinib synergistically inhibits cell growth of EGFR L858R/T790M cells. FIG. 3A and FIG. 3B show that a SOS1 inhibitor of the present disclosure (Compound A) in combination with osimertinib synergistically inhibits cell growth of EGFR ex19 E746_A750del cells. FIG. 4A and FIG. 4B show that a SOS1 inhibitor of the present disclosure (Compound A) in combination with osimertinib synergistically inhibits cell growth of EGFR L858R/T790M cells.

[272] Example 6: Inhibition of tumor growth in MET-amplified murine model

[273] Mice are maintained under specific pathogen-free conditions, and food and water are 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 inoculate Ba/F3 EGFR mutant cell lines, 1×10^6 cells are harvested on the day of use and injected in growth-factor-reduced Matrigel/PBS (50% final concentration in 100 μ L). 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 as indicated in FIG. 7 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: $(L \times w^2) / 2$, in which L and w refer to the length and width of the tumor diameter, respectively. When tumors reach an average size of 100-200 mm³, mice are randomized and treated with vehicle or indicated compounds using the reported schedule. Results are expressed as mean and standard deviation of the mean. No apparent toxicity or body weight loss was observed. FIG. 7 shows that a SOS1 inhibitor of the present disclosure (Compound A) is effective in inhibiting tumor growth in EGFR-mediated lung cancer, particularly MET amplified lung cancer, alone as a monotherapy.

[274] Example 7: Inhibition of tumor growth in EGFR exon 20 insertion murine model

[275] Mice are maintained under specific pathogen-free conditions, and food and water are 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 inoculate Ba/F3 EGFR mutant cell lines, 1×10^6 cells are harvested on the day of use and injected in growth-factor-reduced Matrigel/PBS (50% final concentration in 100 μ L). 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 as indicated in FIG. 6, FIG. 8, and FIG. 11 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: $(L \times w^2) / 2$, in which L and w refer to the length and width of the tumor diameter, respectively. When tumors reach an average size of 100-200 mm³, mice are randomized and treated with vehicle or indicated compounds using the reported schedule. Results are expressed as mean and standard deviation of the mean. No apparent toxicity or body weight loss was observed. FIG. 6 and FIG. 8 show that a SOS1 inhibitor of the present disclosure (Compound A) synergistically inhibits tumor growth in combination with osimertinib in EGFR exon 20

insertion lung cancer. FIG. 11 shows that a SOS1 inhibitor of the present disclosure (Compound A) synergistically inhibits tumor growth in combination with osimertinib in a PDX model (NSCLC-squamous, EGFR-Ex20 D772_N773insDNP) that is refractory to osimertinib.

[276] Example 8: Inhibition of tumor growth in EGFR L858R/T790M murine models

[277] Mice are maintained under specific pathogen-free conditions, and food and water are provided *ad libitum*. Female 6- to 8-week old athymic BALB/c nude (NCr) nu/nu mice are used to inoculate EGFR L858R/T790M cell lines. For example, H1975 cells (5×10^6) or Ba/F3 EGFR mutant cells (1×10^6) are harvested on the day of use and injected in growth-factor-reduced Matrigel/PBS (50% final concentration in 100 μ L). 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 as indicated in FIG. 9 and FIG. 10 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: $(L \times w^2) / 2$, in which L and w refer to the length and width of the tumor diameter, respectively. When tumors reach an average size of 100-200 mm³ (FIG. 9) or 200-300 mm³ (FIG. 10), mice are randomized and treated with vehicle or indicated compounds using the reported schedule. Results are expressed as mean and standard deviation of the mean. No apparent toxicity or body weight loss was observed. FIG. 9 shows that a SOS1 inhibitor of the present disclosure (Compound A) in combination with osimertinib synergistically reduces tumor volume of a mouse Ba/F3 cell line that expresses L858R and T790M EGFR mutations. FIG. 10 shows that a SOS1 inhibitor of the present disclosure (Compound A) in combination with osimertinib synergistically reduces H1975 xenograft tumor volume (NSCLC, EGFR L858R/T790M).

[278] Example 9: Inhibition of cell proliferation using SOS1 inhibitors in combination treatments

[279] A variety of EGFR mutant cell lines, including Ba/F3-EGFR_Ex20_ASV insertion cells, Ba/F3 EGFR L858R/T790M cells, Ba/F3 EGFR L858R/T790M/L792H cells, Ba/F3 EGFR G719S cells, Ba/F3 EGFR L861Q cells, PC9-EGFR Ex19 E746_A750 cells, H1975-EGFR L858R/T790M cells, and H820-EGFR L858R/T790M with MET amplification cells, are available commercially. These exemplary cells can be maintained in a humidified incubator at 37 °C with 5% CO₂ and grown in RPMI 1640 with 10% FBS (Gibco) and 50 IU mL⁻¹ penicillin/streptomycin (Gibco). 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, 3-fold dilution series of either vehicle; osimertinib; savolitinib; a SOS1 inhibitor of the present disclosure (e.g., Compound A); osimertinib and Compound A; savolitinib and Compound A; or osimertinib, savolitinib, and Compound A (40 μ L final volume per well) and growth inhibition is monitored ~72 hours later (for Ba/F3 EGFR mutant lines) or 5 days later for other cell lines according to the manufacturer's recommended instructions, where 20 μ L 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 alone or in combination with osimertinib and/or savolitinib are monitored as stated above.

[280] Example 10: Inhibition of tumor growth in MET-amplified murine model

[281] Mice are maintained under specific pathogen-free conditions, and food and water are 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. For Ba/F3 EGFR mutant cell line models and other cell line models, including H820-EGFR L858R/T790M with MET amplification cells, $1-5 \times 10^6$ cells are harvested on the day of use and injected in growth-

factor-reduced Matrigel/PBS (50% final concentration in 100 μ L) subcutaneously into the flank. 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: $(L \times w^2) / 2$, in which L and w refer to the length and width of the tumor diameter, respectively. When tumors reach an average size of 100-200 mm^3 , mice are randomized and treated with either vehicle; osimertinib; savolitinib; a SOS1 inhibitor of the present disclosure (e.g., Compound A); osimertinib and Compound A; savolitinib and Compound A; or osimertinib, savolitinib, and Compound A.

[282] Example 11: Inhibition of tumor growth in EGFR mutant murine model

[283] Mice are maintained under specific pathogen-free conditions, and food and water are provided *ad libitum*. For PDX and cell line models, including H820 cell line derived tumor models, BALB/c nude (NCr) mice are implanted with respective tumor fragments (2-3 mm in diameter) or 5×10^6 cells are injected with growth-factor-reduced Matrigel/PBS (50% final concentration in 100 μ L) in the flank. 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: $(L \times w^2) / 2$, in which L and w refer to the length and width of the tumor diameter, respectively. When tumors reach an average size of 100-200 mm^3 , mice are randomized and treated with either vehicle; osimertinib; savolitinib; a SOS1 inhibitor of the present disclosure (e.g., Compound A); osimertinib and Compound A; savolitinib and Compound A; or osimertinib, savolitinib, and Compound A.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of reducing proliferation of cancer cells comprising an epidermal growth factor receptor (EGFR) exon 20 insertion, the method comprising administering to the cells (a) a SOS1 inhibitor and (b) osimertinib, 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.
3. A method of downregulating EGFR signaling output in a plurality of non-small cell lung cancer cells, comprising:
 - (i) assessing EGFR 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) osimertinib if an EGFR exon 20 insertion 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 MET inhibitor, wherein (a) is administered prior to, concurrently with, or subsequent to administering (b).
5. The method of claim 4, wherein the cancer is an EGFR-mediated cancer.
6. The method of claim 4 or 5, wherein the cancer exhibits MET amplification.
7. The method of any one of claims 4 to 6, wherein the MET inhibitor is savolitinib.
8. The method of any one of claims 4 to 7, further comprising administering (c) an additional agent or additional therapy.
9. The method of claim 8, wherein the additional agent is an EGFR inhibitor.
10. The method of claim 9, wherein the EGFR inhibitor is selected from gefitinib, erlotinib, afatinib, lazertinib, osimertinib, dacomitinib, neratinib, cetuximab, panitumumab, lapatinib, necitumumab, nazartinib, vandetanib, poziotinib, mobocertinib, zipalertinib, sunvozertinib, BAY-2927088, BLU-451, BLU-945, STX-721, and zorifertinib.
11. The method of claim 9, wherein the EGFR inhibitor is osimertinib.
12. The method of claim 8, wherein the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation.
13. 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 0.1 as ascertained by Bliss independent criterion.
14. A method of treating an EGFR-mediated cancer in a subject, comprising administering to the subject (a) a SOS1 inhibitor and (b) osimertinib, 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 0.1 as ascertained by Bliss independent criterion.

15. The method of claim 13 or 14, wherein the synergistic value is ascertained by Bliss independent 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

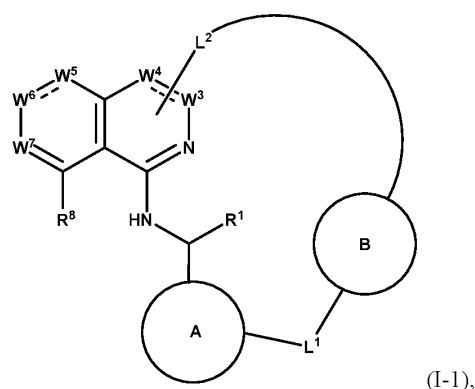
$Y_A Y_B$ is the product of Y_A and Y_B .

16. The method of any one of claims 13 to 15, wherein the synergistic value is at least 0.4.

17. The method of any one of claims 13 to 15, wherein the synergistic value is at least 1.

18. The method of any one of claims 13 to 15, wherein the synergistic value is at least 5.

19. The method of any one of claims 1 to 18, wherein the SOS1 inhibitor is a compound of Formula (I-1):



or a pharmaceutically acceptable salt or solvate thereof, wherein:



is selected from C₅₋₇ carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R¹¹;



is absent or selected from C₃₋₈ carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{11a};

L¹ is selected from a bond, C₁₋₆ alkylene, and C₁₋₆ haloalkylene;

L² is selected from C₅₋₂₅ alkylene, C₅₋₂₅ alkenylene, C₅₋₂₅ alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}, wherein L²

is covalently bound to one of W³, W⁴, W⁵, W⁶, or W⁷;

W³ is selected from N(R^{3b}), N, C(R³), and C(O);

W⁴ is selected from N(R^{4b}), N, C(R⁴), and C(O);

W⁵ is selected from N(R^{5b}), N, and C(R⁵);

W⁶ is selected from C(R⁶) and C(O);

W⁷ is C(R⁷);

R¹ is C₁₋₃ alkyl optionally substituted with one or more R^{11c};

R⁸ is selected from hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰;

R³, R⁴, R⁵, R⁶, and R⁷ are each independently selected from a bond to L², hydrogen, halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰;

R^{3b}, R^{4b}, and R^{5b} are each independently selected from a bond to L², hydrogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, and -CH₂S(O)₂N(R¹²)(R¹³), wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R²⁰;

R¹¹ and R^{11a} are each independently selected at each occurrence from halogen, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, 3- to 10-membered heterocycle, -OR¹², -SR¹², -N(R¹²)(R¹³), -C(O)OR¹², -OC(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)OR¹⁵, -N(R¹⁴)S(O)₂R¹⁵, -C(O)R¹⁵, -S(O)R¹⁵, -OC(O)R¹⁵, -C(O)N(R¹²)(R¹³), -C(O)C(O)N(R¹²)(R¹³), -N(R¹⁴)C(O)R¹⁵, -S(O)₂R¹⁵, -S(O)₂N(R¹²)(R¹³), -S(=O)(=NH)N(R¹²)(R¹³), -CH₂C(O)N(R¹²)(R¹³), -CH₂N(R¹⁴)C(O)R¹⁵, -CH₂S(O)₂R¹⁵, -CH₂S(O)₂N(R¹²)(R¹³), -CH₂N(R¹²)S(O)₂(R¹³), and -P(O)(R¹⁷)(R^{17a}), wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R^{11e} is independently selected at each occurrence from halogen, -OR¹², and -N(R¹²)(R¹³);

R¹² is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹³ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl; or R¹² and R¹³, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R²⁰;

R¹⁴ is independently selected at each occurrence from hydrogen, C₁₋₆ alkyl, and C₁₋₆ haloalkyl;

R¹⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R²⁰;

R¹⁷ and R^{17a} are each independently selected at each occurrence from C₁₋₆ alkyl and C₃₋₆ cycloalkyl, wherein C₁₋₆ alkyl and C₃₋₆ cycloalkyl are optionally substituted with one, two or three R²⁰; or R¹⁷ and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R²⁰ is independently selected at each occurrence from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, -CH₂-(3- to 10-membered heterocycle), -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), -OCH₂C(O)OR²², and -OC(O)R²⁵, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, -CH₂-(C₃₋₁₀ carbocycle), 3- to 10-membered heterocycle, and -CH₂-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OR²¹, -SR²¹, -N(R²²)(R²³), -C(O)OR²², -C(O)N(R²²)(R²³), -C(O)C(O)N(R²²)(R²³), -OC(O)N(R²²)(R²³), -N(R²⁴)C(O)N(R²²)(R²³), -N(R²⁴)C(O)OR²⁵, -N(R²⁴)C(O)R²⁵, -N(R²⁴)S(O)₂R²⁵, -C(O)R²⁵, -S(O)₂R²⁵, -S(O)₂N(R²²)(R²³), and -OC(O)R²⁵;

R²¹ is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²² is independently selected at each occurrence from H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₃₋₁₀ carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C₁₋₆ alkyl;

R²³ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁴ is independently selected at each occurrence from H and C₁₋₆ alkyl;

R²⁵ is independently selected at each occurrence from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle, wherein C₁₋₆ alkyl, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ carbocycle, and 3- to 10-membered heterocycle; and

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

20. The method of any one of claims 1 to 18, wherein the SOS1 inhibitor is selected from BI-3406,

MRTX0902, BAY 293, RMC-5845, and BI-1701963.

21. The method of any one of claims 4 to 20, wherein the cancer is lung cancer.
22. The method of any one of claims 4 to 21, wherein the cancer is a non-small cell lung cancer.
23. The method of any one of claims 4 to 22, wherein cancer cells of the subject comprise an EGFR mutation.
24. The method of claim 23, wherein the EGFR mutation is selected from an L858R mutation, a T790M mutation, an exon 19 deletion, and an exon 20 insertion.
25. The method of claim 23, wherein the EGFR mutation is an exon 20 insertion.
26. The method of any one of claims 1 to 25, wherein cancer cells of the subject comprise overexpression of MET.
27. The method of any one of claims 1 to 25, wherein cancer cells of the subject comprise MET-amplification.
28. The method of any one of the preceding claims, wherein the subject exhibits relapse of the cancer.
29. The method of any one of the preceding claims, wherein the subject has previously been treated with platinum-based chemotherapy.
30. The method of any one of the preceding claims, wherein the subject has previously been treated with a tyrosine kinase inhibitor (TKI) against EGFR prior to administering (a) and (b).
31. The method of claim 30, wherein the subject has previously been treated with a non-exon 20 insertion EGFR TKI.
32. The method of claim 31, wherein the non-exon 20 insertion EGFR TKI is selected from gefitinib, erlotinib, afatinib, lazertinib, osimertinib, dacomitinib, neratinib, cetuximab, panitumumab, lapatinib, necitumumab, nazartinib, vandetanib, BLU-945, and zorifertinib.
33. The method of claim 30, wherein the subject has previously been treated with an EGFR exon 20 insertion TKI.
34. The method of claim 33, wherein the EGFR exon 20 insertion TKI is selected from poziotinib, mobocertinib, amivantamab, zipalertinib, sunvozertinib, BAY-2927088, BLU-451, and STX-721.
35. The method of any one of claims 30 to 34, wherein the subject exhibits resistance or intolerance to the TKI.
36. The method of claim 35, wherein resistance to the TKI is characterized by one or more changes selected from (1) progression of the cancer, (2) *EGFR* gene mutation, (3) loss of EGFR T790M mutation, (4) *EGFR* gene amplification, (5) *MET* amplification, (6) *HER2* amplification, (7) RAS-MAPK pathway activation, (8) PI3K pathway activation, (9) cell-cycle gene alteration, (10) oncogenic fusion, (11) histologic transformation, and (12) phenotypic transformation.

37. The method of any one of the preceding claims, further comprising administering (c) an additional agent or additional therapy.
38. The method of claim 37, wherein the additional agent is selected from an EGFR TKI other than osimertinib, an immunomodulatory agent, an anti-nausea agent, an antiemetic, a pain reliever, a steroid, and a chemotherapeutic agent.
39. The method of claim 37, wherein the additional agent is selected from an immunomodulatory agent, a cytokine blockade agent, and a checkpoint immune blockade agent.
40. The method of claim 37, 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.
41. The method of claim 37, wherein the additional agent is a MET inhibitor.
42. The method of claim 41, wherein the MET inhibitor is savolitinib.
43. The method of claim 37, wherein the additional therapy is selected from surgery, cell therapy, chemotherapy, and radiation.
44. The method of any one of the preceding claims, wherein the administration of (a) and (b) reduces incidence of one or more adverse event associated with osimertinib.
45. The method of claim 44, wherein the adverse event is selected from diarrhea, rash, nausea, stomatitis, vomiting, paronychia, fatigue, dry skin, anorexia, headache, anemia, pneumonia, pruritus, constipation, and cough.
46. The method of claim 44, wherein the adverse event is selected from diarrhea, rash, nausea, dry skin, and paronychia.
47. The method of any one of the preceding claims, wherein the administration of (a) and (b) exhibits a synergistic effect.
48. The method of claim 47, wherein the synergistic effect is characterized by a synergistic value of at least 0.05 as ascertained by Bliss independent criterion.
49. 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.
50. The method of any one of the preceding claims, wherein osimertinib is administered at a dose less than about 25% the standard monotherapy dose.
51. The method of any one of the preceding claims, wherein (a) and (b) are administered in the same formulation.

52. The method of any one of the preceding claims, wherein (a) and (b) are administered in separate formulations.
53. A kit for use in reducing proliferation of cancer cells comprising an epidermal growth factor receptor (EGFR) exon 20 insertion, the kit comprising:
- (1) a composition comprising a SOS1 inhibitor of Formula (I-1);
 - (2) a composition comprising osimertinib; and
 - (3) instructions for using the composition(s) of (1) and (2).
54. The kit of claim 53, wherein the SOS1 inhibitor and the osimertinib are formulated in a same unit dosage form.
55. The kit of claim 53, wherein the SOS1 inhibitor and the osimertinib are formulated in different unit dosage forms.
56. A pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (I-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) osimertinib, and (iii) a pharmaceutically acceptable excipient.
57. A method of treating an EGFR-mediated cancer in a subject, comprising administering to the subject a pharmaceutical composition comprising (i) a SOS1 inhibitor of Formula (I-1), or a pharmaceutically acceptable salt or solvate thereof, (ii) osimertinib, and (iii) a pharmaceutically acceptable excipient.
58. The method of claim 1, 3, 4, 14, or 57, wherein the subject is a naïve subject that has not been treated with a TKI against EGFR prior to administering (a) and (b).