(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 May 2025 (22.05.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/106901 A1

(51) International Patent Classification:
*A61K 31/506* (2006.01) *A61K 45/06* (2006.01)
*A61K 31/551* (2006.01) *A61P 35/00* (2006.01)
*A61K 31/5517* (2006.01) *C07K 16/00* (2006.01)
*A61K 39/395* (2006.01)

(21) International Application Number:
PCT/US2024/056246

(22) International Filing Date:
15 November 2024 (15.11.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/600,143 17 November 2023 (17.11.2023) US

(71) Applicant: **QUANTA THERAPEUTICS, INC.** [US/US]; 2 Tower Place, Floor 14, South San Francisco, California 94080 (US).

(72) Inventors: **LIN, Hong**; c/o 2 Tower Place, Floor 14, South San Francisco, California 94080 (US). **PITT, Cameron**; c/o 2 Tower Place, Floor 14, South San Francisco, California 94080 (US).

(74) Agent: **MARTINEZ, Jose**; WILSON SONSINI GOODRICH & ROSATI, P.C., 650 Page Mill Road, Palo Alto, California 94304 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) **Title:** COMBINATION CANCER THERAPIES WITH A KRAS MODULATOR AND AN RTK-MAPK PATHWAY INHIBITOR

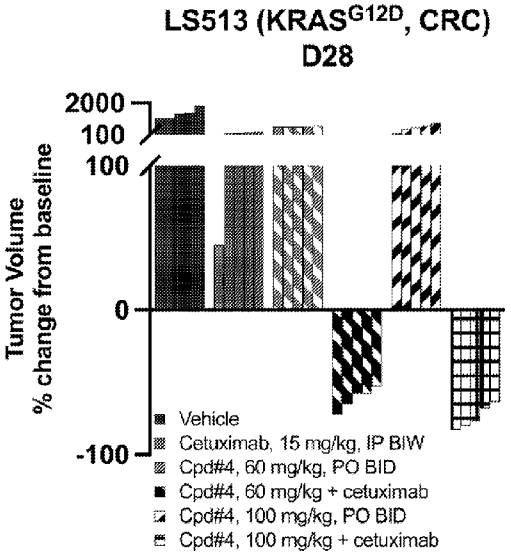



FIG. 1A

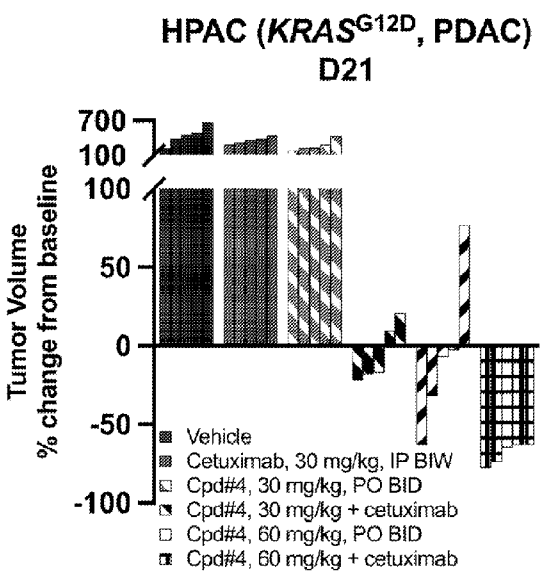



FIG. 1B

(57) **Abstract:** Provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a RTK-MAPK pathway inhibitor and a compound of Formula (I).

*[Continued on next page]*

WO 2025/106901 A1

**Declarations under Rule 4.17:**
— *of inventorship (Rule 4.17(iv))*

**Published:**
— *with international search report (Art. 21(3))*

# COMBINATION CANCER THERAPIES WITH A KRAS MODULATOR AND AN RTK-MAPK PATHWAY INHIBITOR

## CROSS-REFERENCE

**[0001]** This application claims the benefit of U.S. Provisional Patent Application No. 63/600,143 filed on November 17, 2023, the entire content of which is incorporated herein by reference.

## BACKGROUND OF THE INVENTION

**[0002]** The small GTPase protein Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (KRAS) is a member of the Ras family of cell signaling switches, regulating growth and survival of normal and cancerous cells (e.g., see Cully, M. and J. Downward, SnapShot: Ras Signaling. Cell, 2008. 133(7): p. 1292-1292 e1). KRAS mutations drive approximately 25% of human cancers by aberrant regulation of the mitogen-activated protein kinase (MAPK) signaling cascade and other effector pathways (e.g., see Stephen, A.G., et al., Dragging ras back in the ring. Cancer Cell, 2014. 25(3): p. 272-81). Though Ras has been recognized as a target in cancer for about 40 years, Ras-driven cancers remain among the most difficult to treat due to insensitivity to available targeted therapies. Ras, encoded by the three major genes KRAS, NRAS and HRAS, has the highest frequency of mutation of any oncogene. All oncogenic Ras mutations drive the switch to accumulate in the active GTP-bound state. The most common Ras mutation found across human tumor types is KRAS G12D (e.g., see The AACR Project GENIE Consortium. Cancer Discovery, 2017. 7(8): p. 818-831. Dataset Version 4). Activating mutations in codon 12 impair the small GTPases' ability to perform their role in hydrolyzing GTP. This regulatory impairment is fundamental for initiating and maintaining tumor progression.

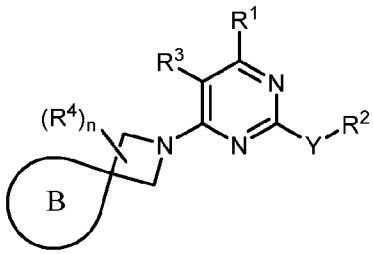
**[0003]** Despite extensive efforts, small molecules have not been identified which block effector binding or restore GTPase activating protein (GAP) sensitivity, though some have been found which block interaction of Ras with the guanine nucleotide exchange factor (GEF), SOS, which activates Ras at the plasma membrane. KRAS G12C mutations, most common in lung adenocarcinoma, have been clinically shown to be susceptible to direct inhibition by covalent modification with small molecule inhibitors trapping the protein in the inactive GDP-bound state. KRAS G12D mutation confers a significantly slower intrinsic rate of GTP hydrolysis than G12C, resulting in more constitutive activation. Thus, pharmacological targeting the of inactive state is unlikely to achieve similar results against G12D, despite the existence of a similar binding pocket in the GDP-state. Additionally, a cysteine present at the site of the activating mutation yields itself to covalent chemistry, while aspartic acid does not provide typical medicinal chemistry approaches for selective covalent modification.

**[0004]** In order to potentially exploit the accumulation of KRAS G12D and other mutant variants in the GTP-bound state as a vulnerability to achieve selective inhibition of cancer cells while sparing normal Ras function, it is attractive for small molecule inhibitors to bind to the GTP-state and stabilize a conformation that is incompetent for oncogenic signaling interactions with effector proteins. Furthermore, it has been shown that only constitutive activation of Raf, MEK and ERK kinases in the MAPK cascade downstream of Ras can bypass the requirement for Ras proteins in proliferative signaling (e.g., see Drosten, M., et al., Genetic analysis of Ras signalling pathways in cell proliferation, migration and survival. EMBO J, 2010. 29(6): p. 1091-104). As all evidence has indicated that MAPK signaling is essential for the growth effects of Ras in cancer, KRAS-mutant-selective inhibition in this pathway is considered the critical functional readout for potential clinical benefit of novel therapeutic approaches.

## SUMMARY OF THE INVENTION

**[0005]** While the compounds disclosed herein are potent inhibitors of KRas signaling and exhibit single agent activity inhibiting the in vitro proliferation of cell lines harboring a KRas mutation or other KRAS-activating genetic alteration, the relative potency and/or observed maximal effect of any given KRas inhibitor can vary between KRAS mutant cell lines. The reason or reasons for the range of potencies and observed maximal effect is not fully understood but certain cell lines appear to possess differing intrinsic resistance to the mechanism of action, which relies on binding to certain conformational states of KRAS proteins. Thus, there is a need to develop alternative approaches to maximize the potency, efficacy, therapeutic index and/or clinical benefit of KRas inhibitors in vitro and in vivo. Due to known feedback loops in the Ras signaling pathway, upstream inhibition of RTK signaling or downstream inhibition of MAPK signaling may be required for complete blockade of KRas mutant activity in the presence of KRas inhibitors.

**[0006]** In an aspect, the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of an RTK-MAPK pathway inhibitor and a compound represented by the structure of Formula (I):




Formula (I),

or a pharmaceutically acceptable salt thereof wherein:

B is selected from a 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle, wherein the 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle are each optionally substituted with one or more substituents independently selected from halogen, -CN, -$NO_2$, =O, -$N(R^{21})_2$, -$B(OR^{21})_2$, -$OR^{21}$, -$SR^{21}$, -$S(O)_2(R^{21})$, -$S(O)_2N(R^{21})_2$, -$NR^{21}S(O)_2R^{21}$, -$C(O)N(R^{21})_2$, -$C(O)NR^{21}OR^{21}$, -$N(R^{21})C(O)R^{21}$, -$N(R^{21})C(O)N(R^{21})_2$, -$N(R^{21})C(O)OR^{21}$, -$C(O)R^{21}$, $C(O)OR^{21}$, -$OC(O)R^{21}$, -$OC(O)N(R^{21})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

$R^1$ is selected from hydrogen and 5- to 15-membered heterocycle, wherein the 5- to 15-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -$B(OR^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$C(=NR^{20})N(R^{20})_2$, -$C_{1-6}$ alkyl($=NOR^{20}$), -$C(O)NR^{20}OR^{20}$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$N(R^{20})_2$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, -$NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl-$SO_2R^{20}$, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle, wherein the $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, -$B(OR^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$C(O)NR^{20}OR^{20}$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$N(R^{20})_2$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, -$NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, and $C_3$-$C_{12}$ carbocycle;

Y is selected from a bond, -O-, -S-, and -$N(R^5)$-;

$R^2$ is selected from heterocycle, aryl, $C_1$-$C_6$ alkyl, -L-heterocycle, -L-$N(R^{23})_2$, -L-$OR^{23}$, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-$NHC(=NH)NH_2$, -L-$C(O)N(R^{23})_2$, -L-$C_1$-$C_6$ haloalkyl, -L-$OR^{23}$, -L-$NR^{23}C(O)$-aryl, -L-COOH, -L-$NR^{23}S(O)_2(R^{23})$, -L-$S(O)_2N(R^{23})_2$, -L-$N(R^{23})C(O)(OR^{23})$, -L-$OC(O)N(R^{23})_2$, and -L-$C(=O)OC_1$-$C_6$ alkyl, wherein the heterocycle, the heterocycle portion of -L-heterocycle, and the cycloalkyl portion of the -L-cycloalkyl are each optionally substituted with one or more $R^6$, and wherein the aryl, aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$;

$R^3$ is selected from hydrogen, halogen, -CN, -$NO_2$, -$N(R^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$N(R^{20})C(O)R^{20}$, -

$N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

each $R^4$ is independently selected from halogen, $-NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

n is selected from 0, 1, 2, 3, and 4;

each $R^5$ is independently selected from hydrogen and $C_1$-$C_6$ alkyl;

each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, $=CH_2$, $=NO$-$C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, $-N(R^5)S(O)_2(R^5)$, -Q-phenyl, -Q-phenyl$SO_2F$, -NHC(O)phenyl, - NHC(O)phenyl$SO_2F$, $C_1$-$C_3$ alkyl substituted pyrazolyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, $-C(O)N(R^5)_2$, tert-butyldimethylsilyloxy$CH_2$-, $-N(R^5)_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$ alkyl)C(=O), oxo, ($C_1$-$C_3$ haloalkyl)C(=O)-, $-SO_2F$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, $-CH_2OC(O)N(R^5)_2$, $-CH_2NHC(O)OC_1$-$C_6$ alkyl, $-CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)C_1$-$C_6$ alkyl, $-CH_2$(pyrazolyl), $-CH_2NHSO_2C_1$-$C_6$ alkyl, $-CH_2OC(O)$heterocycle, -$OC(O)N(R^5)_2$, -OC(O)NH($C_1$-$C_3$ alkyl)O($C_1$-$C_3$ alkyl), -OC(O)NH($C_1$-$C_3$ alkyl)O($C_1$-$C_3$ alkyl)phenyl($C_1$-$C_3$ alkyl)$N(CH_3)_2$, -OC(O)NH($C_1$-$C_3$ alkyl)O($C_1$-$C_3$ alkyl)phenyl, -OC(O)heterocycle, -O-$C_1$-$C_3$ alkyl, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, and $-CH_2$heterocycle, wherein the phenyl of -NHC(O)phenyl and -OC(O)NH($C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl)phenyl are optionally substituted with one or more substituents selected from -C(O)H and OH, and wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo and hydroxy; and wherein the heterocycle of $-CH_2$heterocyclyl is optionally substituted with oxo;

each Q is selected from a bond, S, and O;

each $R^7$ is independently selected from halogen, hydroxy, HC(=O)-, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, $-C(O)N(R^5)_2$, and $-N(R^5)_2$;

each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, hydroxy, $C_{1-6}$ alkoxy, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle, and 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, $-NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally

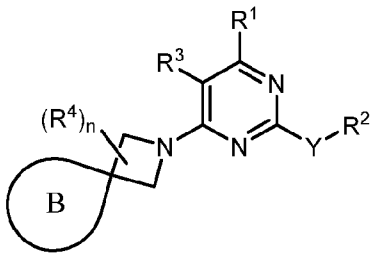
substituted with one or more substituents independently selected from halogen, -OH, $-NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle; and

each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle.

**[0007]** In an aspect, the present disclosure provides a compound of Formula (I-A)




Formula (I-A),

or a pharmaceutically acceptable salt thereof wherein:

$R^1$ is selected from 8- to 10-membered heterocycle, wherein the 8- to 10-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, -$C_{1-6}$ alkyl(=$NOR^{20}$), $-C(O)R^{20}$, =O, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl-$SO_2R^{20}$, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, $-B(OR^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, =$N(R^{20})$, =$NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$

aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, and $C_3$-$C_{12}$ carbocycle;

B is selected from a 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle, wherein the 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle are each optionally substituted with one or more substituents independently selected from halogen, -CN, -$NO_2$, =O, -$N(R^{21})_2$, -$B(OR^{21})_2$, -$OR^{21}$, -$SR^{21}$, -$S(O)_2(R^{21})$, -$S(O)_2N(R^{21})_2$, -$NR^{21}S(O)_2R^{21}$, -$C(O)N(R^{21})_2$, -$C(O)NR^{21}OR^{21}$, -$N(R^{21})C(O)R^{21}$, -$N(R^{21})C(O)N(R^{21})_2$, -$N(R^{21})C(O)OR^{21}$, -$C(O)R^{21}$, $C(O)OR^{21}$, -$OC(O)R^{21}$, -$OC(O)N(R^{21})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

Y is selected from a bond, and -O-;

$R^2$ is selected from heterocycle, aryl, $C_1$-$C_6$ alkyl, -L-heterocycle, -L-$N(R^{23})_2$, -L-$OR^{23}$, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-$NHC(=NH)NH_2$, -L-$C(O)N(R^{23})_2$, -L-$C_1$-$C_6$ haloalkyl, -L-$OR^{23}$, -L-$NR^{23}C(O)$-aryl, -L-COOH, -L-$NR^{23}S(O)_2(R^{23})$, -L-$S(O)_2N(R^{23})_2$, -L-$N(R^{23})C(O)(OR^{23})$, -L-$OC(O)N(R^{23})_2$, and -L-$C(=O)OC_1$-$C_6$ alkyl, wherein the heterocycle, the heterocycle portion of -L-heterocycle, and the cycloalkyl portion of the -L-cycloalkyl are each optionally substituted with one or more $R^6$, and wherein the aryl, aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$;

$R^3$ is selected from hydrogen, halogen, -CN, -$NO_2$, -$N(R^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

each $R^4$ is independently selected from halogen, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

n is selected from 0, 1, 2, 3, and 4;

each $R^5$ is independently selected from hydrogen and $C_1$-$C_6$ alkyl;

each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, $=CH_2$, =NO-$C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, -$N(R^5)S(O)_2(R^5)$, -Q-phenyl, -Q-phenyl$SO_2F$, -NHC(O)phenyl, -NHC(O)phenyl$SO_2F$, $C_1$-$C_3$ alkyl substituted pyrazolyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, -$C(O)N(R^5)_2$, tert-butyldimethylsilyloxy$CH_2$-, -$N(R^5)_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$ alkyl)C(=O), oxo, ($C_1$-$C_3$ haloalkyl)C(=O)-, -$SO_2F$,

($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC_1$-$C_6$ alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)C_1$-$C_6$ alkyl, -$CH_2$(pyrazolyl), -$CH_2NHSO_2C_1$-$C_6$ alkyl, -$CH_2OC(O)$heterocycle, -$OC(O)N(R^5)_2$, -$OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl), -$OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl$(C_1$-$C_3$ alkyl)$N(CH_3)_2$, -$OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl, -$OC(O)$heterocycle, -O-$C_1$-$C_3$ alkyl, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, and -$CH_2$heterocycle, wherein the phenyl of -NHC(O)phenyl and -$OC(O)NH(C_1$-$C_3$ alkyl)$(C_1$-$C_3$ alkyl)phenyl are optionally substituted with one or more substituents selected from -C(O)H and OH, and wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo and hydroxy; and wherein the heterocycle of -$CH_2$heterocyclyl is optionally substituted with oxo;

each Q is selected from a bond, S, and O;

each $R^7$ is independently selected from halogen, hydroxy, HC(=O)-, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, -$C(O)N(R^5)_2$, and -$N(R^5)_2$;

each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, hydroxy, $C_{1-6}$ alkoxy, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle, and 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

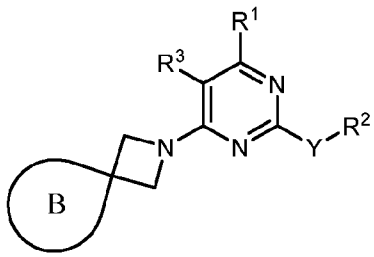
each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with

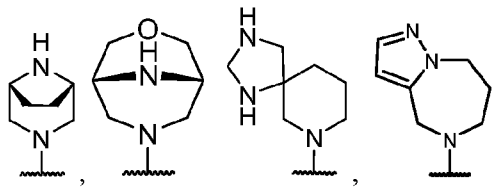
one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle.

**[0008]** In certain embodiments, Formula (I-A) is represented by Formula (I-B),



Formula (I-B),

or a pharmaceutically acceptable salt thereof wherein:

wherein $R^1$ is selected from  , each of which is optionally substituted with one or more substituents independently selected from halogen, -$S(O)_2(R^{20})$, -$C(O)N(R^{20})_2$, -$C_{1-6}$ alkyl(=$NOR^{20}$), -$C(O)R^{20}$, =O, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, -$OR^{20}$, -$N(R^{20})_2$, -$NO_2$, =O, =$N(R^{20})$, =$NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl;

Y is -O-;

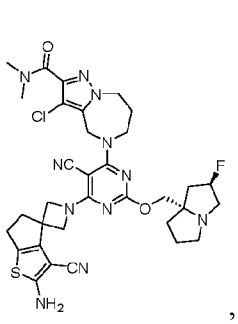
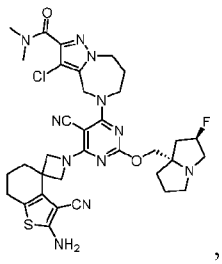
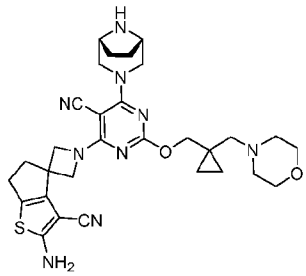
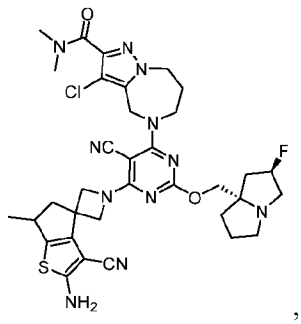
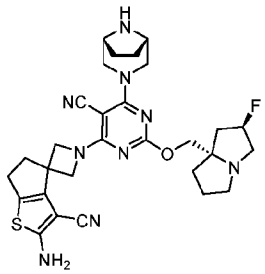
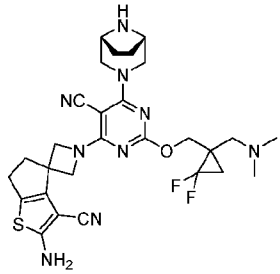
$R^2$ is selected from -L-heterocycle, and -L-$N(R^{23})_2$, wherein the heterocycle portion of -L-heterocycle is optionally substituted with one or more $R^6$.

B is selected from a 7- to 15-membered heterocycle, wherein the 7- to 15-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, =O, -$N(R^{21})_2$, -$OR^{21}$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl;

$R^3$ is selected from hydrogen, halogen, -CN, -$N(R^{20})_2$, -$OR^{20}$, -$C(O)R^{20}$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl; and

each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and $C_{3-12}$ carbocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, and oxo.

**[0009]** A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of cetuximab and a compound selected from


,

,

,

,

, and

, or a pharmaceutically acceptable salt of any one thereof.

## INCORPORATION BY REFERENCE

**[0010]** 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. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0011]** 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:

**[0012]** **FIGS. 1A-1B** illustrate that combination treatment enhances tumor growth inhibition and tumor regression as compared to single agent treatment in LS513, KRASG12D colorectal cancer (**FIG. 1A**), and HPAC, KRASG12D pancreatic cancer (**FIG. 1B**), xenograft models.

## DETAILED DESCRIPTION OF THE INVENTION

**[0013]** The following description sets forth numerous exemplary configurations, methods, parameters, and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure, but is instead provided as a description of exemplary embodiments.

**[0014]** In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the disclosure. However, one skilled in the art will understand that the disclosure may be practiced without these details.

**Definitions**

**[0015]** 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 invention belongs. All patents and publications referred to herein are incorporated by reference.

**[0016]** "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, and preferably having from one to fifteen carbon atoms (*i.e.*, $C_1$-$C_{15}$ alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*i.e.*, $C_1$-$C_{13}$ alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*i.e.*, $C_1$-$C_8$ alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*i.e.*, $C_1$-$C_5$ alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*i.e.*, $C_1$-$C_4$ alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*i.e.*, $C_1$-$C_3$ alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*i.e.*, $C_1$-$C_2$ alkyl). In other embodiments, an alkyl comprises one carbon atom (*i.e.*, $C_1$ alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*i.e.*, $C_5$-$C_{15}$ alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*i.e.*, $C_5$-$C_8$ alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*i.e.*, $C_2$-$C_5$ alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*i.e.*, $C_3$-$C_5$ alkyl). In certain embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond.

**[0017]** The term "$C_{x-y}$" 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 "$C_{1-6}$alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from 1 to 6 carbons. The term –$C_{x-y}$alkylene- refers to a substituted or unsubstituted alkylene chain with from x to y carbons in the alkylene chain. For example –$C_{1-6}$alkylene- may be selected from

methylene, ethylene, propylene, butylene, pentylene, and hexylene, any one of which is optionally substituted.

**[0018]** "Alkoxy" refers to a radical bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl chain as defined above.

**[0019]** "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and preferably having from two to twelve carbon atoms (*i.e.*, $C_2$-$C_{12}$ alkenyl). In certain embodiments, an alkenyl comprises two to eight carbon atoms (*i.e.*, $C_2$-$C_8$ alkenyl). In certain embodiments, an alkenyl comprises two to six carbon atoms (*i.e.*, $C_2$-$C_6$ alkenyl). In other embodiments, an alkenyl comprises two to four carbon atoms (*i.e.*, $C_2$-$C_4$ alkenyl). The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

**[0020]** "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, and preferably having from two to twelve carbon atoms (*i.e.*, $C_2$-$C_{12}$ alkynyl). In certain embodiments, an alkynyl comprises two to eight carbon atoms (*i.e.*, $C_2$-$C_8$ alkynyl). In other embodiments, an alkynyl comprises two to six carbon atoms (*i.e.*, $C_2$-$C_6$ alkynyl). In other embodiments, an alkynyl comprises two to four carbon atoms (*i.e.*, $C_2$-$C_4$ alkynyl). The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like.

**[0021]** The terms "$C_{x\text{-}y}$alkenyl" and "$C_{x\text{-}y}$alkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively. The term –$C_{x\text{-}y}$alkenylene- refers to a substituted or unsubstituted alkenylene chain with from x to y carbons in the alkenylene chain. For example, –$C_{2\text{-}6}$alkenylene- may be selected from ethenylene, propenylene, butenylene, pentenylene, and hexenylene, any one of which is optionally substituted. An alkenylene chain may have one double bond or more than one double bond in the alkenylene chain. The term –$C_{x\text{-}y}$alkynylene- refers to a substituted or unsubstituted alkynylene chain with from x to y carbons in the alkenylene chain. For example, –$C_{2\text{-}6}$alkenylene- may be selected from ethynylene, propynylene, butynylene, pentynylene, and hexynylene, any one of which is optionally substituted. An alkynylene chain may have one triple bond or more than one triple bond in the alkynylene chain.

**[0022]** "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation, and preferably having from one to twelve carbon atoms,

for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group may be through any two carbons within the chain. In certain embodiments, an alkylene comprises one to ten carbon atoms (*i.e.*, $C_1$-$C_8$ alkylene). In certain embodiments, an alkylene comprises one to eight carbon atoms (*i.e.*, $C_1$-$C_8$ alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*i.e.*, $C_1$-$C_5$ alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*i.e.*, $C_1$-$C_4$ alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*i.e.*, $C_1$-$C_3$ alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*i.e.*, $C_1$-$C_2$ alkylene). In other embodiments, an alkylene comprises one carbon atom (*i.e.*, $C_1$ alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*i.e.*, $C_5$-$C_8$ alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*i.e.*, $C_2$-$C_5$ alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*i.e.*, $C_3$-$C_5$ alkylene).

**[0023]** "Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon double bond, and preferably having from two to twelve carbon atoms. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group may be through any two carbons within the chain. In certain embodiments, an alkenylene comprises two to ten carbon atoms (*i.e.*, $C_2$-$C_{10}$ alkenylene). In certain embodiments, an alkenylene comprises two to eight carbon atoms (*i.e.*, $C_2$-$C_8$ alkenylene). In other embodiments, an alkenylene comprises two to five carbon atoms (*i.e.*, $C_2$-$C_5$ alkenylene). In other embodiments, an alkenylene comprises two to four carbon atoms (*i.e.*, $C_2$-$C_4$ alkenylene). In other embodiments, an alkenylene comprises two to three carbon atoms (*i.e.*, $C_2$-$C_3$ alkenylene). In other embodiments, an alkenylene comprises two carbon atom (*i.e.*, $C_2$ alkenylene). In other embodiments, an alkenylene comprises five to eight carbon atoms (*i.e.*, $C_5$-$C_8$ alkenylene). In other embodiments, an alkenylene comprises three to five carbon atoms (*i.e.*, $C_3$-$C_5$ alkenylene).

**[0024]** "Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon triple bond, and preferably having from two to twelve carbon atoms. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group may be through any two

carbons within the chain. In certain embodiments, an alkynylene comprises two to ten carbon atoms (*i.e.*, $C_2$-$C_{10}$ alkynylene). In certain embodiments, an alkynylene comprises two to eight carbon atoms (*i.e.*, $C_2$-$C_8$ alkynylene). In other embodiments, an alkynylene comprises two to five carbon atoms (*i.e.*, $C_2$-$C_5$ alkynylene). In other embodiments, an alkynylene comprises two to four carbon atoms (*i.e.*, $C_2$-$C_4$ alkynylene). In other embodiments, an alkynylene comprises two to three carbon atoms (*i.e.*, $C_2$-$C_3$ alkynylene). In other embodiments, an alkynylene comprises two carbon atom (*i.e.*, $C_2$ alkynylene). In other embodiments, an alkynylene comprises five to eight carbon atoms (*i.e.*, $C_5$-$C_8$ alkynylene). In other embodiments, an alkynylene comprises three to five carbon atoms (*i.e.*, $C_3$-$C_5$ alkynylene).

**[0025]** "Aryl" refers to a radical derived from an aromatic monocyclic or aromatic multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or aromatic multicyclic hydrocarbon ring system contains only hydrogen and carbon and from five to eighteen carbon atoms, where at least one of the rings in the ring system is aromatic, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene.

**[0026]** "Aralkyl" refers to a radical of the formula -$R^c$-aryl where $R^c$ is an alkylene chain as defined above, for example, methylene, ethylene, and the like.

**[0027]** "Aralkenyl" refers to a radical of the formula –$R^d$-aryl where $R^d$ is an alkenylene chain as defined above. "Aralkynyl" refers to a radical of the formula -$R^e$-aryl, where $R^e$ is an alkynylene chain as defined above.

**[0028]** "Carbocycle" refers to a saturated, unsaturated or aromatic rings in which each atom of the ring is carbon. Carbocycle may include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. 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 carbocyclic. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, and naphthyl. Bicyclic carbocycles may be fused, bridged or spiro-ring systems. In some cases, spiro-ring carbocycles have at least two molecular rings with only one common atom.

**[0029]** The term "unsaturated carbocycle" refers to carbocycles with at least one degree of unsaturation and excluding aromatic carbocycles. Examples of unsaturated carbocycles include cyclohexadiene, cyclohexene, and cyclopentene.

**[0030]** "Cycloalkyl" refers to a fully saturated monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, and preferably having from three to twelve carbon atoms. In certain embodiments, a cycloalkyl comprises three to ten carbon atoms. In other embodiments, a cycloalkyl comprises five to seven carbon atoms. The cycloalkyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like.

**[0031]** "Cycloalkenyl" refers to an unsaturated non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, preferably having from three to twelve carbon atoms and comprising at least one double bond. In certain embodiments, a cycloalkenyl comprises three to ten carbon atoms. In other embodiments, a cycloalkenyl comprises five to seven carbon atoms. The cycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls includes, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

**[0032]** "Cycloalkylalkyl" refers to a radical of the formula $-R^c$-cycloalkyl where $R^c$ is an alkylene chain as described above.

**[0033]** "Cycloalkylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-cycloalkyl where $R^c$ is an alkylene chain as described above.

**[0034]** "Halo" or "halogen" refers to halogen substituents such as bromo, chloro, fluoro and iodo substituents.

**[0035]** As used herein, the term "haloalkyl" or "haloalkane" refers to an alkyl radical, as defined above, that is substituted by one or more halogen radicals, for example, trifluoromethyl, dichloromethyl, bromomethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally further substituted. Examples of halogen substituted alkanes ("haloalkanes") include halomethane (e.g., chloromethane, bromomethane, fluoromethane, iodomethane), di-and trihalomethane (e.g., trichloromethane, tribromomethane, trifluoromethane, triiodomethane), 1-haloethane, 2-haloethane, 1,2-dihaloethane, 1-halopropane, 2-halopropane, 3-halopropane, 1,2-dihalopropane, 1,3-dihalopropane, 2,3-dihalopropane, 1,2,3-trihalopropane, and any other suitable combinations of alkanes (or substituted alkanes) and halogens (e.g., Cl, Br, F, I, etc.). When an alkyl group is substituted with more than one halogen radicals, each halogen may be independently selected e.g., 1-chloro,2-fluoroethane.

**[0036]** "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

**[0037]** "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more amine radicals, for example, propan-2-amine, butane-1,2-diamine, pentane-1,2,4-triamine and the like.

**[0038]** "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxy radicals, for example, propan-1-ol, butane-1,4-diol, pentane-1,2,4-triol, and the like.

**[0039]** "Alkoxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more alkoxy radicals, for example, methoxymethane, 1,3-dimethoxybutane, 1-methoxypropane, 2-ethoxypentane, and the like.

**[0040]** "Cyanoalkyl" as used herein refers to an alkyl radical, as defined above, that is substituted by one or more cyano radicals, for example, acetonitrile, 2-ethyl-3-methylsuccinonitrile, butyronitrile, and the like.

**[0041]** "Heterocycle" as used herein refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. 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. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. A bicyclic heterocycle includes any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits. In an exemplary embodiment, an aromatic ring, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, morpholine, piperidine or cyclohexene. A bicyclic heterocycle includes any combination of ring sizes such as 4-5 fused ring systems, 5-5 fused ring systems, 5-6 fused ring systems, 6-6 fused ring systems, 5-7 fused ring systems, 6-7 fused ring systems, 5-8 fused ring systems, and 6-8 fused ring systems. Bicyclic heterocycles may be fused, bridged, or spiro-ring systems. A spiro-ring system may be referred as a "spiroheterocycle", "spiro heterocycle", or "spiro-heterocycle". In some cases, spiro-heterocycles, spiro heterocycles, or spiroheterocycles have at least two molecular rings with only one common atom. The spiro-heterocycle, spiro heterocycle, or spiroheterocycle comprises one or more heteroatoms.

**[0042]** "Heterocyclene" refers to a divalent heterocycle linking the rest of the molecule to a radical group.

**[0043]** "Heteroaryl" or "aromatic heterocycle" refers to a radical derived from a heteroaromatic ring radical that comprises one to eleven carbon atoms and at least one

heteroatom wherein each heteroatom may be selected from N, O, and S. As used herein, the heteroaryl ring may be selected from monocyclic or bicyclic and fused or bridged ring systems rings wherein at least one of the rings in the ring system is aromatic, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The heteroatom(s) in the heteroaryl radical may be optionally 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 heteroaryls include, but are not limited to, pyridine, pyrimidine, oxazole, furan, pyran, thiophene, isoxazole, benzimidazole, benzthiazole, and imidazopyridine.

**[0044]** An "X-membered heteroaryl" refers to the number of endocylic atoms, i.e., X, in the ring. For example, a 5-membered heteroaryl ring or 5-membered aromatic heterocycle has 5 endocyclic atoms, e.g., triazole, oxazole, thiophene, etc.

**[0045]** The term "unsaturated heterocycle" refers to heterocycles with at least one degree of unsaturation and excluding aromatic heterocycles. Examples of unsaturated heterocycles include dihydropyrrole, dihydrofuran, oxazoline, pyrazoline, and dihydropyridine. Heterocycles may be optionally substituted by one or more substituents such as those substituents described herein.

**[0046]** The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons or substitutable heteroatoms, e.g., NH, 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, *i.e.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In certain embodiments, substituted refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group. 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, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

**[0047]** In some embodiments, substituents may include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazino ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$,

$-R^b$-OC(O)-N($R^a$)$_2$, $-R^b$-N($R^a$)$_2$, $-R^b$-C(O)$R^a$, $-R^b$-C(O)O$R^a$, $-R^b$-C(O)N($R^a$)$_2$, $-R^b$-O-$R^c$-C(O)N($R^a$)$_2$, $-R^b$-N($R^a$)C(O)O$R^a$, $-R^b$-N($R^a$)C(O)$R^a$, $-R^b$-N($R^a$)S(O)$_t$$R^a$ (where t is 1 or 2), $-R^b$-S(O)$_t$$R^a$ (where t is 1 or 2), $-R^b$-S(O)$_t$O$R^a$ (where t is 1 or 2), and $-R^b$-S(O)$_t$N($R^a$)$_2$ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, and heterocycle, any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro (-$NO_2$), imino (=N-H), oximo (=N-OH), hydrazine (=N-$NH_2$), $-R^b$-O$R^a$, $-R^b$-OC(O)-$R^a$, $-R^b$-OC(O)-O$R^a$, $-R^b$-OC(O)-N($R^a$)$_2$, $-R^b$-N($R^a$)$_2$, $-R^b$-C(O)$R^a$, $-R^b$-C(O)O$R^a$, $-R^b$-C(O)N($R^a$)$_2$, $-R^b$-O-$R^c$-C(O)N($R^a$)$_2$, $-R^b$-N($R^a$)C(O)O$R^a$, $-R^b$-N($R^a$)C(O)$R^a$, $-R^b$-N($R^a$)S(O)$_t$$R^a$ (where t is 1 or 2), $-R^b$-S(O)$_t$$R^a$ (where t is 1 or 2), $-R^b$-S(O)$_t$O$R^a$ (where t is 1 or 2) and $-R^b$-S(O)$_t$N($R^a$)$_2$ (where t is 1 or 2); wherein each $R^a$ is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, wherein each $R^a$, valence permitting, may be optionally substituted with alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro (-$NO_2$), imino (=N-H), oximo (=N-OH), hydrazine (=N-$NH_2$), $-R^b$-O$R^a$, $-R^b$-OC(O)-$R^a$, $-R^b$-OC(O)-O$R^a$, $-R^b$-OC(O)-N($R^a$)$_2$, $-R^b$-N($R^a$)$_2$, $-R^b$-C(O)$R^a$, $-R^b$-C(O)O$R^a$, $-R^b$-C(O)N($R^a$)$_2$, $-R^b$-O-$R^c$-C(O)N($R^a$)$_2$, $-R^b$-N($R^a$)C(O)O$R^a$, $-R^b$-N($R^a$)C(O)$R^a$, $-R^b$-N($R^a$)S(O)$_t$$R^a$ (where t is 1 or 2), $-R^b$-S(O)$_t$$R^a$ (where t is 1 or 2), $-R^b$-S(O)$_t$O$R^a$ (where t is 1 or 2) and $-R^b$-S(O)$_t$N($R^a$)$_2$ (where t is 1 or 2); and wherein each $R^b$ is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each $R^c$ is a straight or branched alkylene, alkenylene or alkynylene chain.

**[0048]** As used herein, the term "electrophile" or "electrophilic moiety" is any moiety capable of reacting with a nucleophile (e.g., a moiety having a lone pair of electrons, a negative charge, a partial negative charge and/or an excess of electrons, for example an —SH group). Electrophiles typically are electron poor or comprise atoms which are electron poor. In certain embodiments, an electrophile contains a positive charge or partial positive charge, has a resonance structure which contains a positive charge or partial positive charge, or is a moiety in which delocalization or polarization of electrons results in one or more atoms which contains a positive charge or partial positive charge. In some embodiments, an electrophile comprises a conjugated double bond, for example an α,β-unsaturated carbonyl or α,β-unsaturated thiocarbonyl compound.

**[0049]** As used herein, the term "optional" or "optionally" means that the subsequently described event of 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, "optionally substituted aryl" means that the aryl group may or may not be substituted and that the description includes both substituted aryl groups and aryl groups having no substitution.

**[0050]** As used in the specification and claims, the singular form "a", "an" and "the" includes plural references unless the context clearly dictates otherwise.

**[0051]** The term "salt" or "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic 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. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

**[0052]** The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

**[0053]** The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

**[0054]** The phrase "pharmaceutically acceptable excipient" or "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as

pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

**[0055]** In certain embodiments, the term "prevent" or "preventing" as related to a disease or disorder may refer to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

**[0056]** The terms "treat," "treating" or "treatment," as used herein, may include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

**[0057]** The term "G12 mutants", as used herein, refers to other oncogenic alleles of KRAS at amino acid position 12 (ie. G12X).

**[0058]** The term "RTK-MAPK pathway" refers to the signaling cascade between Receptor Tyrosine Kinases (RTKs), including positive regulators of RTK activity, e.g., SHP2 or SOS1, and the RAF-MEK-ERK (i.e. MAPK) pathway.

**[0059]** The term "RTK-MAPK pathway inhibitor" refers to an agent, e.g., a compound or antibody, that is capable of negatively modulating or inhibiting all or a portion of the activity of at least one protein within the RTK-MAPK pathway.

**[0060]** The term "RAF-MEK-ERK pathway" refers to the series of kinases activated sequentially downstream of activation of the RAS family of small GTPases.

**[0061]** The term "RAF-MEK-ERK pathway inhibitor" refers to an agent, e.g., a compound or antibody, that is capable of negatively modulating or inhibiting all or a portion of the activity of at least one protein within the RAF-MEK-ERK pathway.

**[0062]** The term "KRas G12D-associated cancer" as used herein refers to cancers associated with or mediated by or having a KRas G12D mutation.

**[0063]** The term "KRas G12V-associated cancer" as used herein refers to cancers associated with or mediated by or having a KRas G12V mutation.

**[0064]** The term "KRas wildtype-associated cancer" as used herein refers to cancers associated with or mediated by or having a KRas wildtype.

**[0065]** The terms "ERBB family" or "ERBB family member" refers to a member of a mammalian transmembrane protein tyrosine kinase family including: EGFR, ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4).

**[0066]** The terms "ERBB family inhibitor" refers to an agent, e.g., a compound or antibody, that is capable of negatively modulating or inhibiting all or a portion of the activity of at least one member of the ERBB family.

**[0067]** The terms "EGFR inhibitor" refers to an agent, e.g., a compound or antibody, that is capable of negatively modulating or inhibiting all or a portion of the activity of Epidermal Growth Factor Receptor (EGRF).

**[0068]** The terms "SHP-2" or "SHP2" refers to the mammalian non-receptor protein tyrosine phosphatase encoded by the PTPN11 gene that is involved in signaling through the Ras-mitogen-activated protein kinase, the JAK-STAT or the phosphoinositol 3-kinase-AKT pathways.

**[0069]** The terms a "SHP-2 inhibitor" or a "SHP2 inhibitor" refers to a compound that is capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of SHP-2 phosphatase.

**[0070]** The term "SOS1" refers to a mammalian Son of sevenless homolog 1 (SOS1) enzyme.

**[0071]** The term a "SOS1 inhibitor" refers to a compound that is capable of negatively modulating or inhibiting all or a portion of the interaction of SOS1 with Ras family mutant or SOS1 activating mutation thereby reducing and/or modulating the nucleotide exchange activity of Ras family member - SOS1 complex.

**[0072]** The terms "subject," "individual," and "patient" may be used interchangeably and refer to humans, as well as non-human mammals (e.g., non-human primates, canines, equines, felines, porcines, bovines, ungulates, lagomorphs, and the like). In various embodiments, the subject can be a human (e.g., adult male, adult female, adolescent male, adolescent female, male

child, female child) under the care of a physician or other health worker in a hospital, as an outpatient, or other clinical context. In certain embodiments, the subject may not be under the care or prescription of a physician or other health worker.

**[0073]** As used herein, the phrase "a subject in need thereof" refers to a subject, as described infra, that suffers from, or is at risk for, a pathology to be prophylactically or therapeutically treated with a compound or salt described herein.

**[0074]** The terms “determining,” “measuring,” “evaluating,” “assessing,” “assaying,” and “analyzing” are often used interchangeably herein to refer to forms of measurement. The terms include determining if an element is present or not (for example, detection). These terms can include quantitative, qualitative or quantitative and qualitative determinations. Assessing can be relative or absolute. “Detecting the presence of” can include determining the amount of something present in addition to determining whether it is present or absent depending on the context.

**[0075]** The terms “administer”, “administered”, “administers” and “administering” are defined as providing a composition to a subject via a route known in the art, including but not limited to intravenous, intraarterial, oral, parenteral, buccal, topical, transdermal, rectal, intramuscular, subcutaneous, intraosseous, transmucosal, or intraperitoneal routes of administration. In certain embodiments, oral routes of administering a composition can be used. The terms “administer”, “administered”, “administers” and “administering” a compound should be understood to mean providing a compound of the disclosure or a prodrug of a compound of the disclosure to the individual in need.

**[0076]** The term “effective amount” or “therapeutically effective amount” refers to that amount of a compound or salt described herein that is sufficient to effect the intended application including but not limited to disease treatment, as defined below. The therapeutically effective amount may vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., 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. The term can also apply to a dose that can induce a particular response in target cells, e.g., reduction of proliferation or down regulation of activity of a target protein. The specific dose can vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

**[0077]** As used herein, a "therapeutically effective amount of a combination" of two compounds is an amount that together synergistically increases the activity of the combination in

comparison to the therapeutically effective amount of each compound in the combination, i.e., more than merely additive.

**[0078]** As used herein, "synergy," "synergetic," "synergism," or "synergistic effect" refer to two or more compounds or compositions, that individually produce an effect, however, together produce a combined effect that is greater than their individual effects.

**[0079]** The term "about" or "approximately" can mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, up to 15%, up to 10%, up to 5%, or up to 1% of a given value.

**[0080]** It is intended that every maximum numerical limitation given throughout this specification includes every lower numerical limitation, as if such lower numerical limitations were expressly written herein. Every minimum numerical limitation given throughout this specification will include every higher numerical limitation, as if such higher numerical limitations were expressly written herein. Every numerical range given throughout this specification will include every narrower numerical range that falls within such broader numerical range, as if such narrower numerical ranges were all expressly written herein.

**[0081]** The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

**[0082]** Any aspect or embodiment described herein can be combined with any other aspect or embodiment as disclosed herein.

## COMPOSITIONS AND INHIBITORS

### RTK-MAPK Pathway Inhibitors

**[0083]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0084]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound of Formula (I-A), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0085]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound of Formula (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0086]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

i) a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound of Formula (I-A), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0087]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0088]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

i) a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66,

67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0089]** In some embodiments, the compound is compound 2. In some cases, the compound is compound 3. In some cases, the compound is compound 4. In some cases, the compound is compound 14. In some cases, the compound is compound 25. In some cases, the compound is compound 74.

**[0090]** In some embodiments, the RTK-MAPK pathway inhibitor is selected from afatinib, dacomitinib, poziotinib, erlotinib, gefitinib, sapitinib, tarloxotinib, cetuximab, RMC-4550, SHP-099 (6-(4-Amino-4-methylpiperidin-l-yl)-3-(2,3-dichlorophenyl)pyrazin-2-amine dihydrochloride); RMC-4550 (3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazin-2-yl)methanol), RMC-4360, and TNO155 (Novartis).

**RAF-MEK-ERK pathway inhibitor**

**[0091]** In an aspect, provided herein are methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a combination of:

i) a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0092]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0093]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a combination of:

i) a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound of Formula (II), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0094]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-A), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0095]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0096]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

i) a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0097]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[0098]** In some embodiments, the compound is compound 2. In some cases, the compound is compound 3. In some cases, the compound is compound 4. In some cases, the compound is

compound 14. In some cases, the compound is compound 25. In some cases, the compound is compound 74.

**ERBB family Inhibitors**

**[0099]** In an aspect, provided herein are methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a combination of:

i) a ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00100]** In an aspect, provided herein are methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

i) a ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00101]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a ERBB family inhibitor, or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof.

**[00102]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a ERBB family inhibitor, or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-A), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof.

**[00103]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a ERBB family inhibitor, or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-B), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof.

**[00104]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00105]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

i) a ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00106]** In some embodiments, the compound is compound 2. In some cases, the compound is compound 3. In some cases, the compound is compound 4. In some cases, the compound is compound 14. In some cases, the compound is compound 25. In some cases, the compound is compound 74.

**[00107]** The ERBB family inhibitors used in the methods herein may be reversible or irreversible ERBB family inhibitors. In one embodiment, the ERBB family inhibitor inhibits the activity of more than one ERBB family member.

**[00108]** The modulation or inhibition of one or more ERBB family members may occur through modulating or inhibiting kinase enzymatic activity of one or more ERBB family member or by blocking homodimerization or heterodimerization of ERBB family members. In some

embodiments of the methods herein, the ERBB inhibitor refers to the use of a single ERBB inhibitor. In some embodiments of the methods herein, the term ERBB inhibitor refers to the use of two ERBB inhibitors.

**[00109]** In some embodiments, the ERBB family inhibitor is an irreversible inhibitor. In some cases, irreversible ERBB family inhibitors inhibit the activity of EGFR and HER2 by forming a covalent bond with the sulfhydryl group of cysteine 797 and cysteine 773, respectively, that blocks the binding of ATP to the intracellular catalytic domain. As such, these inhibitors are active against, for example, cell lines harboring EGFR exon 19 deletions/insertions, and L858R and T790M resistant mutations.

**[00110]** In some embodiments, exemplary irreversible ERBB family inhibitors for use in the methods include afatinib ((E)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-((tetrahydrofuran-3-yl)oxy)quinazolin- 6-yl)-4-(dimethylamino)but-2-enamide); dacomitinib ((2E)-N-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl}-4-(1-piperidinyl)-2-butenamide); canertinib (N-(4-((3-chloro-4-fluorophenyl)amino)-7-(3-morpholinopropoxy)quinazolin-6-yl)acrylamide); poziotinib (1-(4-((4-((3,4-dichloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)prop-2-en-1-one); AV 412 (N-[4-[(3-Chloro-4- fluorophenyl)amino]-7-[3 -methyl-3-(4-methyl-1-piperazinyl)-1-butyn-1-yl]-6-quinazolinyl]-2- propenamide); PF 6274484 (N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]-2-propenamide) and HKI 357 ((2E)-N-[[4-[[(3-Chloro-4-[(3- fluorophenyl)methoxy]phenyl]amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-2-butenamide), and pharmaceutically acceptable salts or pharmaceutical compositions thereof. In some cases, the irreversible ERBB family inhibitor is afatinib. In one embodiment, the irreversible ERBB family inhibitor is dacomitinib. In some cases, the irreversible ERBB family inhibitors suitable for the provided compositions and methods include, but are not limited to, Afatinib; Dacomitinib; Canertinib; Poziotinib, AV 412; PF 6274484 and HKI 357.

**[00111]** In some embodiments, the ERBB family inhibitor is a reversible inhibitor. In some cases, reversible inhibitors include erlotinib ([6,7-Bis-(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)-amine)), gefitinib (4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, sapitinib (2-(4-((4-((3-chloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl)-N-methylacetamide); varlitinib ((R)-N4-(3-chloro-4-(thiazol-2-ylmethoxy)phenyl)-N6-(4-methyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine); TAK-285 (N-(2-(4-((3-chloro-4-(3-(trifluoromethyl)phenoxy)phenyl)amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl)-3-hydroxy-3-methylbutanamide); AEE788 ((S)-6-(4-((4-ethylpiperazin-1-yl)methyl)phenyl)-N-(1- phenylethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine); tarloxotinib 3-[N-[4-(3-Bromo-4-chlorophenylamino)pyrido[3,4-d]pyrimidin-6-yl]carbamoyl]-N,N-dimethyl-N-(1-

methyl-4- nitro-lH-imidazol-5-ylmethyl)-2(E)-propen-l-aminium bromide ); BMS 599626 ((3S)-3-Morpholinylmethyl-[4-[[l-[(3-fluorophenyl)methyl]-lH-indazol-5-yl]amino]-5-methylpyrrolo[2,l-f][l,2,4]triazin-6-yl]-carbamate dihydrochloride); and GW 583340 HC1 (N-[3-Chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[2-[[[2- (methylsulfonyl)ethyl]amino]methyl]-4-thiazolyl]-4-quinazolinamine dihydrochloride), and pharmaceutically acceptable salts or pharmaceutical compositions thereof.

**[00112]** In some embodiments, the reversible ERBB family inhibitor is sapitinib. In some cases, the reversible ERBB family inhibitor is tarloxotinib.

**[00113]** In some embodiments, the ERBB family inhibitor is a combination of an EGFR inhibitor and a HER2 inhibitor, wherein the EGFR inhibitor and the HER2 inhibitor are a combination of two of: AG 1478 HC1 (7V-(3-Chlorophenyl)-6,7-dimethoxy-4-quinazolinanine hydrochloride); AG 494 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-phenyl-2-propenamide; AG 555 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-(3-phenylpropyl)-2-propenamide; AG 556 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-(4-phenylbutyl)-2-propenamide; AG 825 (*E*)-3-[3-[2-Benzothiazolythio)methyl]-4-hydroxy-5-methoxyphenyl]-2-cyano-2-propenamide; CP 724714 (2 -Methoxy-*N*-[(2*E*)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-l-yl]acetamide; BIBU 1361 diHCl (*N*-(3-Chloro-4-fluorophenyl)-6-[4-[(diethylamino)methyl]-l-piperidinyl]-pyrimido[5,4-*d*]pyrimidin-4-amine dihydrochloride); BIBU 1382 ($N^8$-(3-Chloro-4-fluorophenyl)-$N^2$-(l-methyl-4-piperidinyl)-pyrimido[5,4-]pyrimidine-2,8-diamine dihydrochloride); JNJ 28871063 HC1 (5*E*-4-Amino-6-(4-benzyloxy-3-chlorophenylamino)pyrimidine-5-carboxaldehyde *N*-(2-morpholin-4-ylethyl) oxime hydrochloride); PD 153035 (4-[(3-Bromophenyl)amino]-6,7-dimethoxyquinazoline hydrochloride); PD 158780 ($N^4$-(3-Bromophenyl)-$N^6$-methyl-pyrido[3,4-*d*]pyrimidine-4,6-diamine), and pharmaceutically acceptable salts or a pharmaceutical compositions thereof.

**[00114]** In some embodiments, the ERBB family inhibitor is an anti-EGFR antibody, an anti-HER2 antibody or a combination of an anti-EGFR antibody and anti-HER2 antibody, or pharmaceutical compositions thereof. In some cases, antibodies, including monoclonal antibodies, antibody drug conjugates and bispecific antibodies, targeting EGFR and/or HER-2 are used.

**[00115]** In some embodiments, exemplary anti-EGFR monoclonal antibodies approved for human clinical use include, but are not limited to, necitumumab (Eli Lilly), panitumumab

(Amgen) and cetuximab (ImClone). Other anti-EGFR antibodies suitable for use in the methods include EP384, Hl l, 11.6, 225 and 199.12 (Thermo Fisher), or GT133 (GeneTex).

**[00116]** In some embodiments, the anti-EGFR monoclonal antibody is cetuximab.

**[00117]** In some embodiments, exemplary anti-HER-2 monoclonal antibodies, include but are not limited to, pertuzumab (Roche), trastuzumab (Roche) and trastuzumab emtansine (Roche).

**[00118]** In some embodiments, the ERBB family inhibitor is an anti-EGFR antibody, an anti-HER2 antibody or a combination of an anti-EGFR antibody and anti-HER2 antibody, or pharmaceutical compositions thereof. In one embodiment, the anti-EGFR antibody is necitumumab, panitumumab or cetuximab. In one embodiment, the anti-EGFR antibody is cetuximab. In some cases, the anti-HER2 antibodies suitable for use in the methods herein is pertuzumab, trastuzumab, or trastuzumab emtansine.

**[00119]** In some embodiments, the ERBB family inhibitor is a an EGFR inhibitor and a HER2 inhibitor, wherein the EGFR inhibitor and the HER2 inhibitor are independently selected from two agents selected from the group consisting of: AG 1478 HC1 (*N*-(3-Chlorophenyl)-6,7-dimethoxy-4-quinazolinanine hydrochloride); AG 494 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-phenyl-2-propenamide; AG 555 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-(3-phenylpropyl)- 2-propenamide; AG 556 (*E*)-2-Cyano-3-(3,4-dihydroxyphenyl)-*N*-(4-phenylbutyl)-2-propenamide; AG 825 (*E*)-3-[3-[2-Benzothiazolythio)methyl]-4-hydroxy-5-methoxyphenyl]-2-cyano-2-propenamide; CP 724714 (2-Methoxy-*N*-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-l-yl]acetamide; BIBU 1361 diHCl (N-(3-Chloro-4-fluorophenyl)-6-[4-[(diethylamino)methyl]-l-piperidinyl]-pyrimido[5,4- ]pyrimidin-4-amine dihydrochloride); BIBU 1382 ($N^8$-(3-Chloro-4-fluorophenyl)-$N^2$-(l-methyl-4-piperidinyl)-pyrimido[5,4-J]pyrimidine-2,8-diamine dihydrochloride); JNJ 28871063 HC1 (5*E*-4-Amino-6-(4-benzyloxy-3-chlorophenylamino)pyrimidine-5-carboxaldehyde N-(2- morpholin-4-ylethyl) oxime hydrochloride); PD 153035 (4-[(3-Bromophenyl)amino]-6,7-dimethoxyquinazoline hydrochloride); PD 158780 ($N^4$-3-Bromophenyl)- $N^6$-methyl-pyrido[3,4-*d* ]pyrimidine-4,6-diamine) or pharmaceutically acceptable salts or pharmaceutically compositions thereof.

**EGFR Inhibitors**

**[00120]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) an EGFR inhibitor, or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof.

**[00121]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

i) an EGFR inhibitor, or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof.

**[00122]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) an EGFR inhibitor, or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-A), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof.

**[00123]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) an EGFR inhibitor, or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-B), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof.

**[00124]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a combination of:

i) a EGFR inhibitor, or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof.

**[00125]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of: i) a EGFR inhibitor, or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt, or a pharmaceutical composition thereof.

**[00126]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00127]** In some embodiments, the compound is compound 2. In some cases, the compound is compound 3. In some cases, the compound is compound 4. In some cases, the compound is compound 14. In some cases, the compound is compound 25. In some cases, the compound is compound 74.

**[00128]** In some embodiments, Epidermal Growth Factor Receptor (EGFR) is a transmembrane protein tyrosine kinase of the ERBB receptor family. Upon binding epidermal growth factor (EGF), the EGFR receptor can homo-dimerize with another EGFR molecule or hetero-dimerize with another family member such as ErbB2 (HER2), ErbB3 (HER3), or ErbB4 (HER4). Homo- and/or heterodimerization of ERBB receptors results in the phosphorylation of key tyrosine residues in the intracellular domain and leads to the stimulation of numerous intracellular signal transduction pathways involved in cell proliferation and survival. In some cases, overexpression of the EGFR gene has been identified in a variety of cancers including bladder, brain, head and neck, pancreas, lung, breast, ovary, colon, prostate, and kidney.

**[00129]** In some embodiments, the EGFR inhibitor is selected from cetuximab, afatinib and erlotinib.

**SHP-2 Inhibitors**

**[00130]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00131]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

i) a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00132]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-A), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00133]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00134]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a combination of

i) a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00135]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89,

90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00136]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

i) a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00137]** In some embodiments, the compound is compound 2. In some cases, the compound is compound 3. In some cases, the compound is compound 4. In some cases, the compound is compound 14. In some cases, the compound is compound 25. In some cases, the compound is compound 74.

**[00138]** Src homology 2 (SH2) domain-containing phosphatase 2 ("SHP-2") is a mammalian non-receptor protein tyrosine phosphatase encoded by the PTPN11 gene that is involved in signaling through the Ras-mitogen-activated protein kinase, the JAK-STAT or the phosphoinositol 3-kinase (P13K)-AKT-mTOR pathways, SHP-2 polypeptide is comprised of two Src homology 2 (SH2) domains (N-SH2 and C-SH2) located in the N-terminal region and two potential Grb2 SH2 domain binding sites located in the C-terminal region.

**[00139]** In some embodiments, SHP-2 has been shown to exhibit non-mutational drug resistance mechanism in response to anti-tyrosine kinase inhibitors (TKIs). In some cases, an increase in SHP-2 phosphatase activity has been shown to confer resistance to the TKI inhibitor imatinib (e.g., see Li et. ah, (2018) Toxicol. Appl. Pharmacol. 360-249-256). The addition of a SHP-2 inhibitor was shown to overcome resistance by blocking both the RAF/MEK/ERK pathway as well as the PI3K/AKT/mTOR pathways.

**[00140]** Several inhibitors exhibiting activity against SHP-2 have been developed. Exemplary SHP-2 inhibitors include, but are not limited to, SHP-099 (6-(4-Amino-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenyl)pyrazin-2-amine dihydrochloride); RMC-4550 (3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(2,3-dichlorophenyl)-5- methylpyrazin-2-yl)methanol), RMC-4630 (Revolution Medicine) and TNO155 (Novartis). RMC-4630 and

TNO155 are in Phase 1 human clinical trials for adult patients having particular advanced solid tumors.

**[00141]** In some embodiments, methods for manufacturing SHP-2 inhibitors are well known to those skilled in the art and SHP-2 inhibitors may be obtained from a wide-variety of commercial suppliers, in forms suitable for both research or human use. In addition, suitable SHP-2 inhibitors for use in the compositions and methods disclosed herein and methods for preparing such inhibitors are disclosed in US Patent Application Publication Nos: US20190127378; US20180251471; US 20180201623; US 20180186770; US20180170862; US 20180065949; US20170204080; US20170166510; US20170011975; US201200334186; US20120257184; US20110190315; US20090042788; US20080194563; US20080058431; US20080058431; US20040121384; US20040043434; and US20040110800.

**SOS1 Inhibitors**

**[00142]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00143]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

i) a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00144]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-A), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00145]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00146]** In an aspect, provided herein are methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

ii) and a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00147]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a combination of:

i) a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and

ii) a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00148]** In an aspect, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of:

i) a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof,

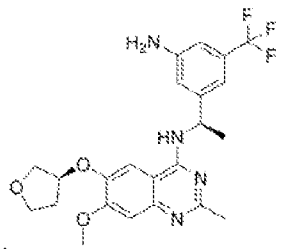
ii) and a compound selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00149]** In some embodiments, the compound is compound 2. In some cases, the compound is compound 3. In some cases, the compound is compound 4. In some cases, the compound is

compound 14. In some cases, the compound is compound 25. In some cases, the compound is compound 74.

**[00150]** In some embodiments, SOS1 inhibitors block the interaction between SOS1 and Ras-family members and prevent the recycling of KRas in to the active GTP-bound form and, therefore, may provide therapeutic benefit for a wide range of cancers, particularly Ras family member-associated cancers. These compounds negatively modulate the activity of KRas through blocking SOS1- KRas interaction in a cell for treating various forms of cancer, including Ras-associated cancer, SOS1-associated cancer and NF1/NF2-associated cancer.

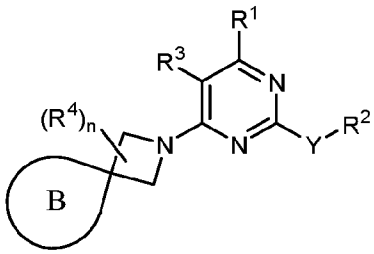
**[00151]** In some embodiments, one SOS1 inhibitor that can be used for the methods described herein is BI-I-13 (aka BI-3406). It has the following structure:



**KRAS Modulators**

**[00152]** The following is a discussion of compounds and salts thereof that may be used in the methods of the disclosure. The compounds and salts may be used in combination with at least one other inhibitor (e.g., RTK-MAPK pathway inhibitor, RAF-MEK-ERK pathway inhibitor, ERBB family inhibitor, EGFR inhibitor, SHP-2 inhibitor, or SOS1 inhibitor). The compounds and salts may be used in combination with one other inhibitor (e.g., RTK-MAPK pathway inhibitor, RAF-MEK-ERK pathway inhibitor, ERBB family inhibitor, EGFR inhibitor, SHP-2 inhibitor, or SOS1 inhibitor). In some cases, a compound of Formulas (I), (I-A), or (I-B), may be used in the methods of the disclosure. In some cases, a compound of Formulas (I), (I-A), or (I-B) may be referred to as a KRAS inhibitor. In some cases, a compound of Formulas (I), (I-A), or (I-B) may be referred to as a KRAS inhibitor. In some cases, a compound of Formulas (I), (I-A), or (I-B) may be referred to as a KRAS modulator.

**[00153]** In certain aspects, the present disclosure provides a compound represented by the structure of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt thereof wherein:

B is selected from a 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle, wherein the 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle are each optionally substituted with one or more substituents independently selected from halogen, -CN, -$NO_2$, =O, -$N(R^{21})_2$, -$B(OR^{21})_2$, -$OR^{21}$, -$SR^{21}$, -$S(O)_2(R^{21})$, -$S(O)_2N(R^{21})_2$, -$NR^{21}S(O)_2R^{21}$, -$C(O)N(R^{21})_2$, -$C(O)NR^{21}OR^{21}$, -$N(R^{21})C(O)R^{21}$, -$N(R^{21})C(O)N(R^{21})_2$, -$N(R^{21})C(O)OR^{21}$, -$C(O)R^{21}$, $C(O)OR^{21}$, -$OC(O)R^{21}$, -$OC(O)N(R^{21})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

$R^1$ is selected from hydrogen and 5- to 15-membered heterocycle, wherein the 5- to 15-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -$B(OR^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$C(=NR^{20})N(R^{20})_2$, -$C_{1-6}$ alkyl($=NOR^{20}$), -$C(O)NR^{20}OR^{20}$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$N(R^{20})_2$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, -$NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl-$SO_2R^{20}$, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle, wherein the $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, -$B(OR^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$C(O)NR^{20}OR^{20}$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$N(R^{20})_2$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, -$NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, and $C_3$-$C_{12}$ carbocycle;

Y is selected from a bond, -O-, -S-, and -$N(R^5)$-;

$R^2$ is selected from heterocycle, $C_1$-$C_6$ alkyl, -L-heterocycle, -L-$N(R^{23})_2$, -L-$OR^{23}$, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-$NHC(=NH)NH_2$, -L-$C(O)N(R^{23})_2$, -L-$C_1$-$C_6$ haloalkyl, -L-$OR^{23}$, -L-$NR^{23}C(O)$-aryl, -L-COOH, -L-$NR^{23}S(O)_2(R^{23})$, -L-$S(O)_2N(R^{23})_2$, -L-$N(R^{23})C(O)(OR^{23})$, -L-$OC(O)N(R^{23})_2$, and -L-$C(=O)OC_1$-$C_6$ alkyl, wherein the heterocycle, the heterocycle portion of -L-heterocycle, and the cycloalkyl portion of the -L-cycloalkyl are each optionally substituted with one or more $R^6$, and wherein the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$;

$R^3$ is selected from hydrogen, halogen, -CN, -$NO_2$, -$N(R^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

each $R^4$ is independently selected from halogen, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

n is selected from 0, 1, 2, 3, and 4;

each $R^5$ is independently selected from hydrogen and $C_1$-$C_6$ alkyl;

each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, =$CH_2$, =NO-$C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, -$N(R^5)S(O)_2(R^5)$, -Q-phenyl, -Q-phenyl$SO_2F$, -NHC(O)phenyl, - NHC(O)phenyl$SO_2F$, $C_1$-$C_3$ alkyl substituted pyrazolyl, tert-butyldimethylsilyloxy$CH_2$-, -$N(R^5)_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$ alkyl)C(=O), oxo, ($C_1$-$C_3$ haloalkyl)C(=O)-, -$SO_2F$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC_1$-$C_6$ alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)C_1$-$C_6$ alkyl, -$CH_2$(pyrazolyl), -$CH_2NHSO_2C_1$-$C_6$ alkyl, -$CH_2OC(O)$heterocycle, -$OC(O)N(R^5)_2$, -$OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl), -$OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl($C_1$-$C_3$ alkyl)$N(CH_3)_2$, -$OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl, -OC(O)heterocycle, -O-$C_1$-$C_3$ alkyl, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, and -$CH_2$heterocycle, wherein the phenyl of -NHC(O)phenyl and -$OC(O)NH(C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl)phenyl are optionally substituted with one or more substituents selected from -C(O)H and OH, and wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo and hydroxy; and wherein the heterocycle of -$CH_2$heterocyclyl is optionally substituted with oxo;

each Q is selected from a bond, S, and O;

each $R^7$ is independently selected from halogen, hydroxy, HC(=O)-, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, and -$N(R^5)_2$;

each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, hydroxy, $C_{1-6}$ alkoxy, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle, and 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl; and wherein optionally two substituents

on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle.

**[00154]** In some embodiments, for a compound or salt for Formula (I), B is selected from an optionally substituted 7- to 15-membered fused heterocycle and optionally substituted $C_7$-$C_{15}$ fused carbocycle. In some cases, and optionally substituted $C_7$-$C_{15}$ fused carbocycle. In some cases, B is an optionally substituted 7- to 15-membered fused heterocycle. In some cases, B is an optionally substituted unsaturated 7- to 15-membered fused heterocycle. In some cases, B is an optionally substituted 7- to 15-membered fused heteroaryl. In some cases, B is selected from an optionally substituted 7- to 15-membered fused heteroaryl and optionally substituted $C_7$-$C_{15}$ fused aryl. In some cases, B is an optionally substituted unsaturated $C_7$-$C_{15}$ fused carbocycle. In some cases, B is an optionally substituted 7- to 15-membered fused heterocycle, wherein the fused heterocycle is partially unsaturated. In some cases, B is an optionally substituted 7- to 15-membered fused heterocycle, wherein the fused heterocycle is partially saturated.

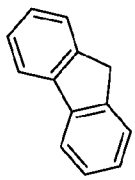
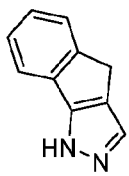
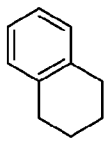
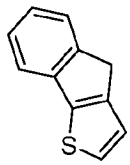
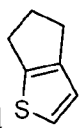
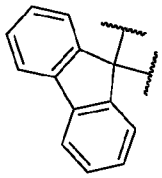
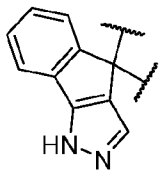
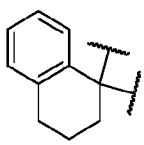
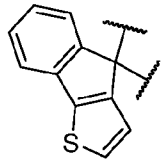
**[00155]** In some embodiments, for a compound or salt for Formula (I), B is selected from an optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle. In some cases, and optionally substituted $C_8$-$C_{15}$ fused carbocycle. In some cases, B is an optionally substituted 8- to 15-membered fused heterocycle. In some cases, B is an optionally substituted unsaturated 8- to 15-membered fused heterocycle. In some cases, B is an

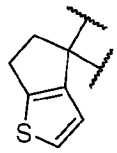
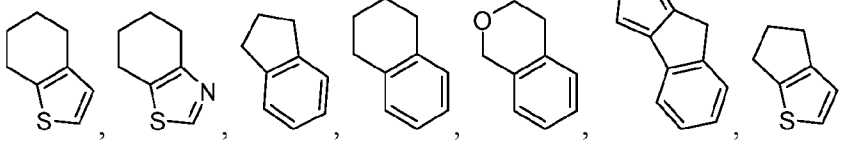
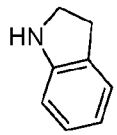
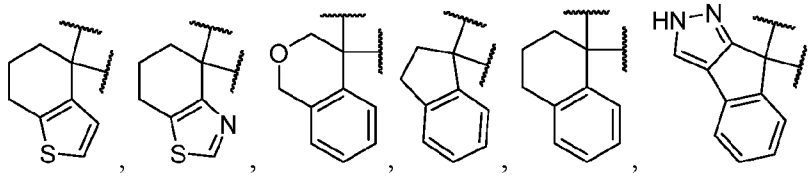
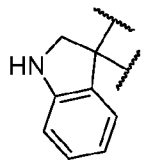
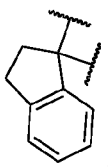
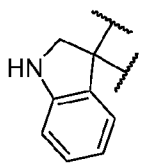
optionally substituted 8- to 15-membered fused heteroaryl. In some cases, B is selected from an optionally substituted 8- to 15-membered fused heteroaryl and optionally substituted $C_8$-$C_{15}$ fused aryl. In some cases, B is an optionally substituted unsaturated $C_8$-$C_{15}$ fused carbocycle. In some cases, B is an optionally substituted 8- to 15-membered fused heterocycle, wherein the fused heterocycle is partially unsaturated. In some cases, B is an optionally substituted 8- to 15-membered fused heterocycle, wherein the fused heterocycle is partially saturated.

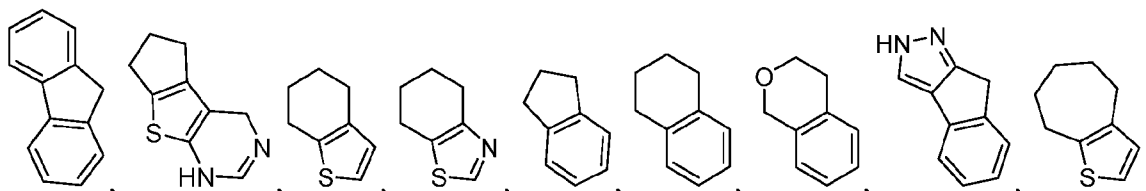
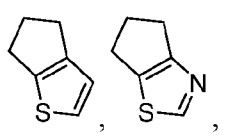
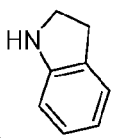
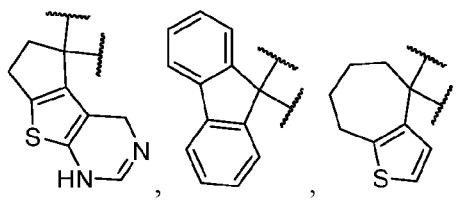
**[00156]** In some embodiments, for a compound or salt for Formula (I), B is selected from an optionally substituted 8- to 15-membered fused heterocycle, wherein the fused heterocycle is formed by combining three rings (e.g., tricyclic). In some cases, B is selected from an optionally substituted 8- to 15-membered fused heterocycle, wherein the fused heterocycle is formed by combining two rings (e.g., bicyclic). In some cases, for B the optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle are each independently bicyclic or tricyclic. In some cases, for B the optionally substituted 8- to 15-membered fused heterocycle is bicyclic. In some cases, for B the optionally substituted 8- to 15-membered fused heterocycle is tricyclic.

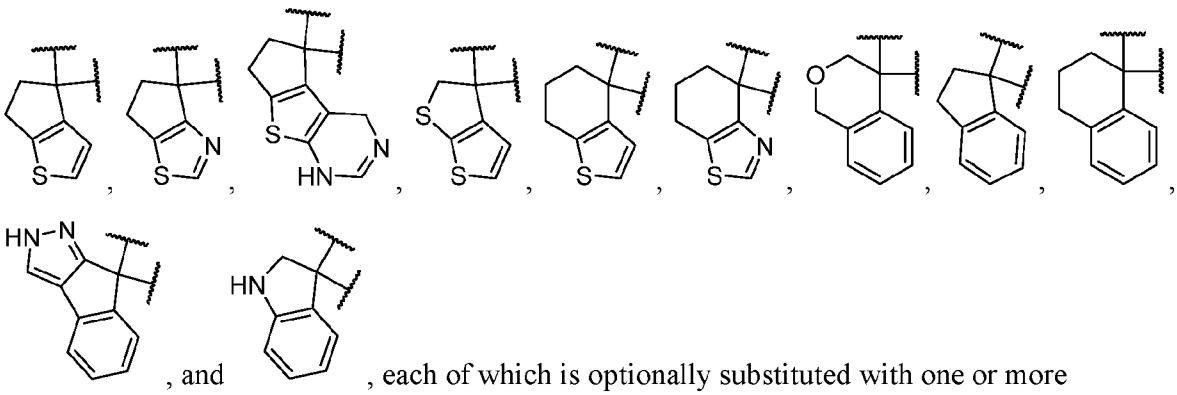
**[00157]** In some embodiments, for a compound or salt for Formula (I), the heterocycle or carbocycle of B is bicyclic. In some cases, the heterocycle or carbocycle of B is tricyclic. In some cases, the tricyclic heterocycle contains three interconnected rings of atoms.

**[00158]** In some embodiments, for a compound or salt for Formula (I), for B, the heterocycle and carbocycle are each independently selected from bicyclic and tricyclic. In some cases, for B, the heterocycle and carbocycle are each independently tricyclic. In some cases, for B, the heterocycle and carbocycle are each independently bicyclic.

**[00159]** In some embodiments, for a compound or salt for Formula (I), for B, the optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle are selected from  ,  ,  ,  , and  , each of which is optionally substituted with one or more substituents. In some cases, for B, the optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle are selected from  ,  ,  ,  , and

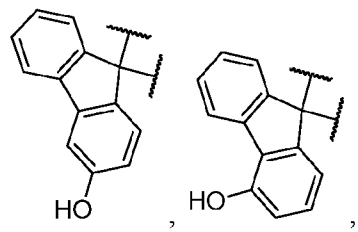

, each of which is optionally substituted with one or more substituents. In some cases, B is selected from  , and  , each of which is optionally substituted with one or more substituents. In some cases, B is selected from  , and  , each of which is optionally substituted with one or more substituents. In some cases, B is selected from  , and  , each of which is optionally substituted with one or more substituents.

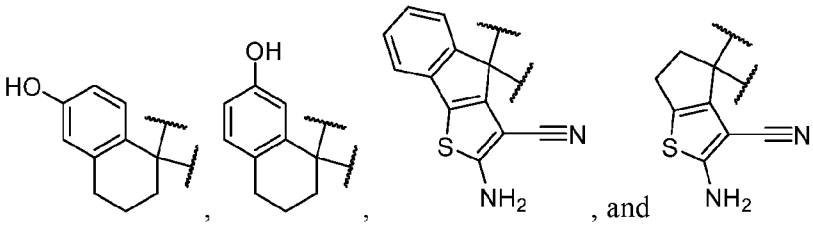
**[00160]** In some embodiments, for a compound or salt for Formula (I), B is selected from  ,  , and  , each of which is optionally substituted with one or more substituents. In some cases, B is selected from  , , ,



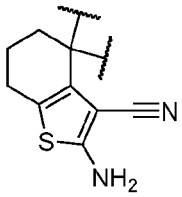
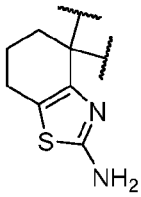
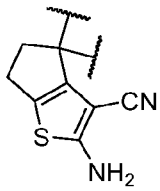
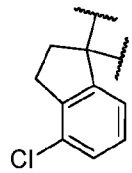
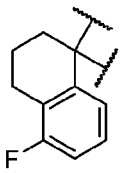
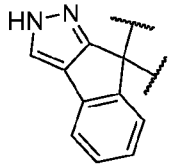
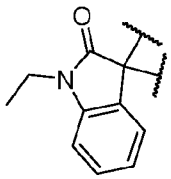
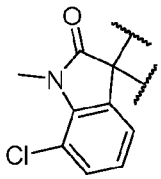
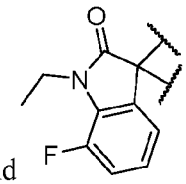
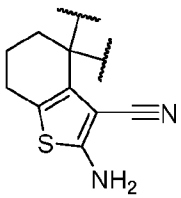
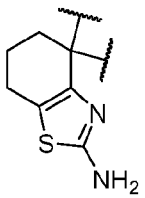
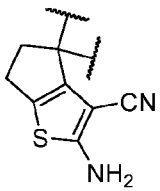
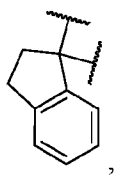
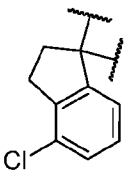
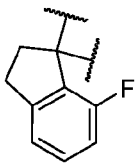
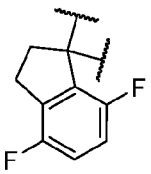
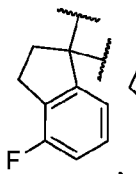
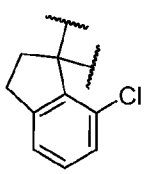
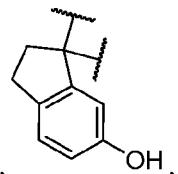
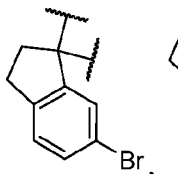
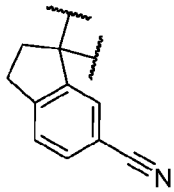
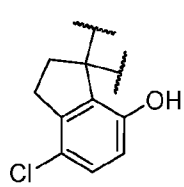
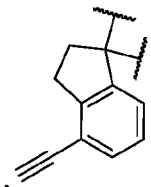
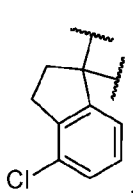
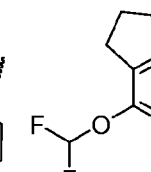
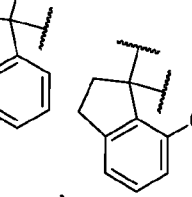
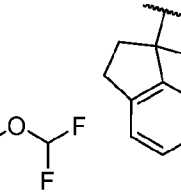
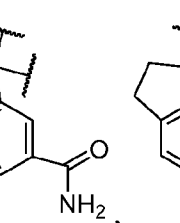
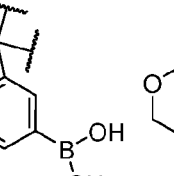
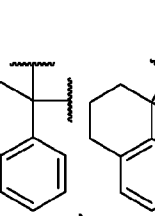
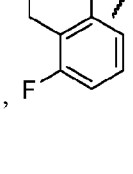
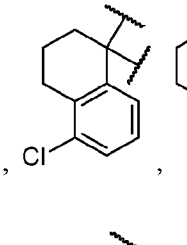
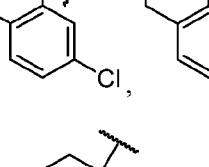
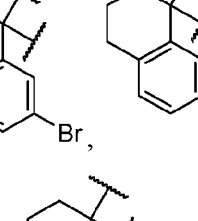
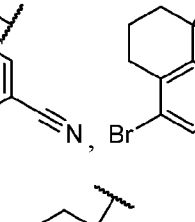
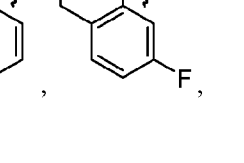
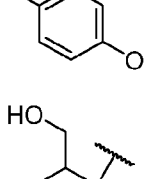
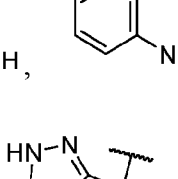
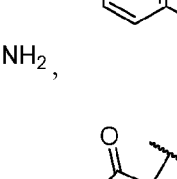
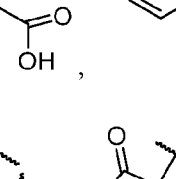
, each of which is optionally substituted with one or more substituents.

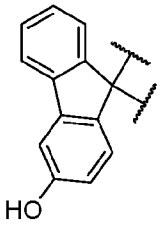
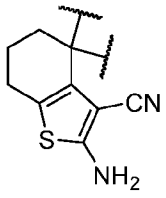
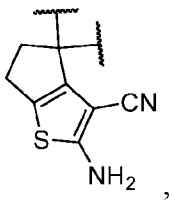
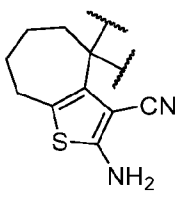
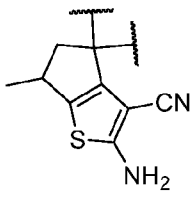
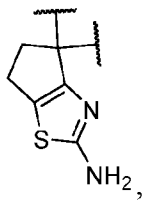
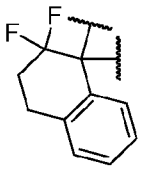
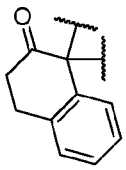
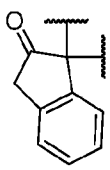
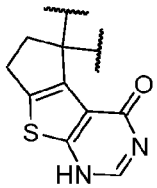
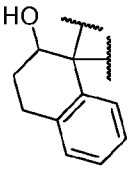
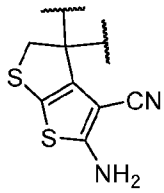
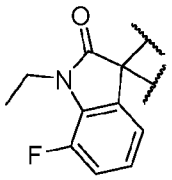
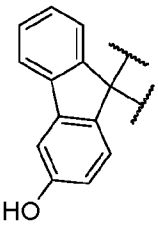
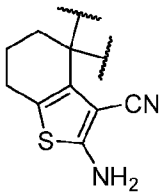
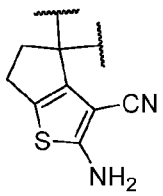
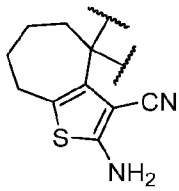
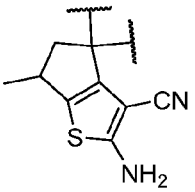
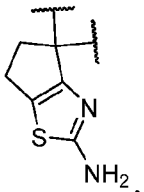
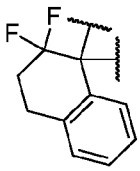
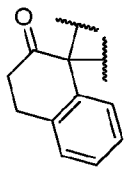
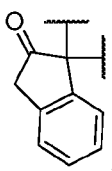
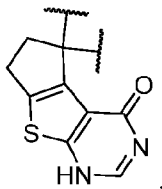
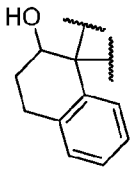
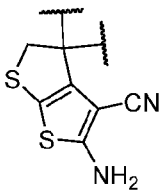
**[00161]** In some embodiments, for a compound or salt for Formula (I), for B, the optional substituents of the heterocycle and carbocycle are each independently selected from halogen, -CN, $-NO_2$, =O, $-N(R^{21})_2$, $-B(OR^{21})_2$, $-OR^{21}$, $-SR^{21}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle. In some cases, the optional substituents of the heterocycle and carbocycle are each independently selected from halogen, -CN, $-NO_2$, =O, $-N(R^{21})_2$, $-B(OR^{21})_2$, -OH, $-SR^{21}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl. In some cases, for B, the one or more optional substituents of the heterocycle and carbocycle are independently selected at each occurrence from halogen, oxo, $-NH_2$, $C_1$-$C_3$ alkyl, $-B(OH)_2$, -OH, -O-$C_1$-$C_3$ haloalkyl, $-C(O)NH_2$, $-NH_2$, =O, -CN, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{2-6}$ alkynyl. In some cases, the optional substituents of the heterocycle and carbocycle are each independently selected from halogen, -CN, =O, $-NH_2$, $-N(C_{1-6}$ alkyl)H $-N(C_{1-6}$ alkyl)$_2$, -OH, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of the heterocycle and carbocycle are each independently selected from oxo, $-NH_2$, halogen, $C_1$-$C_3$ alkyl. In some cases, for B, the optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle are selected from

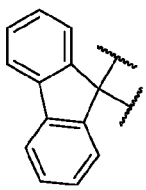
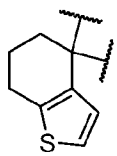
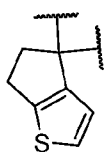
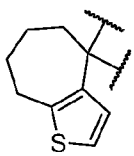
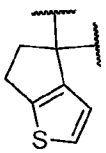
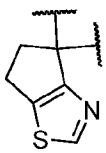
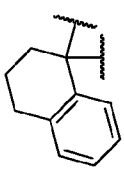
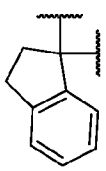
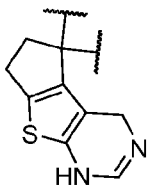
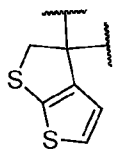


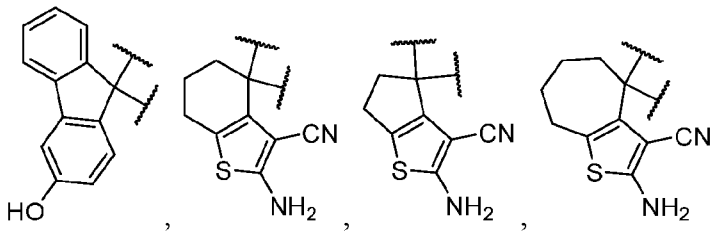
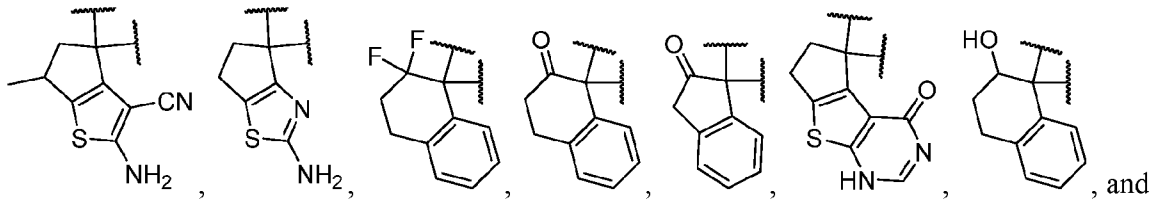
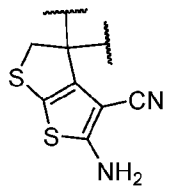


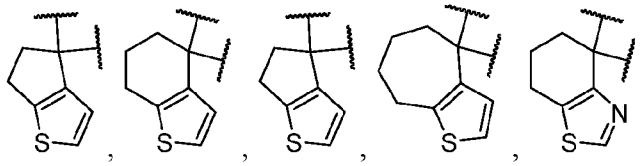
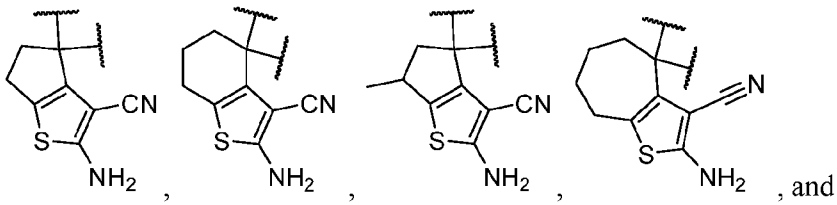
. In some cases, B is selected

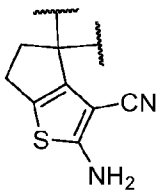
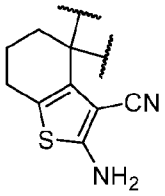
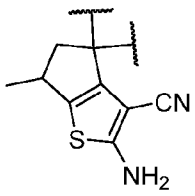
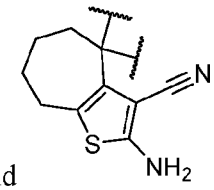
from  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, B is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , , , , , , , , , , , 

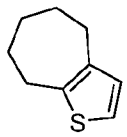
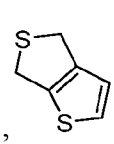
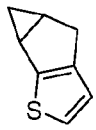
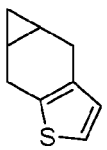
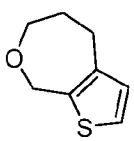
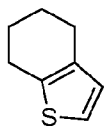
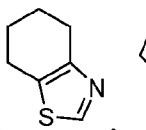
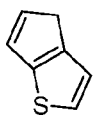
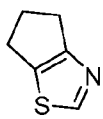
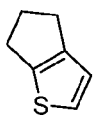
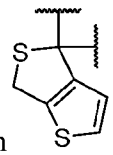
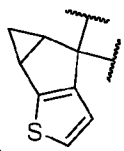
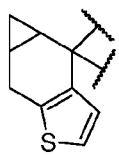
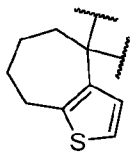
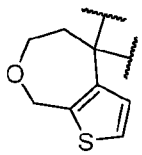
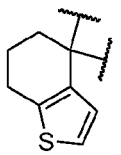
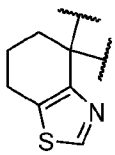
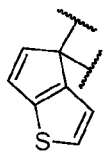
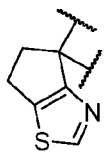
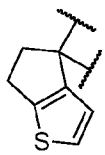
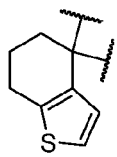
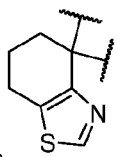
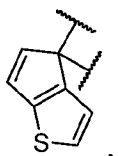
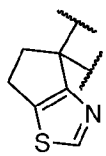
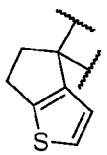












, and . In some cases, B is selected from












, and

.

**[00162]** In some embodiments, for a compound or salt for Formula (I), B is selected from an optionally substituted 7- to 12-membered fused heterocycle and optionally substituted $C_{9-10}$ fused carbocycle. In some cases, the heterocycle of B has at least one sulfur atom. In some cases, the heterocycle of B has one or sulfur atoms. In some cases, the heterocycle of B has at least one nitrogen atom. In some cases, B is selected from









, and

, each of which is optionally substituted. In some cases, the one or more optional substituents of B are independently selected

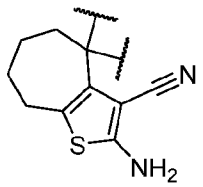
at each occurrence from halogen, $C_1$-$C_3$ alkyl, -$B(OR^{20})_2$, -$OR^{20}$, -$C(O)N(R^{20})_2$, -$N(R^{20})_2$, =O, -CN, -NHCN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of B are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, -OH, -$NH_2$, =O, and -CN. In some cases, B is selected from  ,  , and  .

**[00163]** In some embodiments, for a compound or salt for Formula (I), B is selected from an optionally substituted 8- to 10-membered fused heterocycle having at least one sulfur atom. In some cases, B is selected from  , each of which is optionally substituted. In some cases, the one or more optional substituents of B are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, -$OR^{20}$, -$C(O)N(R^{20})_2$, -$N(R^{20})_2$, =O, -CN, -NHCN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of B are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, -$NH_2$, and -CN. In some cases, B is substituted. In some cases, B is substituted with at least one -$NH_2$. In some cases, B is selected from  . In

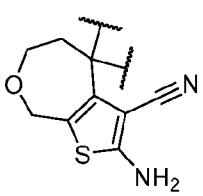
some cases, B is substituted with at least one -$NH_2$ at least one -CN. In some cases, B is selected from  ,  ,  , and  .

**[00164]** In some embodiments, for a compound or salt for Formula (I), B is an optionally substituted 7- to 11-membered fused heterocycle. In some cases, B is an optionally substituted 8- to 10-membered fused heterocycle. In some cases, B is an optionally substituted 7-membered fused heterocycle. In some cases, B is an optionally substituted 8-membered fused heterocycle. In some cases, B is an optionally substituted 9-membered fused heterocycle. In some cases, B is an optionally substituted 10-membered fused heterocycle. In some cases, the heterocycle of B is an unsaturated heterocycle. In some cases, the heterocycle of B is a non-aromatic heterocycle. In some cases, B has at least one sulfur atom. In some cases, B has at two sulfur atoms. In some cases, B has at least one sulfur atom and at least one nitrogen atom. In some cases, B has at least one sulfur atom and at least one oxygen atom. In some cases, B has only 1 heteroatom. In some cases, B has at least 2 heteroatoms. In some cases, B is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  each of which is optionally substituted. In some cases, B is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted. In some cases, B is selected from  ,  ,  ,  , and  , each of which is optionally substituted. In some cases, the one or more optional

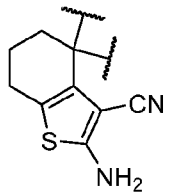
substituents of B, are independently selected at each occurrence from halogen, oxo, $-NH_2$, $C_1$-$C_3$ alkyl, $-B(OH)_2$, -OH, $-O-C_1$-$C_3$ haloalkyl, $-C(O)NH_2$, $-NH_2$, =O, -CN, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of B, are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, $-NH_2$, and -CN. In some cases, B is substituted with at least three substituents. In some cases, B is substituted with at least two substituents. In some cases, B is substituted with at least one substituent. In some cases, B is substituted with at least one substituent selected from halogen, $C_1$-$C_3$ alkyl, $-NH_2$, and -CN. In some cases, B is substituted with at least one substituent selected from halogen. In some cases, B is substituted with at least one substituent selected from $-NH_2$. In some cases, B is substituted with at least one substituent selected from -CN. In some cases, B is selected from



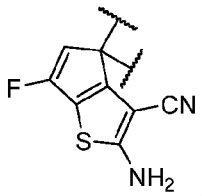
,



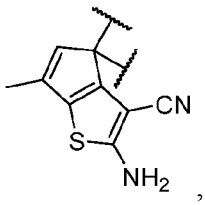
,



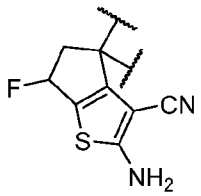
,



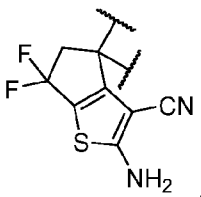
,



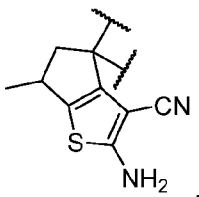
,



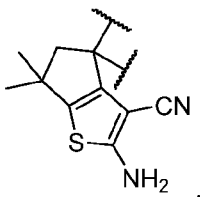
,



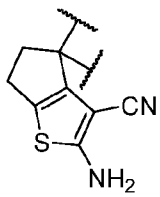
,



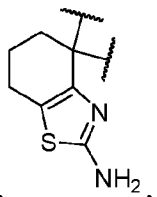
,



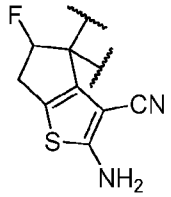
,



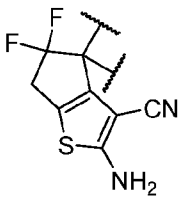
,



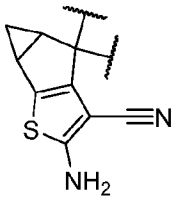
,



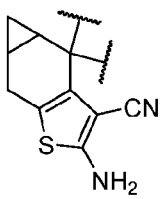
,



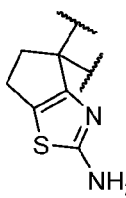
,



,



, and

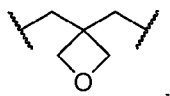
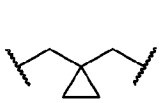
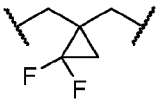
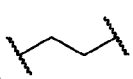


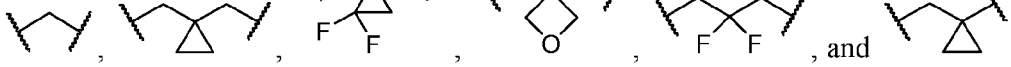
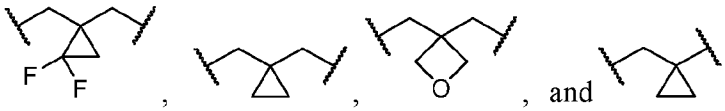
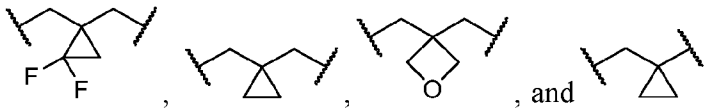
.

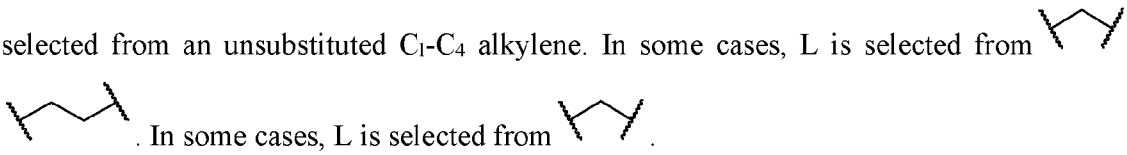
**[00165]** In some embodiments, for a compound or salt for Formula (I), $R^3$ is selected from hydrogen, halogen, -CN, $-NO_2$, $-N(R^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl. In some cases, $R^3$ is selected from hydrogen, halogen, -CN, $-NO_2$, $-N(R^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-C(O)N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl. In some cases, $R^3$ is selected from hydrogen, halogen, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl)H $-N(C_{1-6}$ alkyl$)_2$,-OH, -

$C(O)N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl. In some cases, $R^3$ is selected from hydrogen, -CN, $-C(O)R^{20}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, $R^3$ is selected from hydrogen, -CN, $-C(O)R^{20}$, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ alkyl. In some cases, $R^3$ is selected from hydrogen, -CN, -C(O)H, $C_1$ hydroxyalkyl, and $C_{1-6}$ alkyl. In some cases, $R^3$ is selected from hydrogen, fluorine, and -CN. In some cases, $R^3$ is selected from fluorine. In some cases, $R^3$ is selected from hydrogen. In some cases, $R^3$ is selected from -CN.

**[00166]** In some embodiments, for a compound or salt for Formula (I), Y is -O-. In some cases, Y is a bond. In some cases, Y is -S-. In some cases, Y is $-N(R^5)-$.

**[00167]** In some embodiments, for a compound or salt for Formula (I), L is selected from $C_1$-$C_4$ alkylene. In some cases, L is selected from an unsubstituted $C_1$-$C_4$ alkylene. In some cases, L is selected from an unsubstituted $C_1$ alkylene. In some cases, two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, $-NO_2$, =O, =S, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl. In some cases, two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle. In some cases, two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle. In some embodiments, for a compound or salt for Formula (I), L is selected from $C_1$-$C_4$ alkylene. In some cases, L is selected from unsubstituted $C_1$-$C_4$ alkylene. In some cases, each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents selected from halogen, -OH, $-NO_2$, =O, =S, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl. In some cases, the optional substituents of L are selected from $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are optionally substituted with one or more substituents selected from halogen and $C_{1-6}$ haloalkyl. In some cases, L is selected from  ,  ,  ,  ,  ,  ,  , and  . In some cases, L is selected

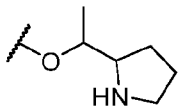
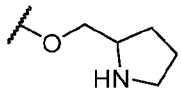
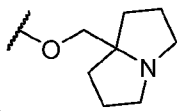
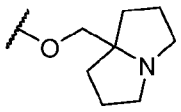
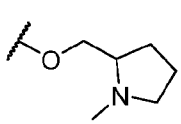
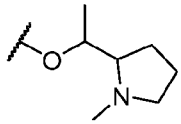
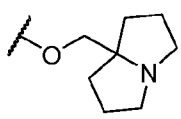
from  . In some cases, each L is independently selected from a substituted $C_1$-$C_4$ alkylene, and wherein two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle 3- to 5-membered heterocycle. In some cases, each L is independently selected from a substituted $C_{2-3}$ alkylene, and wherein two substituents on the same carbon atom of L come together to form a $C_3$ carbocycle or 4-membered heterocycle, wherein the $C_3$ carbocycle is optionally substituted with one or more substituents selected from halogen. In some cases, each L is independently selected from  . In some cases, each L is independently selected from  . In some cases, each L is independently selected from  . In some cases, each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen and $C_1$-$C_4$ alkyl. In some cases, L is selected from  .

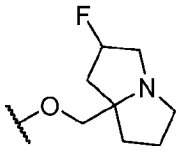
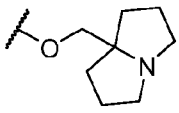
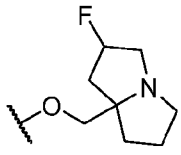
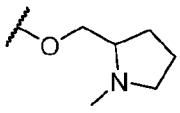
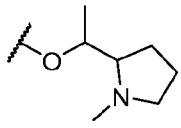
**[00168]** In some embodiments, for a compound or salt for Formula (I), each L is independently selected from an unsubstituted $C_1$-$C_4$ alkylene. In some cases, L is selected from  . In some cases, L is selected from .

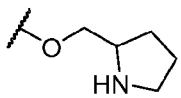
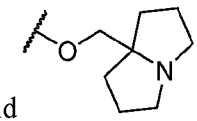
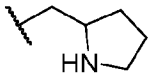
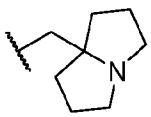
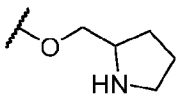
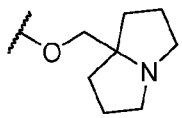
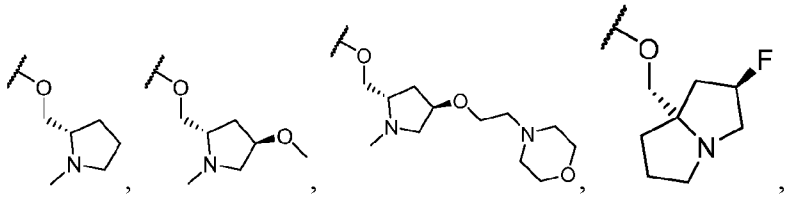
**[00169]** In some embodiments, for a compound or salt for Formula (I), $R^2$ is selected from heterocycle, $C_1$-$C_6$ alkyl, -L-heterocycle, -L-N($R^{23}$)$_2$, -L-O$R^{23}$, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-N($R^{23}$)$_2$, -L-NHC(=NH)$NH_2$, -L-C(O)N($R^{23}$)$_2$, -L-$C_1$-$C_6$ haloalkyl, -L-O$R^{23}$, -L-N$R^{23}$C(O)-aryl, -L-COOH, -L-N$R^{23}$S(O)$_2$($R^{23}$), -L-S(O)$_2$N($R^{23}$)$_2$, -L-N($R^{23}$)C(O)(O$R^{23}$), -L-OC(O)N($R^{23}$)$_2$, and -L-C(=O)O$C_1$-$C_6$ alkyl, wherein the heterocycle, the heterocycle portion of -L-heterocycle, and the cycloalkyl portion of the -L-cycloalkyl are each optionally substituted with one or more $R^6$, and wherein the aryl portion of -L-N$R^{23}$C(O)-aryl, the aryl portion of -L-N$R^{23}$C(O)-aryl, the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$.

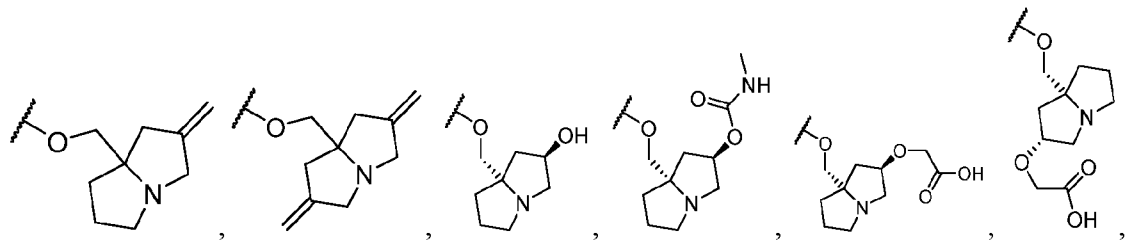
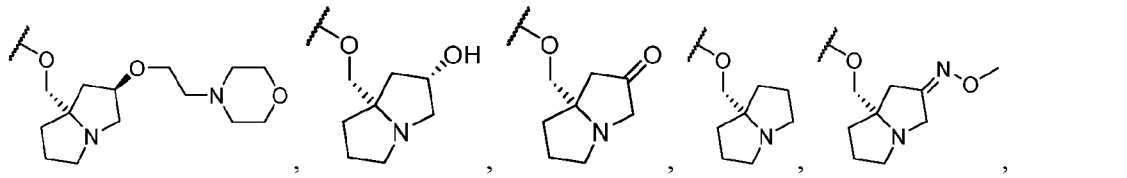
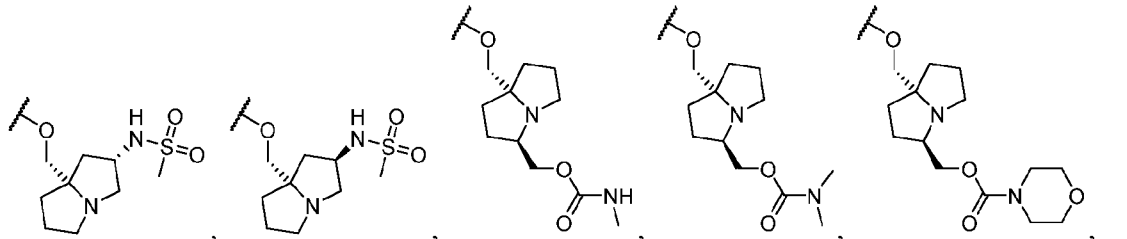
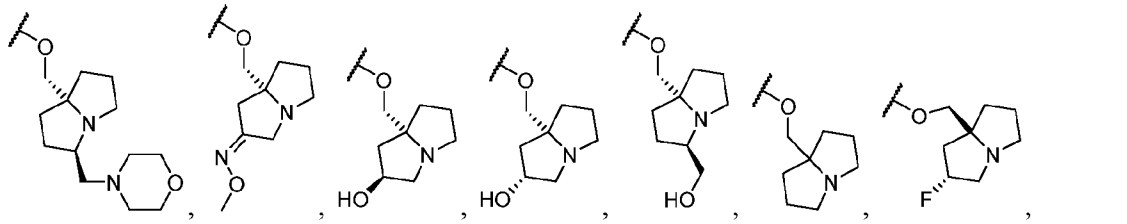
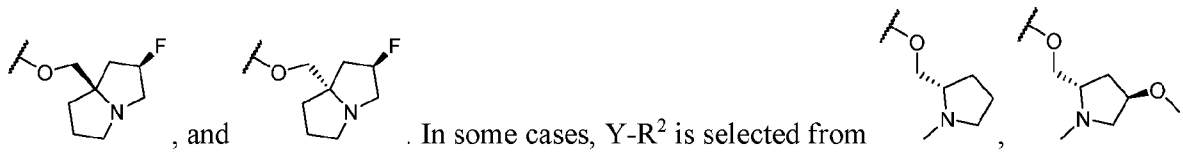
**[00170]** In some embodiments, for a compound or salt for Formula (I), $R^2$ is selected from heterocycle, -L-heterocycle, -L-aryl, -L-heteroaryl, and -L-N($R^{23}$)$_2$, wherein the heterocycle, the

heterocycle portion of -L-heterocycle, are each optionally substituted with one or more $R^6$, and wherein the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$.

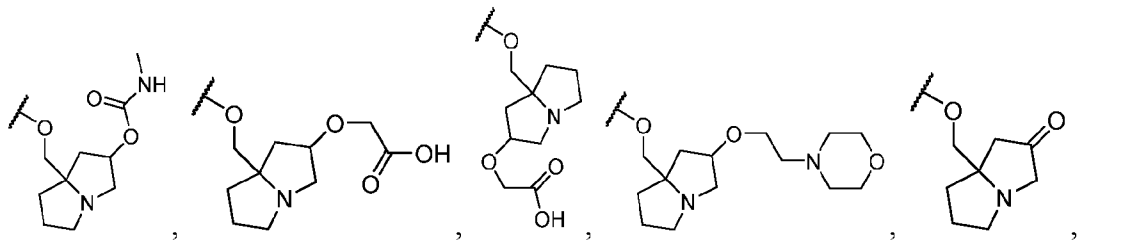
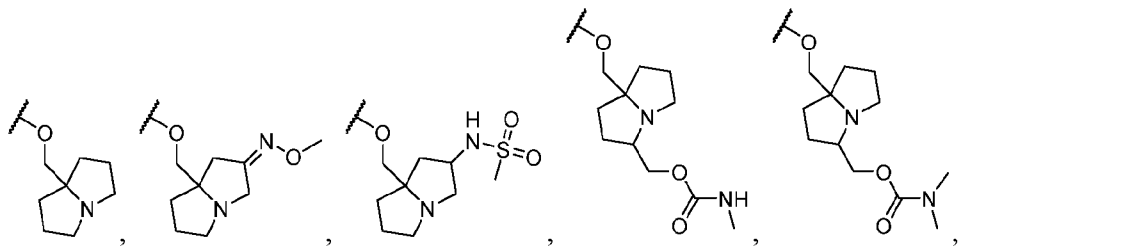
**[00171]** In some embodiments, for a compound or salt for Formula (I), $R^2$ is -L-heterocycle, wherein the heterocycle portion is optionally substituted. In some cases, $R^2$ is -L-heterocycle, wherein the heterocycle portion is a bicyclic heterocycle. In some cases, $R^2$ is -L-heterocycle, wherein the heterocycle portion is a monocyclic heterocycle. In some cases, $R^2$ is -L-heterocycle, wherein the heterocycle portion is a saturated heterocycle. In some cases, $R^2$ is selected from a -L-5- to 10-membered heterocycle. In some cases, $R^2$ is selected from a -($C_1$-$C_2$ alkylene)-5- to 10-membered heterocycle. In some cases, $R^2$ is selected from a -L-5- to 8-membered heterocycle. In some cases, $R^2$ is selected from a -L-5- to 8-membered saturated heterocycle. In some cases, $R^2$ is a -L-5-membered heterocycle. In some cases, $R^2$ is a -L-8-membered heterocycle. In some cases, the heterocycle contains at least 1 nitrogen atom. In some cases, the heterocycle contains at most 1 nitrogen atom. In some cases, the heterocycle contains 1 nitrogen atom. In some cases, the bicyclic heterocycle contains at least 1 nitrogen atom. In some cases, the bicyclic heterocycle contains at most 1 nitrogen atom. In some cases, the bicyclic heterocycle contains 1 nitrogen atom. In some cases, Y-$R^2$ is selected from  ,  and  , wherein the heterocycle portion is optionally substituted. In some cases, Y-$R^2$ is selected from  , wherein the heterocycle portion is optionally substituted. In some cases, the heterocycle portion is optionally substituted with one or more substituents selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, -CN, and $C_1$-$C_3$ aminoalkyl. In some cases, the heterocycle portion is optionally substituted with one or more substituents selected from halogen, hydroxy, -CN, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, and $C_1$-$C_3$ aminoalkyl. In some cases, the heterocycle portion is optionally substituted with one or more substituents selected from $C_1$-$C_3$ alkyl and halogen. In some cases, Y-$R^2$ is selected from  ,  ,  , and

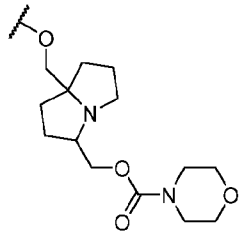
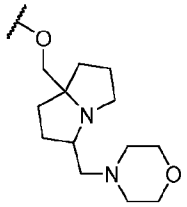
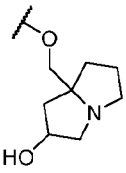
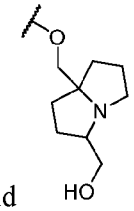
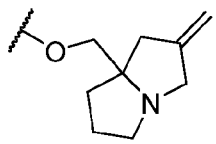
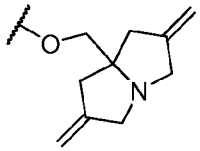
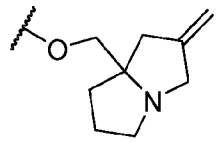

. In some cases, Y-$R^2$ is selected from  , and  . In some cases, Y-$R^2$ is selected from  . In some cases, Y-$R^2$ is  .

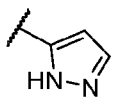
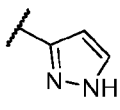
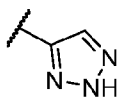
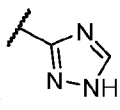
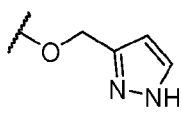
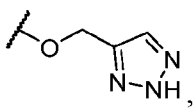
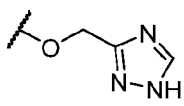
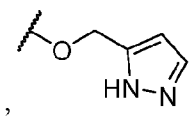
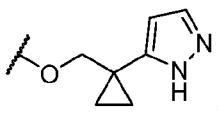
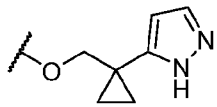
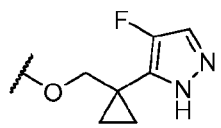
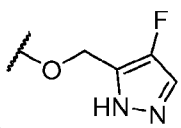
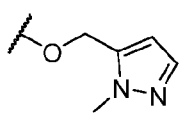
**[00172]** In some embodiments, for a compound or salt of Formula (I), $R^2$ is selected from optionally substituted -L-heterocycle. In some cases, the heterocycle is a bicyclic heterocycle. In some cases, the heterocycle is a monocyclic heterocycle. In some cases, the heterocycle has only 1 nitrogen atom. In some cases, the heterocycle has only 1 nitrogen atom and no other heteroatoms. In some cases, Y-$R^2$ is selected from  and  , wherein the heterocycle portion is optionally substituted. In some cases, Y-$R^2$ is selected from  and  , wherein the heterocycle portion is optionally substituted. In some cases, Y-$R^2$ is selected from  , wherein the heterocycle portion is optionally substituted. In some cases, Y-$R^2$ is selected from  , wherein the heterocycle portion is optionally substituted. In some cases, the heterocycle is optionally substituted with one or more substituent selected from halogen, hydroxy, $C_1$-$C_3$ alkyl, -$N(R^5)S(O)_2(R^5)$, -$OC(O)N(R^5)_2$, oxo, =$CH_2$, =NO-$C_1$-$C_3$ alkyl, -$CH_2OC(O)$heterocycle, -$CH_2$heterocycle, -$CH_2OC(O)N(R^5)_2$, and -O-$C_1$-$C_3$ alkyl, wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo, and hydroxy. In some cases, the heterocycle is substituted with at least one halogen. In some cases, the heterocycle is substituted with at least one =$CH_2$. In some cases, Y-$R^2$ is selected from  .

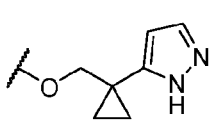
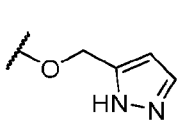
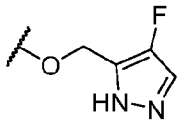






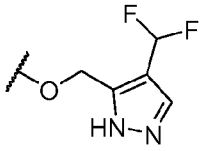
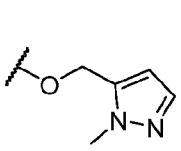
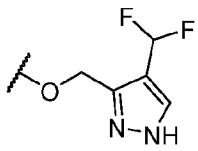
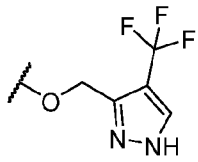
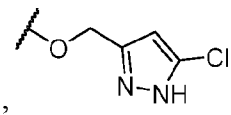
, and . In some cases, Y-$R^2$ is selected from , , and . In some cases, Y-$R^2$ is selected from , ,

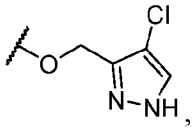
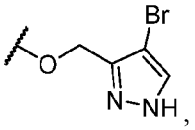
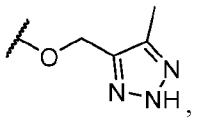
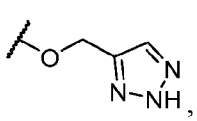
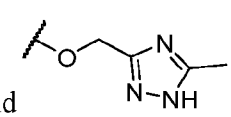



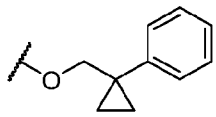
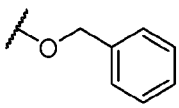
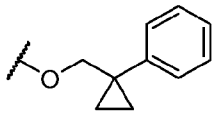
 ,  ,  , and  . In some cases, Y-$R^2$ is selected from  and  . In some cases, Y-$R^2$ is selected from  .

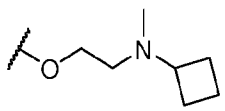
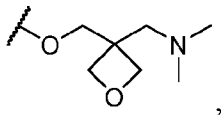
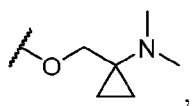
**[00173]** In some embodiments, for a compound or salt of Formula (I), $R^2$ is -L-heteroaryl, wherein the heteroaryl portion is optionally substituted with one or more $R^7$. In some cases, the heteroaryl is selected from a 5- to 6-membered heteroaryl, wherein the heteroaryl portion is optionally substituted with one or more $R^7$. In some cases, the heteroaryl is selected from a 5-membered heteroaryl, wherein the heteroaryl portion is optionally substituted with one or more $R^7$. In some cases, the heteroaryl has at least one nitrogen atom. In some cases, the heteroaryl has two nitrogen atoms. In some cases, the heteroaryl has three nitrogen atoms. In some cases, the heteroaryl is selected from  ,  , and  , which is optionally substituted. In some cases, the heteroaryl is  ,  ,  , and  , which is optionally substituted. In some cases, Y-$R^2$ is selected from  ,  ,  ,  , and  , wherein the heteroaryl portion is optionally substituted with one or more $R^7$. In some cases, each $R^7$ is independently selected from $C_1$-$C_4$ alkyl, halogen, and $C_1$-$C_4$ haloalkyl. In some cases, Y-$R^2$ is selected from  and  . In some cases, Y-$R^2$ is selected from  and  . In

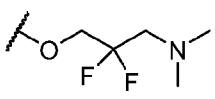
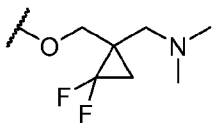
some cases, Y-$R^2$ is selected from  ,  ,  ,

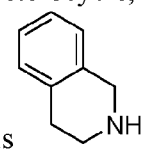
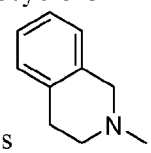
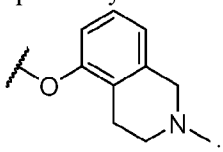
 ,  ,  ,  ,  ,

 ,  ,  ,  , and  .

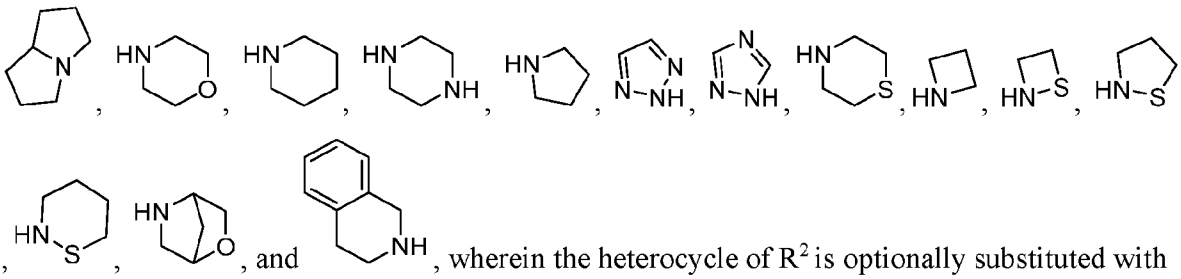
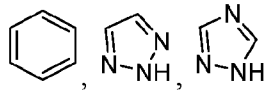
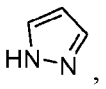
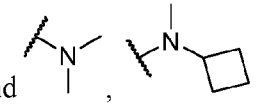
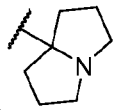
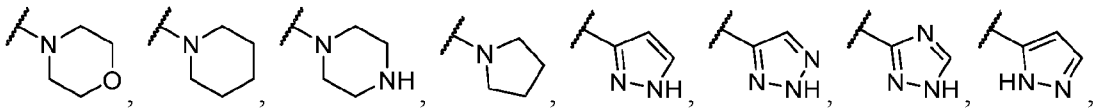
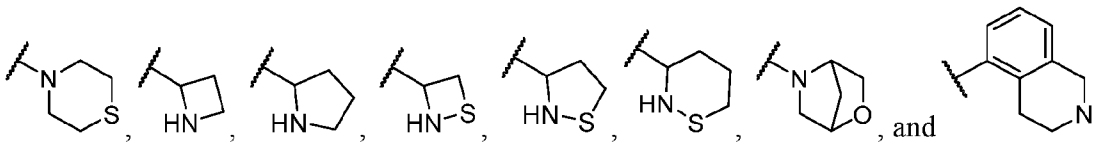
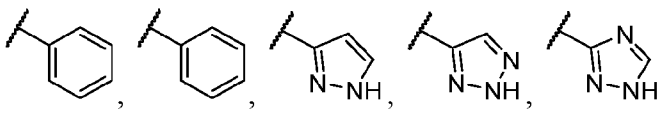
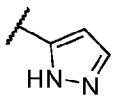
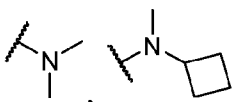
**[00174]** In some embodiments, for a compound or salt of Formula (I), $R^2$ is -L-aryl, optionally substituted with one or more $R^7$. In some cases, wherein Y-$R^2$ is selected from  , wherein the heterocycle portion is optionally substituted with one or more $R^7$. In some cases, Y-$R^2$ is selected from  and  .

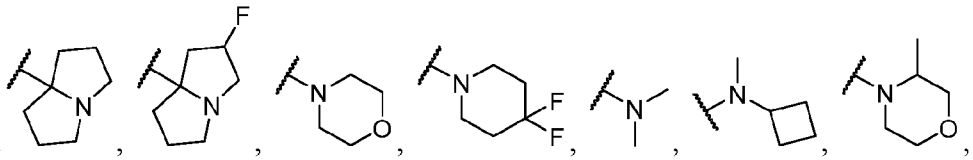
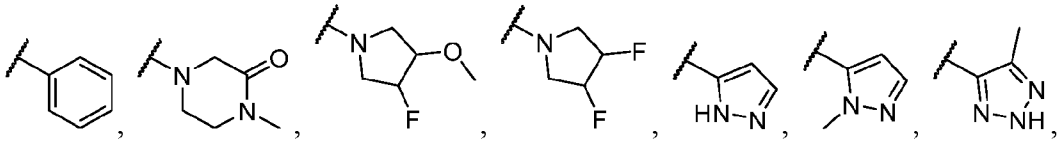
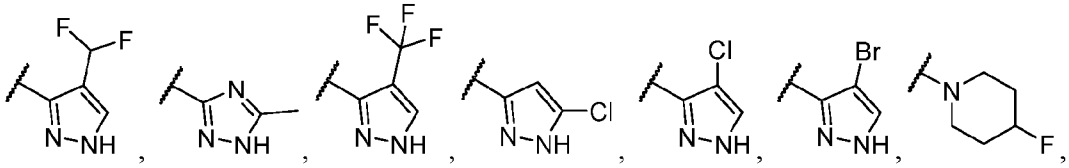
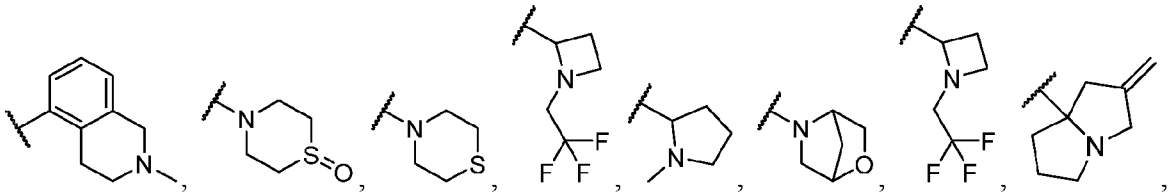
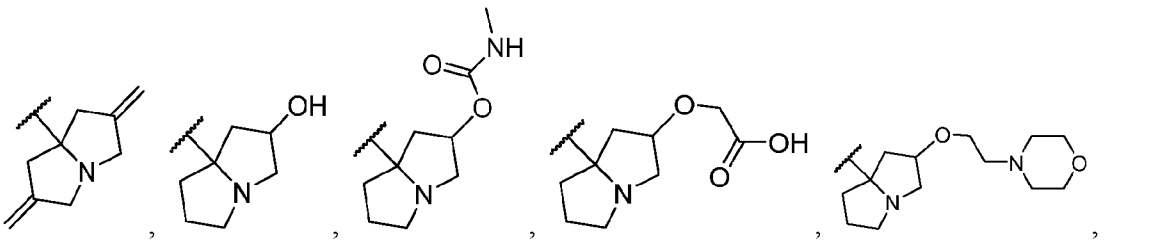
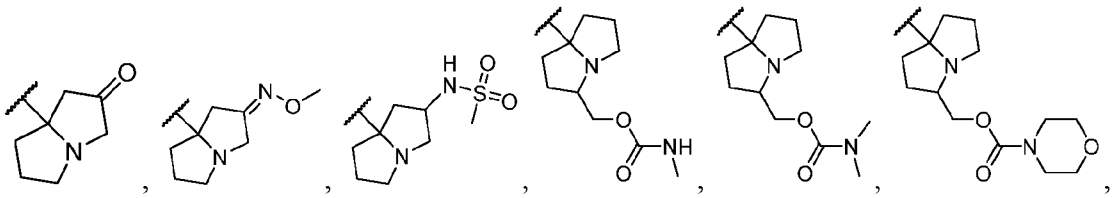
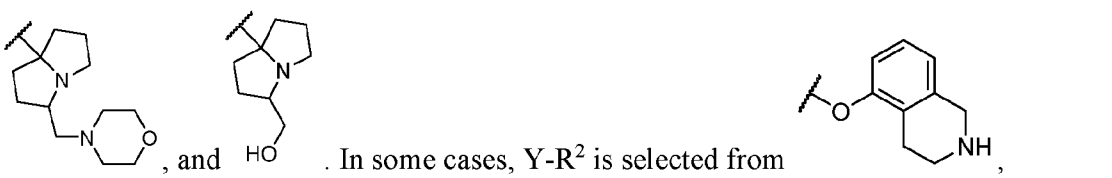
**[00175]** In some embodiments, for a compound or salt of Formula (I), $R^2$ is -L-N($R^{23}$)$_2$. In some cases, Y-$R^2$ is selected from  ,  ,  ,

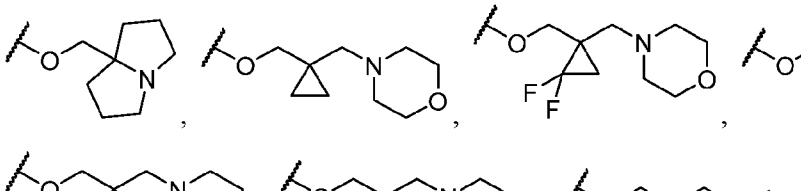
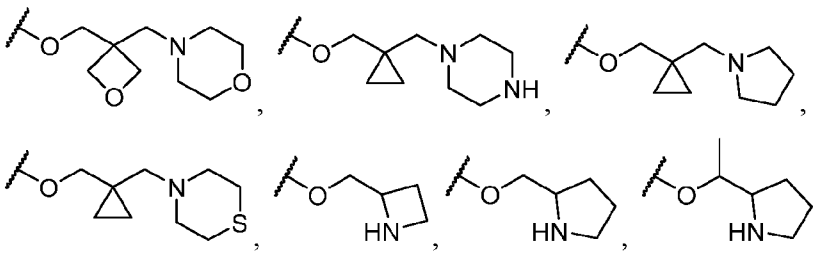
 , and  .

In some embodiments, for a compound or salt of Formula (I), $R^2$ is heterocycle, optionally substituted with one or more $R^6$. In some cases, the heterocycle of $R^2$ is  , which is optionally substituted. In some cases, the heterocycle of $R^2$ is  , In some cases, Y-$R^2$ is  .

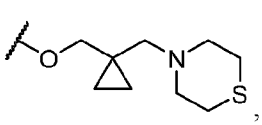
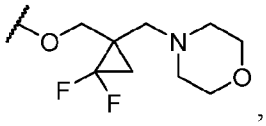
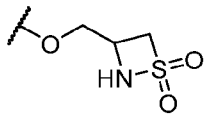
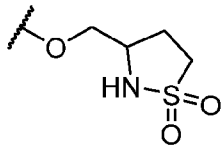
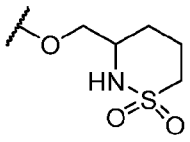
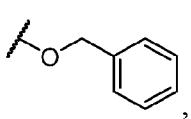
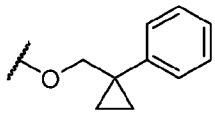
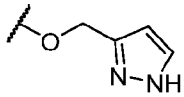
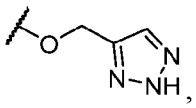
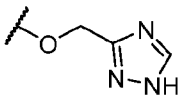
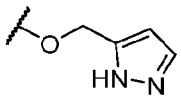
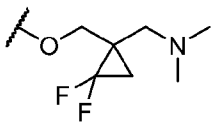
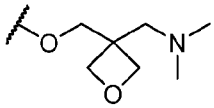
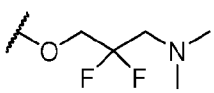
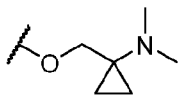
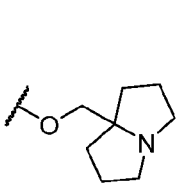
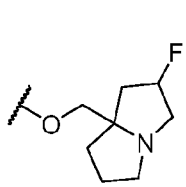
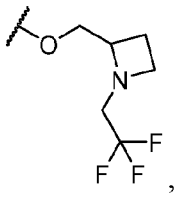
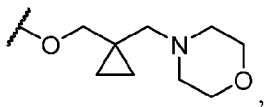
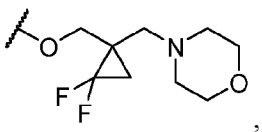
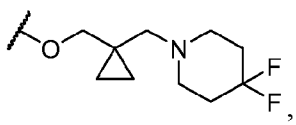
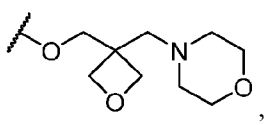
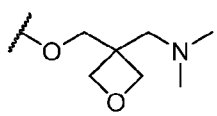
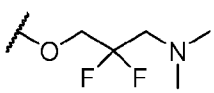
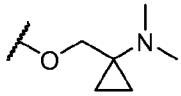
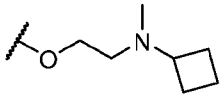
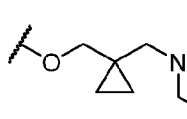
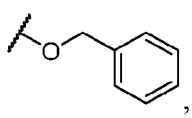
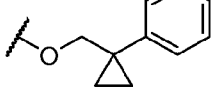
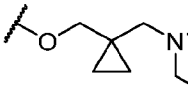
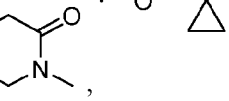
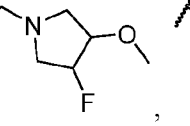
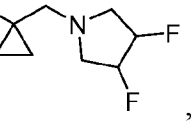
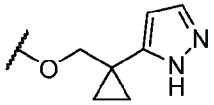
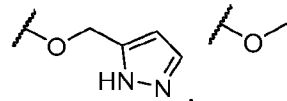
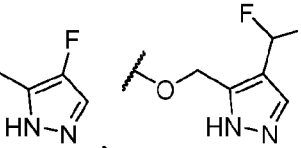
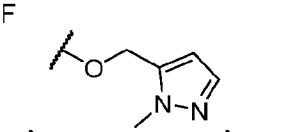
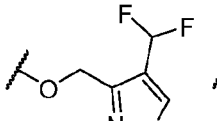
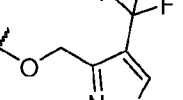
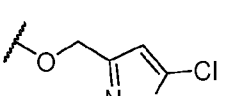
**[00176]** In some embodiments, for a compound or salt of Formula (I), $R^2$ is selected from heterocycle, -L-heterocycle, wherein the heterocycle, and the heterocycle portion of -L-heterocycle, are each optionally substituted with one or more $R^6$; -L-aryl, and -L-heteroaryl,

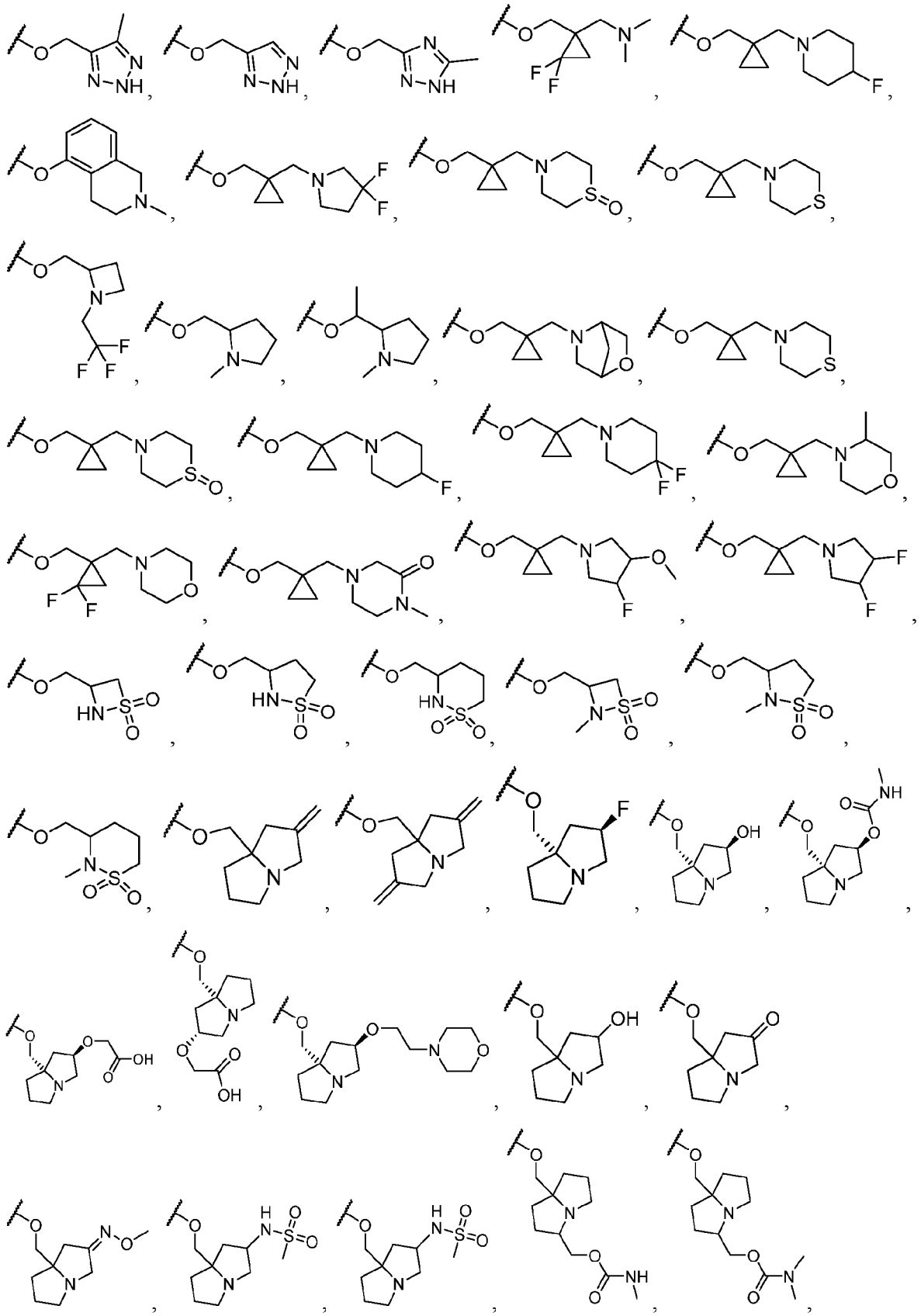
wherein the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$; and -L-$N(R^{23})_2$. In some cases, the heterocycle of $R^2$ is selected from  , wherein the heterocycle of $R^2$ is optionally substituted with one or more $R^6$; wherein the aryl and heteroaryl of $R^2$ is selected from  , and  , wherein the aryl and the heteroaryl are each optionally substituted with one or more $R^7$; and  . In some cases, the heterocycle of $R^2$ is selected from  ,  ,  , and , wherein the heterocycle is optionally substituted with one or more $R^6$; wherein the aryl and heteroaryl of $R^2$ is selected from  , and  , wherein the aryl and the heteroaryl are each optionally substituted with one or more $R^7$; and  . In some cases, each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, -$N(R^5)S(O)_2(R^5)$, -$OC(O)N(R^5)_2$, =$CH_2$, oxo, =NO-$C_1$-$C_3$ alkyl, -$CH_2OC(O)$heterocycle, -$CH_2$heterocycle, -$CH_2OC(O)N(R^5)_2$, and -O-$C_1$-$C_3$ alkyl, wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo, and hydroxy; and wherein each $R^7$ is selected from $C_1$-$C_3$ alkyl, halogen and $C_1$-$C_3$ haloalkyl. In some cases, the heterocycle of $R^2$, the aryl and heteroaryl of $R^2$, and -$N(R^{20})_2$ of $R^2$

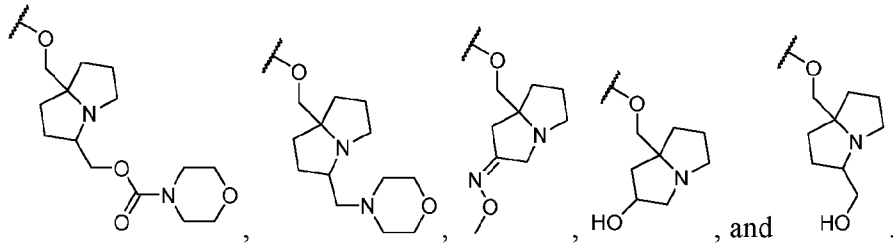
is selected from 







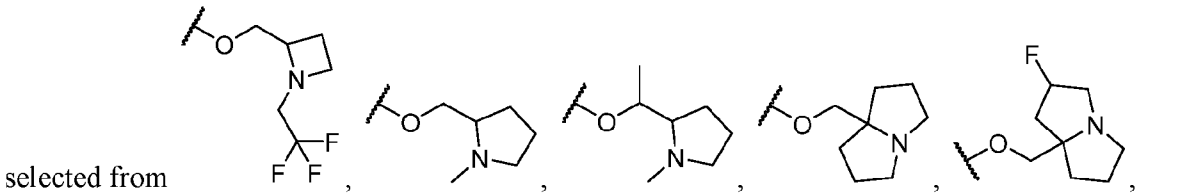




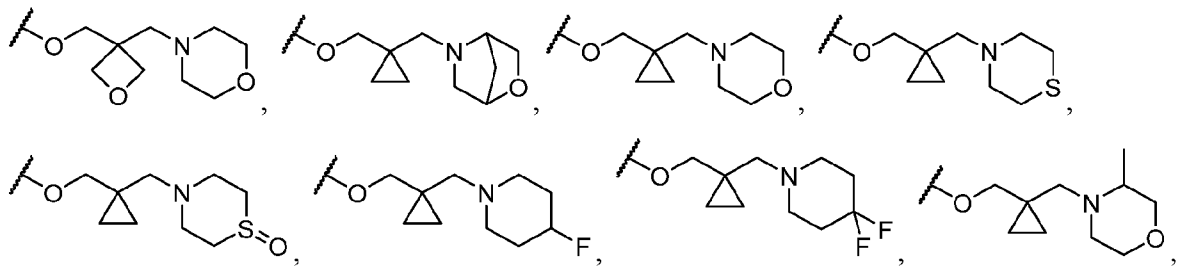

, and . In some cases, Y-$R^2$ is selected from ,

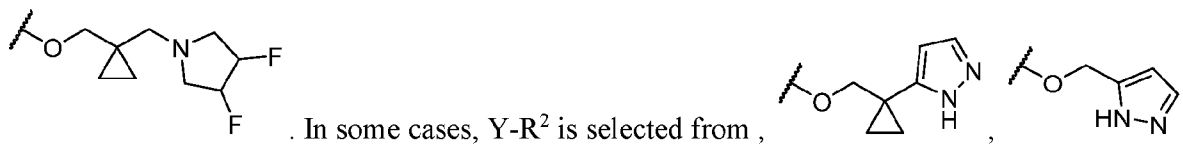




, and

, wherein the heterocycle, and the heterocycle portion of -L-heterocycle, are each optionally substituted with one or more $R^6$;





, and

, wherein the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$; and



, and

. In some cases, Y-$R^2$ is selected from


























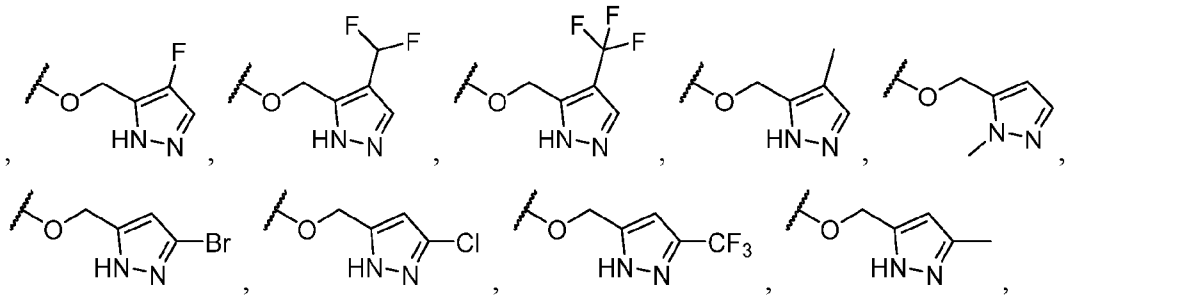



, and . In some cases, Y-$R^2$ is selected from

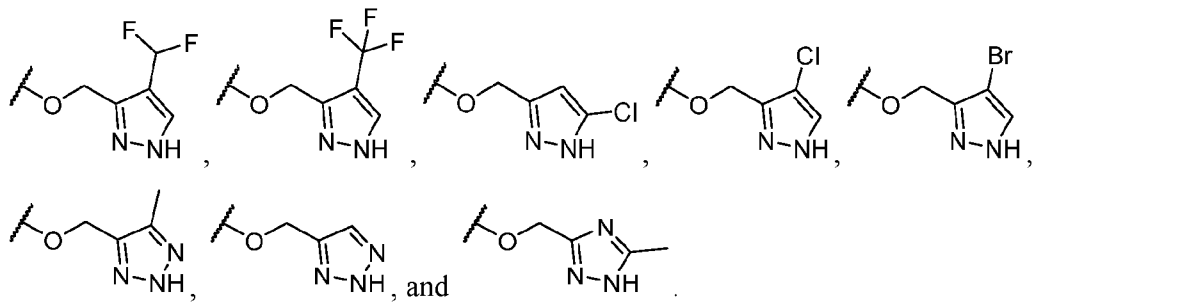



and


. In some cases, Y-$R^2$ is selected from ,






, and .

**[00177]** In some embodiments, for a compound or salt of Formula (I), L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from hydroxy, $C_1$-$C_4$ hydroxyalkyl and $C_1$-$C_4$ alkyl. In some cases, L is

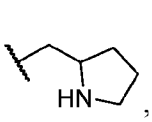
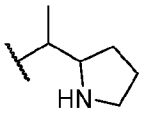
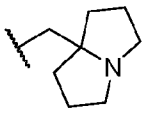
independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from $C_1$-$C_4$ alkyl. In some cases, L is selected from $C_1$-$C_4$ alkylene. In some cases, L is selected from $C_1$-$C_2$ alkylene. In some cases, L is  . In some cases, L is  .

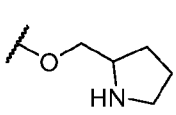
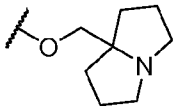
**[00178]** In some embodiments, for a compound or salt of Formula (I), each L is independently selected from an optionally substituted $C_1$-$C_4$ alkylene; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle, wherein the $C_3$-$C_6$ carbocycle is optionally substituted with one or more substituents selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl. In some cases, the optional substituents of L are selected from $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are optionally substituted with one or more substituents selected from halogen and $C_{1-6}$ haloalkyl.

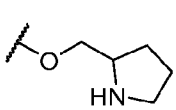
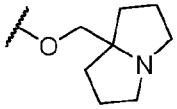
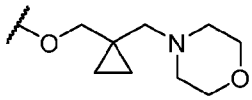
**[00179]** In some embodiments, for a compound or salt of Formula (I), each L is independently selected from a substituted $C_1$-$C_4$ alkylene, wherein two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle. In some cases, the $C_3$-$C_6$ carbocycle is optionally substituted with one or more substituents selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl.

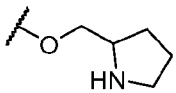
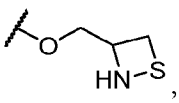
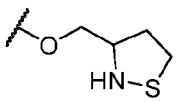
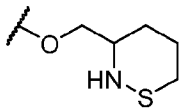
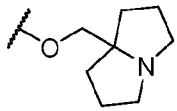
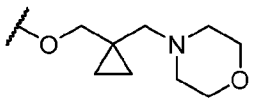
**[00180]** In some embodiments, for a compound or salt of Formula (I), each L is independently selected from a substituted $C_1$-$C_4$ alkylene, and two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle. In some cases, each L is independently selected from a substituted $C_3$ alkylene, and wherein two substituents on the same carbon atom of L come together to form a $C_3$ carbocycle. In some cases, each L is independently selected from  .

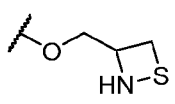
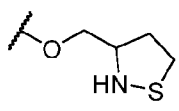
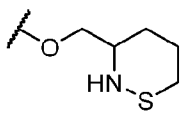
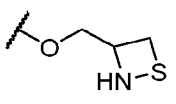
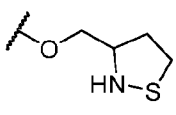
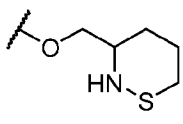
**[00181]** In some embodiments, for a compound or salt of Formula (I), $R^2$ is selected from -L-heterocycle, wherein the heterocycle portion of -L-heterocycle is optionally substituted with one or more $R^6$. In some cases, the heterocycle is a saturated heterocycle. In some cases, the heterocycle has at least one nitrogen atom and at least one sulfur atom. In some cases, the heterocycle has at least one nitrogen atom. In some cases, the heterocycle has at least one sulfur atom.

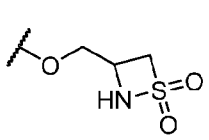
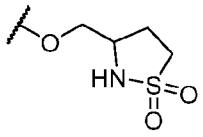
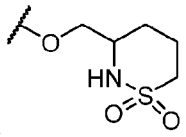
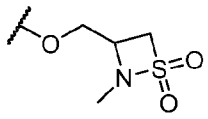
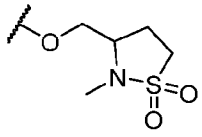
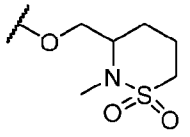
**[00182]** In some embodiments, for a compound or salt of Formula (I), $R^2$ is selected from  ,  , and  , wherein the heterocycle portion is optionally substituted with one or more $R^6$.

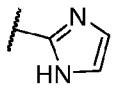
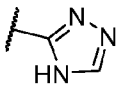
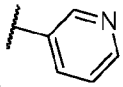
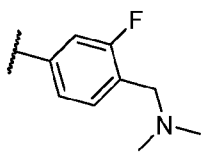
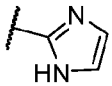
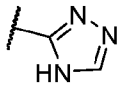
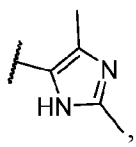
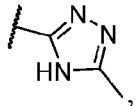
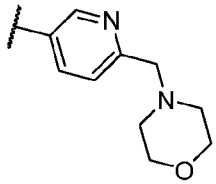
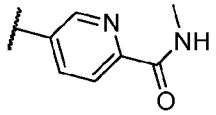
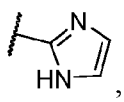
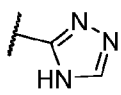
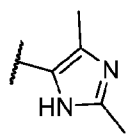
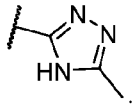
**[00183]** In some embodiments, for a compound or salt of Formula (I), Y-$R^2$ is selected from  and  , wherein the heterocycle portion is optionally substituted with one or more $R^6$.

**[00184]** In some embodiments, for a compound or salt of Formula (I), Y-$R^2$ is selected from  ,  and  , wherein the heterocycle portion is optionally substituted with one or more $R^6$.

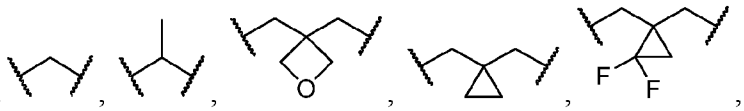
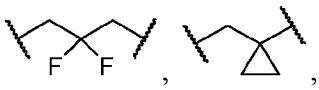
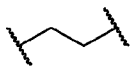
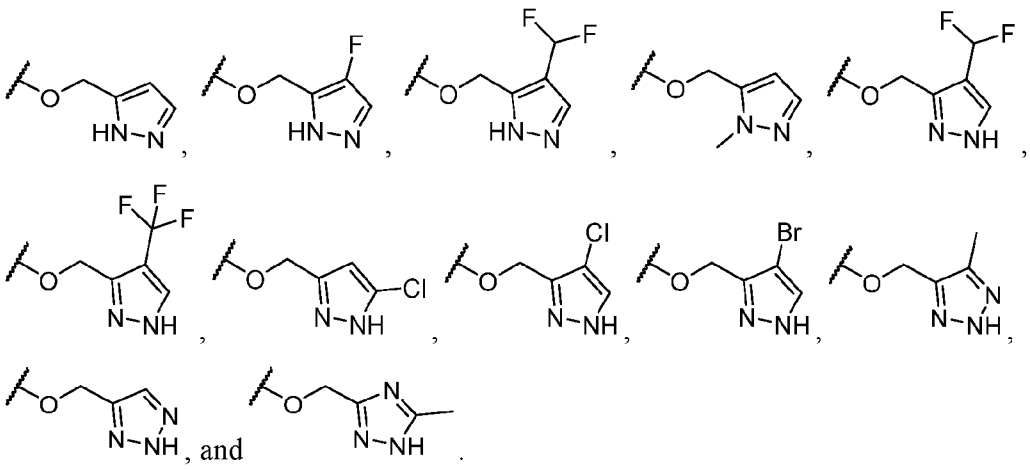
**[00185]** In some embodiments, for a compound or salt of Formula (I), Y-$R^2$ is selected from  ,  ,  ,  ,  and  , wherein the heterocycle portion is optionally substituted with one or more $R^6$.

**[00186]** In some embodiments, for a compound or salt of Formula (I), $R^2$ is selected from -L-saturated heterocycle, wherein the saturated heterocycle portion of the -L-saturated heterocycle is optionally substituted with one or more $R^6$, and contains one nitrogen atom and one sulfur atom. In some cases, Y-$R^2$ is selected from  ,  , and  , wherein the heterocycle portion is optionally substituted with one or more $R^6$. In some cases, Y-$R^2$ is selected from  ,  , and  , wherein the heterocycle portion is optionally substituted with one or more substituents selected from $C_1$-$C_3$ alkyl and oxo. In some

cases, Y-$R^2$ is selected from  ,  , and  . In some cases, Y-$R^2$ is selected from  ,  , and  .

**[00187]** In some embodiments, for a compound or salt of Formula (I), Y is a bond. In some cases, $R^2$ is selected from an optionally substituted heteroaryl and optionally substituted aryl. In some cases, $R^2$ is selected from an optionally substituted heteroaryl. In some cases, the heteroaryl has at least one nitrogen atom. In some cases, the heteroaryl has at least two nitrogen atoms. In some cases, the heteroaryl only contain nitrogen atom(s). In some cases, the heteroaryl is a 6-membered heteroaryl. In some cases, the heteroaryl is a 5-membered heteroaryl. In some cases, the heteroaryl is selected from  ,  , and  , each of which is optionally substituted. In some cases, the heteroaryl is selected from  ,  , and  , each of which is optionally substituted. In some cases, $R^2$ is selected from an optionally substituted aryl. In some cases, the aryl is a phenyl. In some cases, the heteroaryl is optionally substituted with one or more $R^6$, wherein each $R^6$ is selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, -$CH_2$heterocycle, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, and -$C(O)N(R^5)_2$. In some cases, $R^6$ is selected from $C_1$-$C_3$ alkyl, -$CH_2$heterocycle, and -$C(O)N(R^5)_2$. In some cases, the aryl is optionally substituted with one or more $R^7$. In some cases, Y-$R^2$ is selected from  ,  ,  ,  ,  ,  , and  . In some cases, Y-$R^2$ is selected from  ,  ,  , and  .

**[00188]** In some embodiments, for a compound or salt of Formula (I), Y is -O- and $R^2$ is selected from L-5-membered heteroaryl. In some cases, the heteroaryl has at least 1 nitrogen atom. In some cases, the heteroaryl has at least two nitrogen atoms. In some cases, the heteroaryl

has 3 nitrogen atoms. In some cases, L is selected from an optionally substituted $C_1$-$C_4$ alkylene. In some cases, L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl. In some cases, L is selected from  ,  , and  . In some cases, L is selected from  . In some cases, the heteroaryl is optionally substituted with one or more $R^7$. In some cases, each $R^7$ is selected from halogen, $C_1$-$C_4$ alkyl, and $C_1$-$C_4$ haloalkyl. In some cases, Y-$R^2$ is selected from  , and .

**[00189]** In some embodiments, for a compound or salt of Formula (I), each $R^6$ is independently selected from halogen, -OH, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, -CN, $C_1$-$C_3$ aminoalkyl, -Q-phenyl, -Q-phenyl$SO_2F$, -NHC(O)phenyl, -NHC(O)phenyl$SO_2F$, $C_1$-$C_3$ alkyl substituted pyrazolyl, -N($R^5$)$_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$ alkyl)C(=O), oxo, ($C_1$-$C_3$ haloalkyl)C(=O)-, -$SO_2F$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, -$CH_2$OC(O)N($R^5$)$_2$, -$CH_2$NHC(O)O$C_1$-$C_6$ alkyl, -$CH_2$NHC(O)N($R^5$)$_2$, -$CH_2$NHC(O)$C_1$-$C_6$ alkyl, -$CH_2$(pyrazolyl), -$CH_2$NH$SO_2C_1$-$C_6$ alkyl, -$CH_2$OC(O)heterocycle, -OC(O)N($R^5$)$_2$, -OC(O)NH($C_1$-$C_3$ alkyl)O($C_1$-$C_3$ alkyl), -OC(O)NH($C_1$-$C_3$ alkyl)O($C_1$-$C_3$ alkyl)phenyl($C_1$-$C_3$ alkyl)N($CH_3$)$_2$, -OC(O)NH($C_1$-$C_3$ alkyl)O($C_1$-$C_3$ alkyl)phenyl, -OC(O)heterocycle, and -$CH_2$heterocycle, wherein the phenyl of -NHC(O)phenyl and -OC(O)NH($C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl)phenyl are each optionally substituted with -C(O)H and OH, and wherein the heterocycle of -$CH_2$heterocyclyl is optionally substituted with oxo.

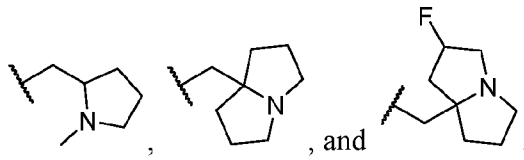
**[00190]** In some embodiments, for a compound or salt of Formula (I), each $R^6$ is independently selected from halogen, -OH, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, -CN,

and $C_1$-$C_3$ aminoalkyl. In some cases, each $R^6$ is independently selected from halogen, $C_1$-$C_3$ alkyl, and $C_1$-$C_3$ haloalkyl.

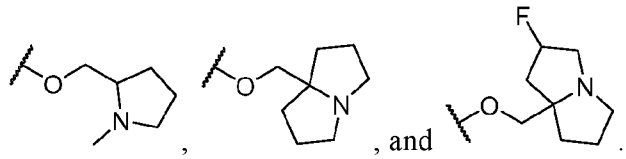
**[00191]** In some embodiments, for a compound or salt of Formula (I), each $R^6$ is independently selected from halogen, -OH, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, -$N(R^5)_2$, and oxo. In some cases, each $R^6$ is independently selected from -OH, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, $C_1$-$C_3$ alkoxy, and -$N(R^5)_2$. In some cases, each $R^6$ is independently selected from $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, and -$N(R^5)_2$. In some cases, each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, -$N(R^5)S(O)_2(R^5)$, -$OC(O)N(R^5)_2$, =$CH_2$, oxo, =NO-$C_1$-$C_3$ alkyl, -$CH_2OC(O)$heterocycle, -$CH_2$heterocycle, -$CH_2OC(O)N(R^5)_2$, and -O-$C_1$-$C_3$ alkyl, wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo, and hydroxy; and wherein each $R^7$ is selected from $C_1$-$C_3$ alkyl, halogen and $C_1$-$C_3$ haloalkyl.

**[00192]** In some embodiments, for a compound or salt of Formula (I), $R^6$ is selected from halogen, -OH, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, -CN, and $C_1$-$C_3$ aminoalkyl. In some cases, $R^6$ is selected from halogen and $C_1$-$C_3$ alkyl. In some cases, $R^6$ is halogen. In some cases, $R^6$ is $C_1$-$C_3$ alkyl. In some cases, $R^6$ is selected from halogen and $C_1$-$C_3$ alkyl. In some cases, $R^6$ is selected from methyl and fluorine.

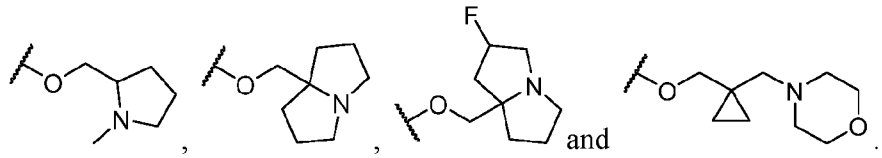
**[00193]** In some embodiments, for a compound or salt of Formula (I), $R^2$ is selected from



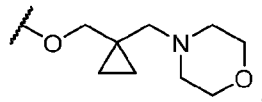
**[00194]** In some embodiments, for a compound or salt of Formula (I), Y-$R^2$ is selected from



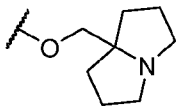
**[00195]** In some embodiments, for a compound or salt of Formula (I), Y-$R^2$ is selected from



**[00196]** In some embodiments, for a compound or salt of Formula (I), Y-$R^2$ is

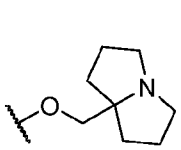
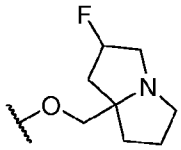


**[00197]** In some embodiments, for a compound or salt of Formula (I), L is selected from unsubstituted $C_1$-$C_4$ alkylene.

**[00198]** In some embodiments, for a compound or salt of Formula (I), Y-$R^2$ is selected from  , wherein the heterocycle portion is optionally substituted with one or more $R^6$.

**[00199]** In some embodiments, for a compound or salt of Formula (I), $R^6$ of $R^2$ is independently selected at each occurrence from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, and $C_1$-$C_3$ aminoalkyl.

**[00200]** In some embodiments, for a compound or salt of Formula (I), $R^6$ of $R^2$ is independently selected at each occurrence from $C_1$-$C_3$ alkyl and halogen.

**[00201]** In some embodiments, for a compound or salt of Formula (I), Y-$R^2$ is selected from  and  .

**[00202]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 5- to 12-membered heterocycle. In some cases, the heterocycle of $R^1$ is selected from a 5- to 12-membered heterocycle, 6- to 12-membered heterocycle, 7- to 12-membered heterocycle, and 8- to 12-membered heterocycle. In some cases, the heterocycle of $R^1$ is selected from a 5- to 11-membered heterocycle, 5- to 10-membered heterocycle, 5- to 9-membered heterocycle, and 5- to 8-membered heterocycle. In some cases, the heterocycle of $R^1$ is selected from a 6- to 11-membered heterocycle, 6- to 10-membered heterocycle, 6- to 9-membered heterocycle, and 6- to 8-membered heterocycle. In some cases, the heterocycle of $R^1$ is selected from a 7- to 11-membered heterocycle, 7- to 10-membered heterocycle, 7- to 9-membered heterocycle, and 7- to 8-membered heterocycle. In some cases, the heterocycle of $R^1$ is selected from a 5- to 6-membered heterocycle and 5- to 9-membered heterocycle. In some cases, the heterocycle of $R^1$ is selected from an 8- to 9-membered heterocycle. In some cases, $R^1$ is selected from an optionally substituted 5- to 7-membered heterocycle. In some cases, $R^1$ is selected from an optionally substituted 6- to 7-membered heterocycle. In some cases, $R^1$ is selected from an optionally substituted 7-membered heterocycle. In cases, the 5- to 12-membered heterocycle of $R^1$ is a bridged heterocycle. In cases, the 5- to 12-membered heterocycle of $R^1$ is not a bridged heterocycle. In some cases, the heterocycle of $R^1$ is saturated. In some cases, the heterocycle of $R^1$ is unsaturated. In some cases, the heterocycle of $R^1$ is an unbridged heterocycle. The heterocycle of $R^1$ is optionally substituted as described elsewhere herein.

**[00203]** In some embodiments, for a compound or salt of Formula (I), the heterocycle of $R^1$ contains at most 1 nitrogen atom. In some embodiments, the heterocycle of $R^1$ contains at most 1

heteroatom atom. In some cases, the heteroatom is selected from nitrogen, oxygen, and sulfur. In some embodiments, the heterocycle of $R^1$ contains at most 2 heteroatom atoms. In some cases, the heterocycle of $R^1$ contains 1 nitrogen atom. In some cases, the heterocycle of $R^1$ contains only 1 nitrogen atom. In some cases, the heterocycle of $R^1$ contains only 1 nitrogen atom and no other heteroatoms.

**[00204]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -OH, $-N(R^{20})_2$, $-NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl. In some cases, the 5- to 12-membered heterocycle of $R^1$ is an unsaturated heterocycle. In some cases, the 5- to 12-membered heterocycle of $R^1$ is selected from a saturated heterocycle and unsaturated heterocycle. In some cases, the 5- to 12-membered heterocycle of $R^1$ is a saturated heterocycle. In some cases, the 5- to 12-membered heterocycle of $R^1$ is an unsaturated heterocycle.

**[00205]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from 5- to 15-membered heterocycle, wherein the 5- to 15-membered heterocycle is optionally substituted. In some cases, $R^1$ is selected from an optionally substituted 6- to 15-membered heterocycle. In some cases, the heterocycle is a spiro heterocycle. In some cases, the heterocycle is a fused heterocycle. In some cases, the heterocycle is a bridged heterocycle. In some cases, the heterocycle is an unsaturated heterocycle.

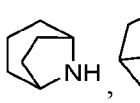
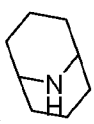
**[00206]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is a 6- to 12-membered fused heterocycle, which is optionally substituted.

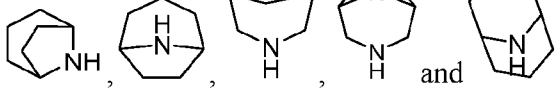
**[00207]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is a 6- to 12-membered spiroheterocycle, which is optionally substituted. In some cases, $R^1$ is selected from optionally substituted 7- to 8-membered spiroheterocycle.

**[00208]** In some embodiments, for a compound or salt of Formula (I), the heterocycle of $R^1$ is a 5- to 12-membered heterocycle, 6- to 12-membered heterocycle, 7- to 12-membered heterocycle, or 8- to 12-membered heterocycle. In some cases, the heterocycle of $R^1$ is a 5- to 11-membered heterocycle, 5- to 10-membered heterocycle, 5- to 9-membered heterocycle, or 5- to 8-membered heterocycle. In some cases, the heterocycle of $R^1$ is a 6- to 11-membered heterocycle, 6- to 10-membered heterocycle, 6- to 9-membered heterocycle, or 6- to 8-membered heterocycle. In some cases, the heterocycle of $R^1$ is a 7- to 11-membered heterocycle, 7- to 10-membered heterocycle, 7- to 9-membered heterocycle, or 7- to 8-membered heterocycle. In some cases, the heterocycle of $R^1$ is a 5- to 6-membered heterocycle or 5- to 9-membered heterocycle. In some cases, the heterocycle of $R^1$ is an 8- to 9-membered heterocycle. In some cases, the

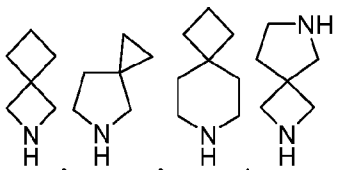
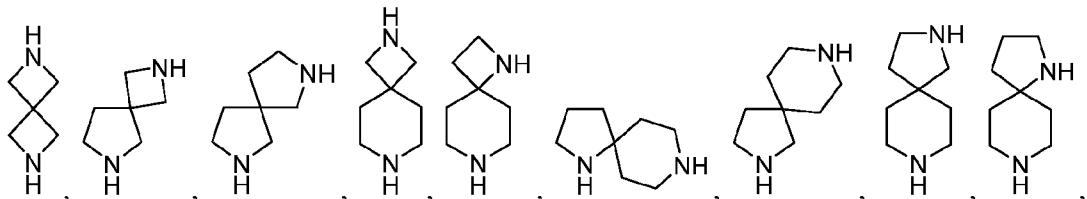
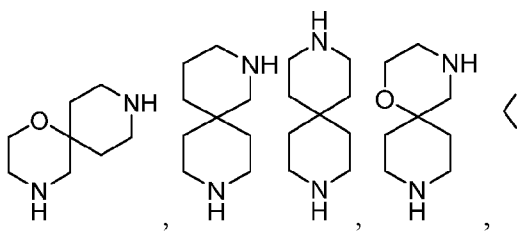
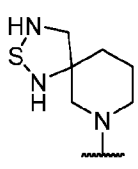
heterocycle of $R^1$ is saturated. The heterocycle is optionally substituted as described elsewhere herein.

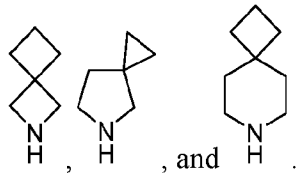
**[00209]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is a 5- to 12-membered monocyclic heterocycle. In some cases, the heterocycle of $R^1$ is a 5- to 12-membered monocyclic heterocycle, 6- to 12-membered monocyclic heterocycle, 7- to 12-membered monocyclic heterocycle, or 8- to 12-membered monocyclic heterocycle. In some cases, the heterocycle of $R^1$ is a 5- to 11-membered monocyclic heterocycle, 5- to 10-membered monocyclic heterocycle, 5- to 9-membered monocyclic heterocycle, or 5- to 8-membered monocyclic heterocycle. In some cases, the heterocycle of $R^1$ is a 6- to 11-membered monocyclic heterocycle, 6- to 10-membered monocyclic heterocycle, 6- to 9-membered monocyclic heterocycle, or 6- to 8-membered monocyclic heterocycle. In some cases, the heterocycle of $R^1$ is a monocyclic 7- to 11-membered heterocycle, 7- to 10-membered monocyclic heterocycle, 7- to 9-membered monocyclic heterocycle, or 7- to 8-membered monocyclic heterocycle. In some cases, the heterocycle of $R^1$ is a 5- to 6-membered monocyclic heterocycle or 5- to 9-membered monocyclic heterocycle. In some cases, the heterocycle of $R^1$ is an 8- to 9-membered monocyclic heterocycle. In some cases, the heterocycle of $R^1$ is saturated. The monocyclic heterocycle is optionally substituted as described elsewhere herein.

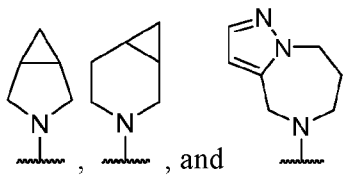
**[00210]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is a bridged heterocycle. In some cases, the heterocycle of $R^1$ is a 5- to 12-membered bridged heterocycle, 6- to 12-membered bridged heterocycle, 7- to 12-membered bridged heterocycle, or 8- to 12-membered bridged heterocycle. In some cases, the heterocycle of $R^1$ is a 5- to 11-membered bridged heterocycle, 5- to 10-membered bridged heterocycle, 5- to 9-membered bridged heterocycle, or 5- to 8-membered bridged heterocycle. In some cases, the heterocycle of $R^1$ is a 6- to 11-membered bridged heterocycle, 6- to 10-membered bridged heterocycle, 6- to 9-membered bridged heterocycle, or 6- to 8-membered bridged heterocycle. In some cases, the heterocycle of $R^1$ is a bridged 7- to 11-membered heterocycle, 7- to 10-membered bridged heterocycle, 7- to 9-membered bridged heterocycle, or 7- to 8-membered bridged heterocycle. In some cases, the heterocycle of $R^1$ is a 5- to 6-membered bridged heterocycle or 5- to 9-membered bridged heterocycle. In some cases, the heterocycle of $R^1$ is an 8- to 9-membered bridged heterocycle. In some cases, the heterocycle of $R^1$ is saturated. In some cases, the bridged heterocycle is selected from  ,  , and  . In some cases, the bridged

heterocycle is selected from  . Each bridged heterocycle is optionally substituted as described elsewhere herein.

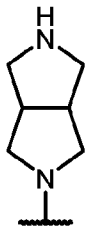
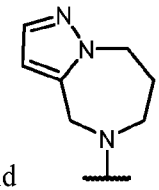
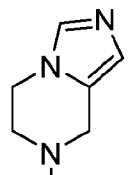
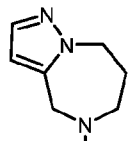
**[00211]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is a spiro heterocycle. The spiro heterocycle of $R^1$ is a 7- to 12-membered spiro heterocycle, 7- to 12-membered spiro heterocycle, or 8- to 12-membered spiro heterocycle. In some cases, the spiro heterocycle of $R^1$ is a 7- to 11-membered spiro heterocycle, 7- to 10-membered spiro heterocycle, 7- to 9-membered spiro heterocycle, or 7- to 8-membered spiro heterocycle. In some cases, the spiro heterocycle of $R^1$ is a 7- to 11-membered spiro heterocycle, 7- to 10-membered spiro heterocycle, 7- to 9-membered spiro heterocycle, or 7- to 8-membered spiro heterocycle. In some cases, the spiro heterocycle of $R^1$ is a 7- to 11-membered spiro heterocycle. In some cases, the spiro heterocycle of $R^1$ is a 7-membered spiro heterocycle. In some cases, the spiro heterocycle of $R^1$ is an 8-membered spiro heterocycle. In some cases, the spiro heterocycle of $R^1$ is a 9-membered spiro heterocycle. In some cases, the spiro heterocycle of $R^1$ is a 10-membered spiro heterocycle. In some cases, the spiro heterocycle of $R^1$ contains at most 1 nitrogen atom. In some cases, the spiro heterocycle of $R^1$ contains only 1 nitrogen atom. In some cases, the spiroheterocycle of $R^1$ contains at most 2 heteroatom atoms. In some cases, the spiro heterocycle of $R^1$ contains at least 2 heteroatom atoms. In some cases, the spiro heterocycle of $R^1$ contains at least 3 heteroatom atoms. In some cases, the heteroatom is selected from nitrogen, oxygen, and sulfur. In some cases, the spiroheterocycle of $R^1$ is bound to the Formula via the nitrogen atom.

In some embodiments, the spiro heterocycle of $R^1$ is selected from  ,  ,  , and  . In some cases, the spiro

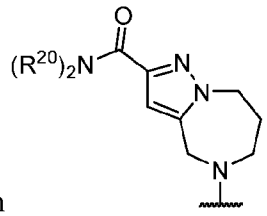
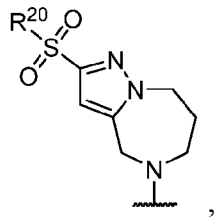
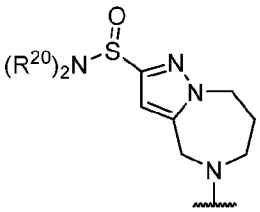
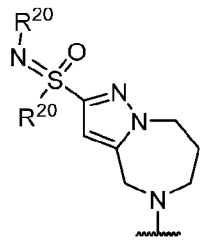
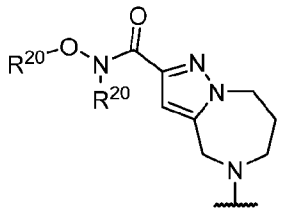
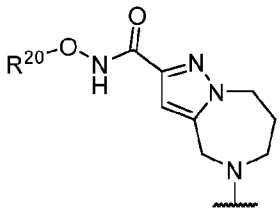
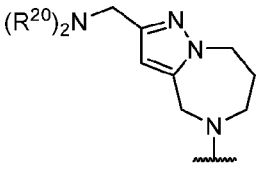
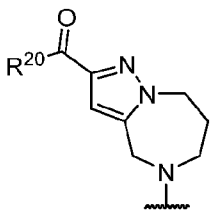
heterocycle of $R^1$ is selected from  . Each spiro heterocycle is optionally substituted as described elsewhere herein.

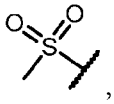
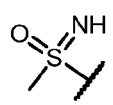
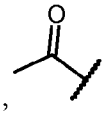
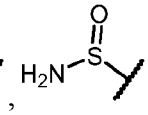
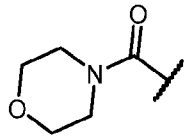
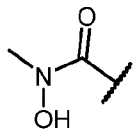
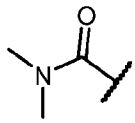
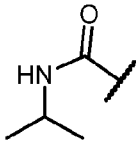
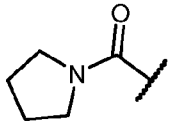
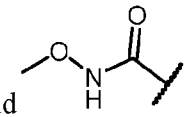
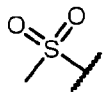
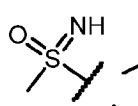
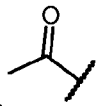
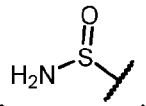
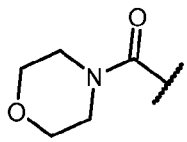
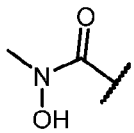
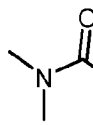
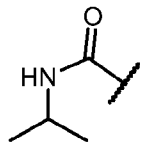
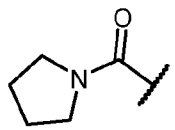
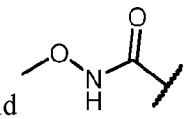
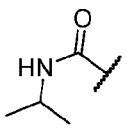
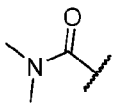
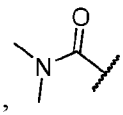
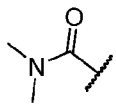
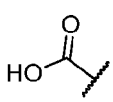
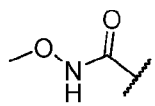
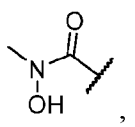
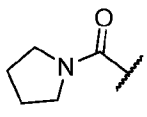
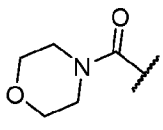
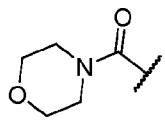
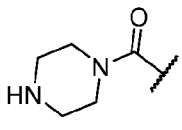
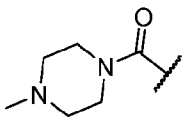
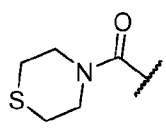
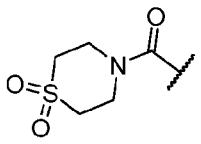
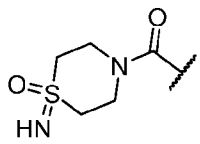
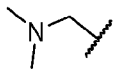
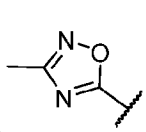
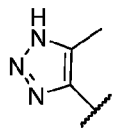
**[00212]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is a fused heterocycle. In some cases, the fused heterocycle of $R^1$ is a 6- to 12-membered fused heterocycle, 6- to 12-membered fused heterocycle, 7- to 12-membered fused heterocycle, or 8- to 12-membered fused heterocycle. In some cases, the fused heterocycle of $R^1$ is a 6- to 11-membered fused heterocycle, 6- to 10-membered fused heterocycle, 6- to 9-membered fused heterocycle, or 6- to 8-membered fused heterocycle. In some cases, the fused heterocycle of $R^1$ is a 7- to 11-membered fused heterocycle, 7- to 10-membered fused heterocycle, 7- to 9-membered fused heterocycle, or 7- to 8-membered fused heterocycle. In some cases, the fused heterocycle of $R^1$ is an 8- to 11-membered fused heterocycle. In some cases, the fused heterocycle of $R^1$ is a 9-membered fused heterocycle. In some cases, the fused heterocycle of $R^1$ is a 10-membered fused heterocycle. In some cases, the fused heterocycle of $R^1$ is an 11-membered fused heterocycle. In some cases, the fused heterocycle of $R^1$ is a 6-membered fused heterocycle. In some cases, the fused heterocycle of $R^1$ is a 7-membered fused heterocycle. In some cases, the fused heterocycle of $R^1$ is a 10-membered fused heterocycle. In some cases, the fused heterocycle is selected from  . Each fused heterocycle is optionally substituted as described elsewhere herein.

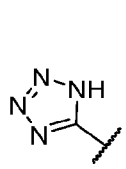
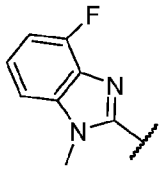
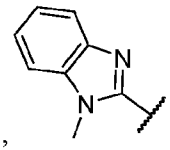
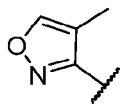
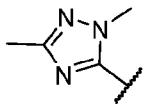
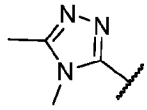
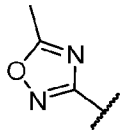
**[00213]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 8- to 10-membered fused heterocycle. In some cases, the 8- to 10-membered fused heterocycle is a bicyclic heterocycle. In some cases, the 8- to 10-membered fused heterocycle is a saturated heterocycle. In some cases, the 8- to 10-membered fused heterocycle is an unsaturated heterocycle. In some cases, the 8- to 10-membered heterocycle is a non-aromatic heterocycle. In some cases, $R^1$ is selected from an optionally substituted 9-membered fused heterocycle. In some cases, $R^1$ is selected from an optionally substituted 10-membered fused heterocycle. In some cases, the 10-membered fused heterocycle is a bicyclic heterocycle. In some cases, the 10-membered fused heterocycle is a saturated heterocycle. In some cases, the 9-membered heterocycle is a non-aromatic heterocycle. In some cases, the 10-membered heterocycle is a non-aromatic heterocycle. In some cases, the fused heterocycle has one saturated ring and one aromatic ring. In some cases, the fused heterocycle has one saturated

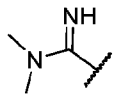
ring and one unsaturated ring. In some cases, the fused heterocycle has two saturated rings. In some cases, the 10-membered heterocycle contains at least 1 nitrogen atom. In some cases, the 10-membered heterocycle contains at least 2 nitrogen atoms. In some cases, the 10-membered heterocycle contains at least 3 nitrogen atoms. In some cases, the 9-membered heterocycle contains at least 1 nitrogen atom. In some cases, the 9-membered heterocycle contains at least 2 nitrogen atoms. In some cases, the 9-membered heterocycle contains at least 3 nitrogen atoms. In some cases, $R^1$ is selected from  and  , each of which is optionally substituted with one or more substituents. In some cases, $R^1$ is  , which is optionally substituted with one or more substituents. In some cases, $R^1$ is  , which is optionally substituted with one or more substituents. In some cases, the one or more optional substituents of $R^1$ are independently selected from halogen, -OH, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(=NR^{20})N(R^{20})_2$, $-C(O)N(R^{20})_2$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$. In some cases, the one or more optional substituents of $R^1$ are independently selected from halogen, -OH, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the optional one or more substituents are independently selected from halogen, =O, -OH, -CN, -NHCN, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, the optional one or more substituents are independently selected from halogen, =O, $C_{1-6}$ alkyl-$N(R^{20})_2$, $-S(O)_2(R^{20})$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, and $-C(O)NR^{20}OR^{20}$. In some cases, the optional one or more

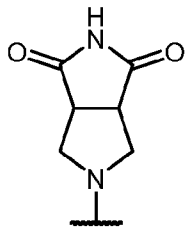
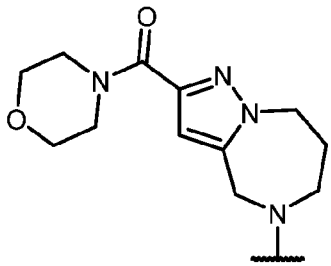
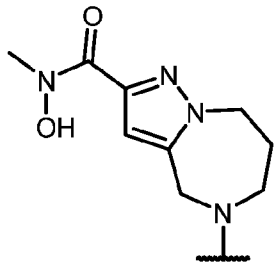
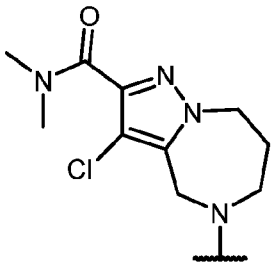
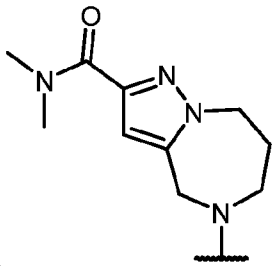
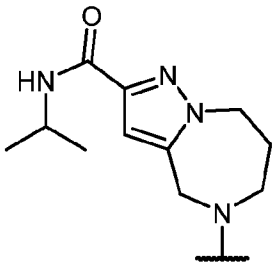
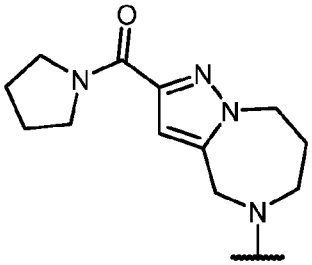
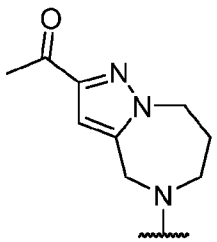
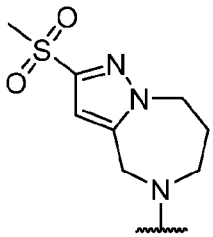
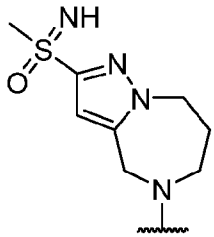
substituents are independently selected from halogen, =O, -$S(O)_2(R^{20})$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$C(O)R^{20}$, -$C(O)N(R^{20})_2$, and -$C(O)NR^{20}OR^{20}$. In some cases, the optional one or more substituents are independently selected from -$C(O)R^{20}$, -$C(O)N(R^{20})_2$, and -$C(O)NR^{20}OR^{20}$. In some cases, the optional one or more substituents are independently selected from -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$. In some cases, the optional one or more substituents are independently selected from -$S(O)N(R^{20})_2$. In some cases, the optional one or more substituents are independently selected from $S(O)_2(R^{20})$. In some cases, the optional one or more substituents are independently selected from $S(O)R^{20}(=NR^{20})$. In some cases, the optional one or more substituents are independently selected from -$C(O)R^{20}$. In some cases, the optional one or more substituents are independently selected from -$C(O)N(R^{20})_2$. In some cases, the optional one or more substituents are independently selected from -$C(O)NR^{20}OR^{20}$. In some cases, $R^1$ is selected from

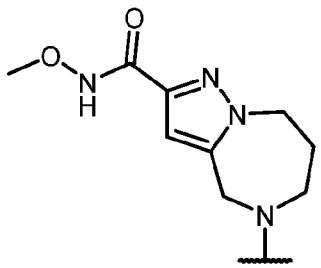

,

,

,

,

,

,

, and

, each of which is further optionally substituted. In some cases, the further one or more optional substituents are selected from halogen, -OH, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the further one or more optional substituents are selected from halogen, -CN, $C_2$ alkenyl, and $C_{1-6}$ alkyl. In some cases, the further one or more optional substituents are selected from halogen, and $C_{1-6}$ alkyl. In some cases, the further one or more optional substituents are selected from halogen. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and 3- to 12-membered heterocycle. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and 3- to 12-membered saturated heterocycle. In some cases, each $R^{20}$ is

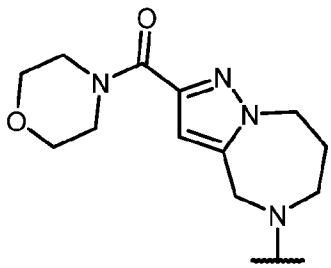
independently selected from 5- to 6-membered saturated heterocycle. In some cases, the heterocycle of $R^{20}$ has at least one nitrogen atom. In some cases, the heterocycle of $R^{20}$ has at least one sulfur atom. In some cases, the heterocycle of $R^{20}$ has at least one oxygen atom. In some cases, the heterocycle of $R^{20}$ contains only 1 heteroatom. In some cases, the heterocycle of $R^{20}$ has at least two heteroatoms. In some cases, the heterocycle of $R^{20}$ contains only 2 heteroatoms. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen, -CN, $C_2$ alkenyl,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, the optional one or more substituents of $R^1$ are independently selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen,  ,  ,

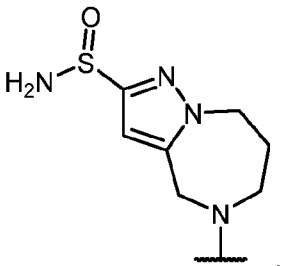
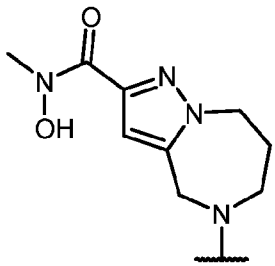
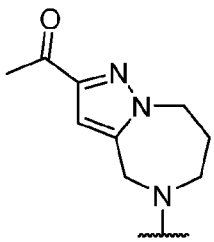
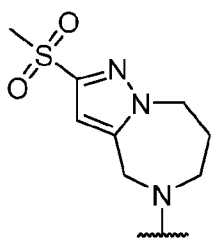







, and

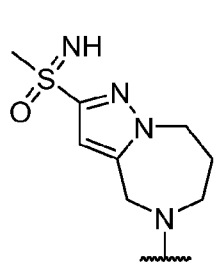
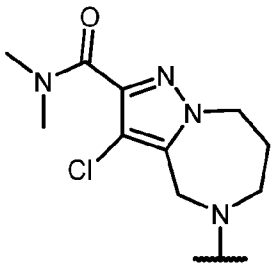
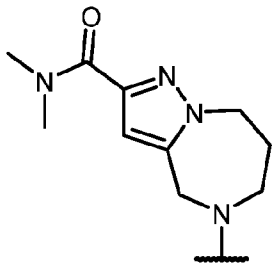
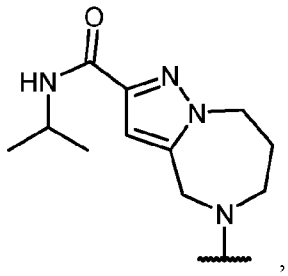
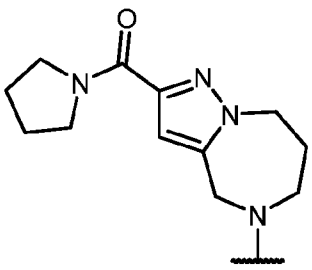
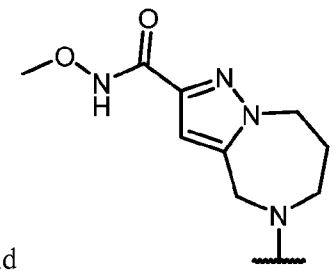
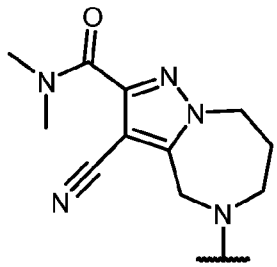
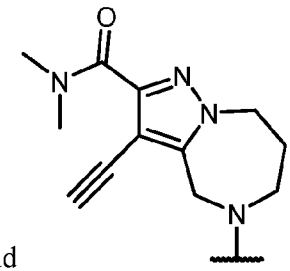
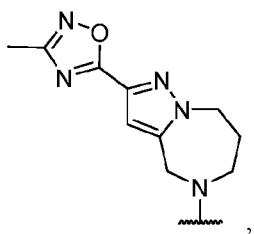
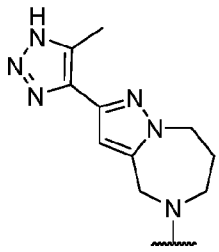
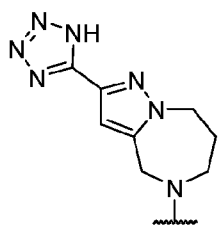
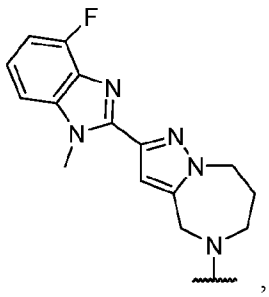
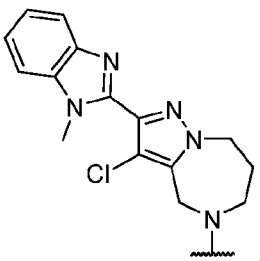
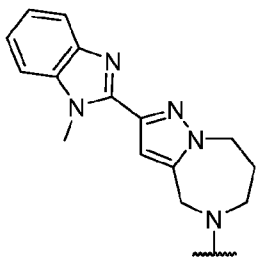
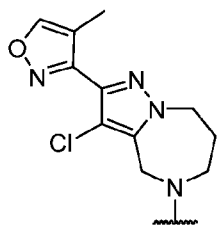
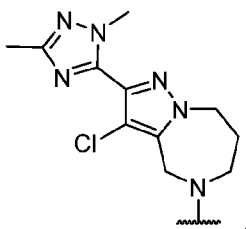
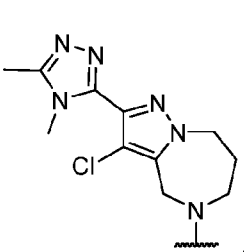
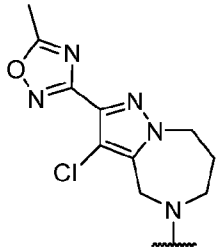
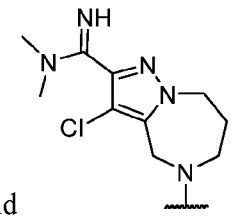

. In some cases, $R^1$ is selected from

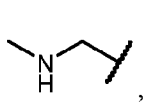
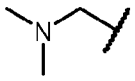
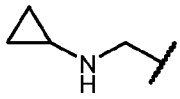










, and

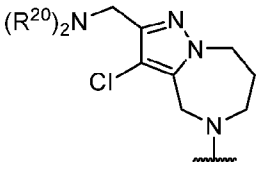
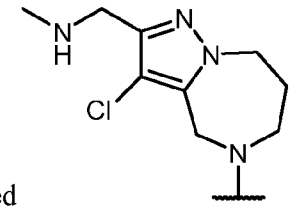

. In some cases, $R^1$ is selected from

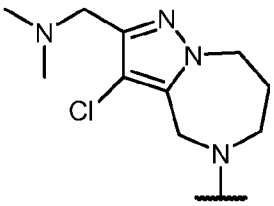
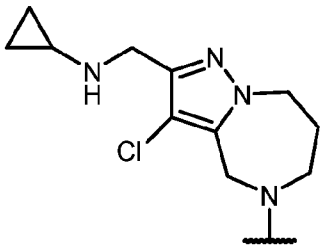

,

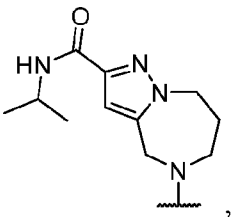
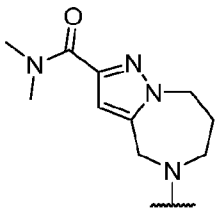
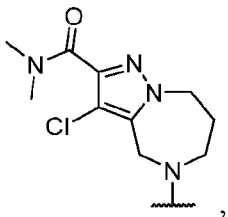
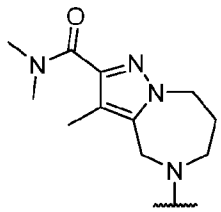
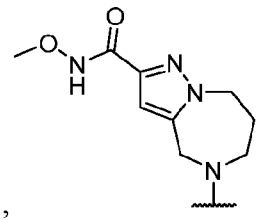





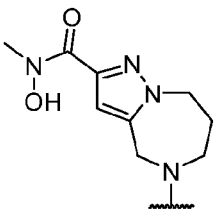
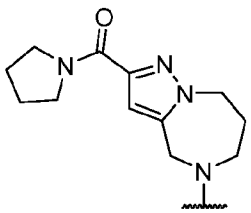
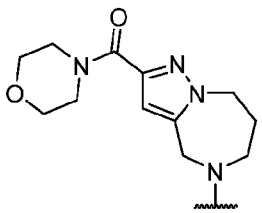
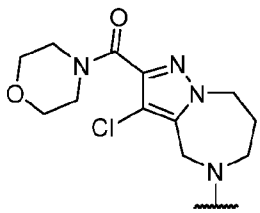

,

,

,

,

, and

. In some cases, $R^1$ is selected from

, and

. In some cases, $R^1$ is selected from

,

,

,

,

,

,

,

,

,

, and

. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen, and $C_{1\text{-}6}$ alkyl-$N(R^{20})_2$. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen,

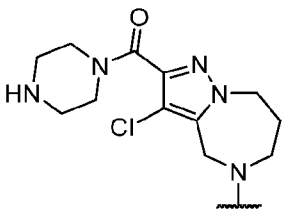
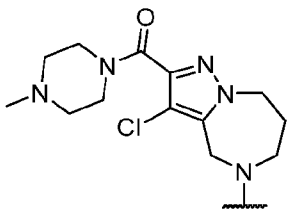
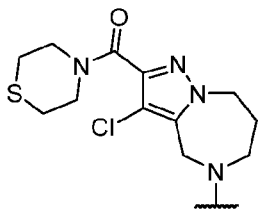
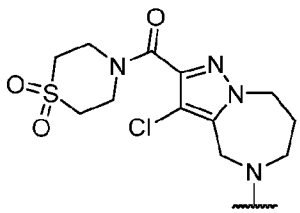

, 
, and 
. In some cases, $R^1$ is selected from

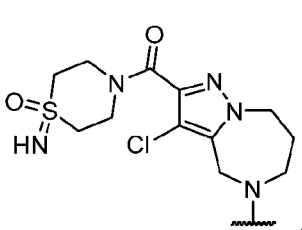
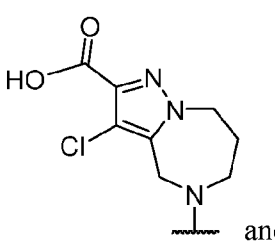
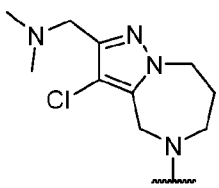

. In some cases, each $R^{20}$ is independently selected from hydrogen, $C_{1-6}$ alkyl, and $C_{3-6}$ carbocycle. In some cases, $R^1$ is selected 
,

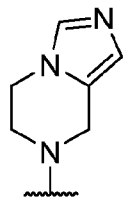

, and 
. In some cases, $R^1$ is selected


, 
, 
, 
, 
,

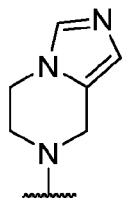

, 
, 
, 
,


, 
, 
, 

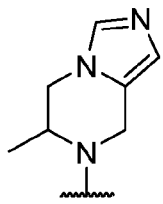

, 
and 
. In some cases, $R^1$ is



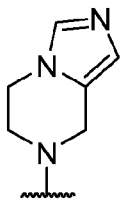
selected from , which is optionally substituted with one more substituents independently selected from halogen, -OH, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(=NR^{20})N(R^{20})_2$, $-C(O)OR^{20}$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted with one or more substituents selected from halogen, $-OR^{20}$, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected



from , which is optionally substituted with one more substituents independently selected from halogen and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from

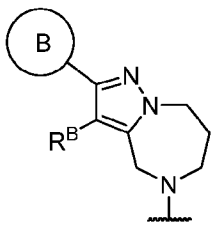


and

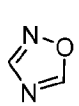
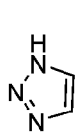
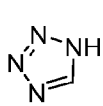
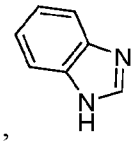
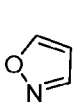
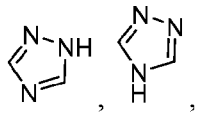
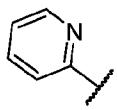
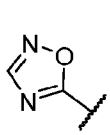
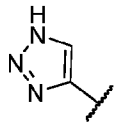
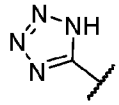
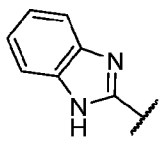
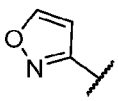
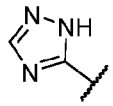
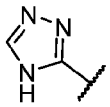
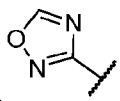
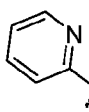
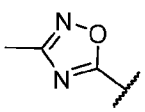
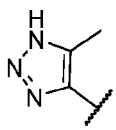
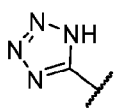
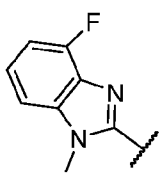
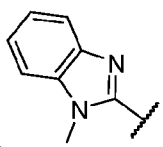
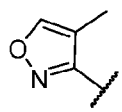
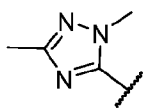
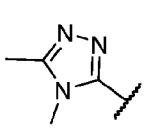
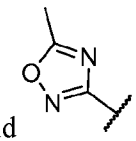


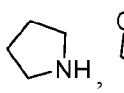
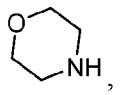
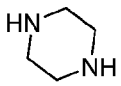
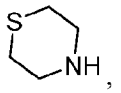
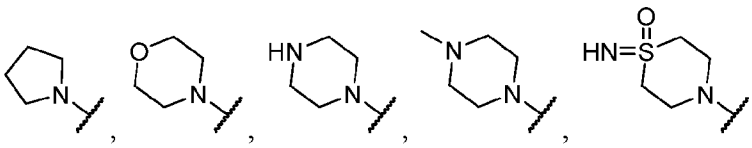
.

**[00214]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from a



, wherein (B) is selected from a 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted independently with one or more $R^{1*}$; and $R^B$ is selected from hydrogen, halogen, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkynyl, and -CN. In some cases, $R^B$ is selected from hydrogen, and halogen. In some cases, $R^B$ is chloride. In some cases, $R^B$ is hydrogen. In some cases, (B) has at least 1, 2, 3, or 4 heteroatoms. In some cases,

 has at least 1, 2, 3, or 4 nitrogen atoms. In some cases,  has at least 1 oxygen atom. In some cases,  is a monocyclic heterocycle. In some cases,  is a bicyclic heterocycle. In some cases,  is selected from an optionally substituted 5-membered heterocycle. In some cases,  is selected from an optionally substituted 9-membered heterocycle. In some cases,  is selected from  ,  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted with one or more $R^{1*}$. In some cases,  is selected from  ,  ,  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted with one or more $R^{1*}$. In some cases, each $R^{1*}$ is independently selected from halogen, $-OR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, $=O$, $=N(R^{20})$, $=NO(R^{20})$, $-CN$, $-NHCN$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, and $C_{1-6}$ alkyl. In some cases,  is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

**[00215]** In some embodiments, for a compound or salt of Formula (I), when $R^1$ is substituted with $-C(O)R^{20}$, $R^{20}$ is selected from a 5- to 12-membered heterocycle, which is optionally substituted. In some cases, $R^1$ is substituted with $-C(O)R^{20}$. In some cases, $R^{20}$ is selected from a 5- to 12-membered unsubstituted heterocycle. In some cases, $R^{20}$ is selected from a 5- to 6-membered heterocycle, which is optionally substituted. In some cases, the heterocycle has at least one nitrogen atom. In some cases, the heterocycle has at least one sulfur atom. In some cases, the heterocycle has at least one oxygen atom. In some cases, the heterocycle has two heteroatoms. In some cases, the heterocycle of $R^{20}$ is selected from  ,  ,  , and  , each of which is optionally substituted. In some cases, $R^{20}$ is selected from  . In some cases, the optional substituents are selected from $C_{1-10}$ alkyl, oxo, and =NH.

**[00216]** In some embodiments, for a compound or salt of Formula (I), each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, and =NH. In some cases, each $R^{20}$ is independently selected from hydrogen; and unsubstituted $C_{1-6}$ alkyl, and 3- to 12-membered heterocycle which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, and =NH.

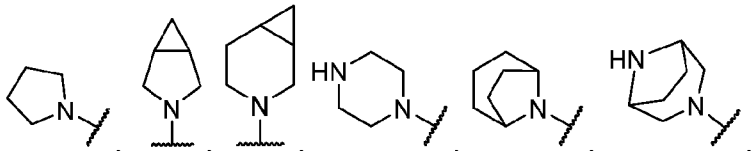
**[00217]** In some embodiments, for a compound or salt of Formula (I), each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, and =NH. In some cases, each $R^{21}$ is independently selected from hydrogen; and unsubstituted $C_{1-6}$ alkyl, and 3- to 12-membered heterocycle which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, and =NH.

**[00218]** In some embodiments, for a compound or salt of Formula (I), each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, -O-

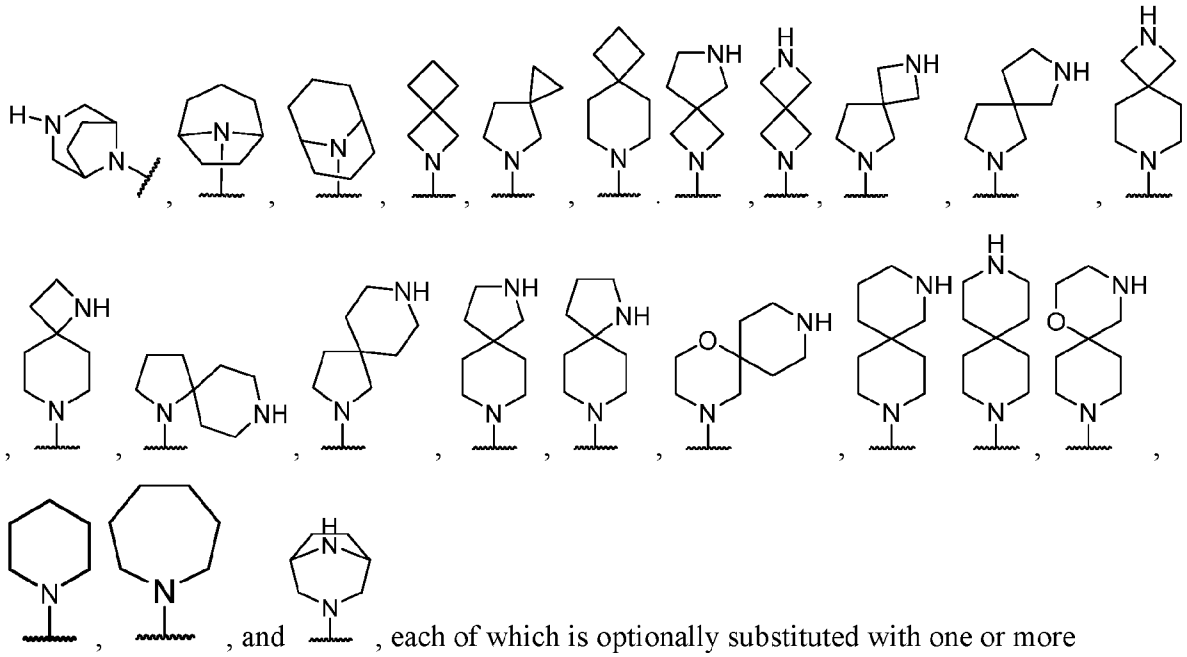
$C_{1-10}$ alkyl, oxo, and =NH. In some cases, each $R^{20}$ is independently selected from hydrogen; and unsubstituted $C_{1-6}$ alkyl, and 3- to 12-membered heterocycle which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, and =NH.

**[00219]** In some embodiments, for a compound or salt of Formula (I), each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, and =NH. In some cases, each $R^{20}$ is independently selected from hydrogen; and unsubstituted $C_{1-6}$ alkyl, and 3- to 12-membered heterocycle which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, and =NH.

**[00220]** In some embodiments, for a compound or salt for Formula (I), $R^1$ is selected from 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted with one or more substituents. In some cases, the one or more optional substituents are independently selected from halogen, -CN, $-NO_2$, =O, $-N(R^{20})_2$, $-B(OR^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents are independently selected from halogen, -OH, $-N(R^{20})_2$, $-NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl. In some cases, the one or more optional substituents are independently selected from halogen, -OH, $-N(R^{20})_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl. In some cases, $R^{20}$ is selected from hydrogen and $C_{1-3}$ alkyl.

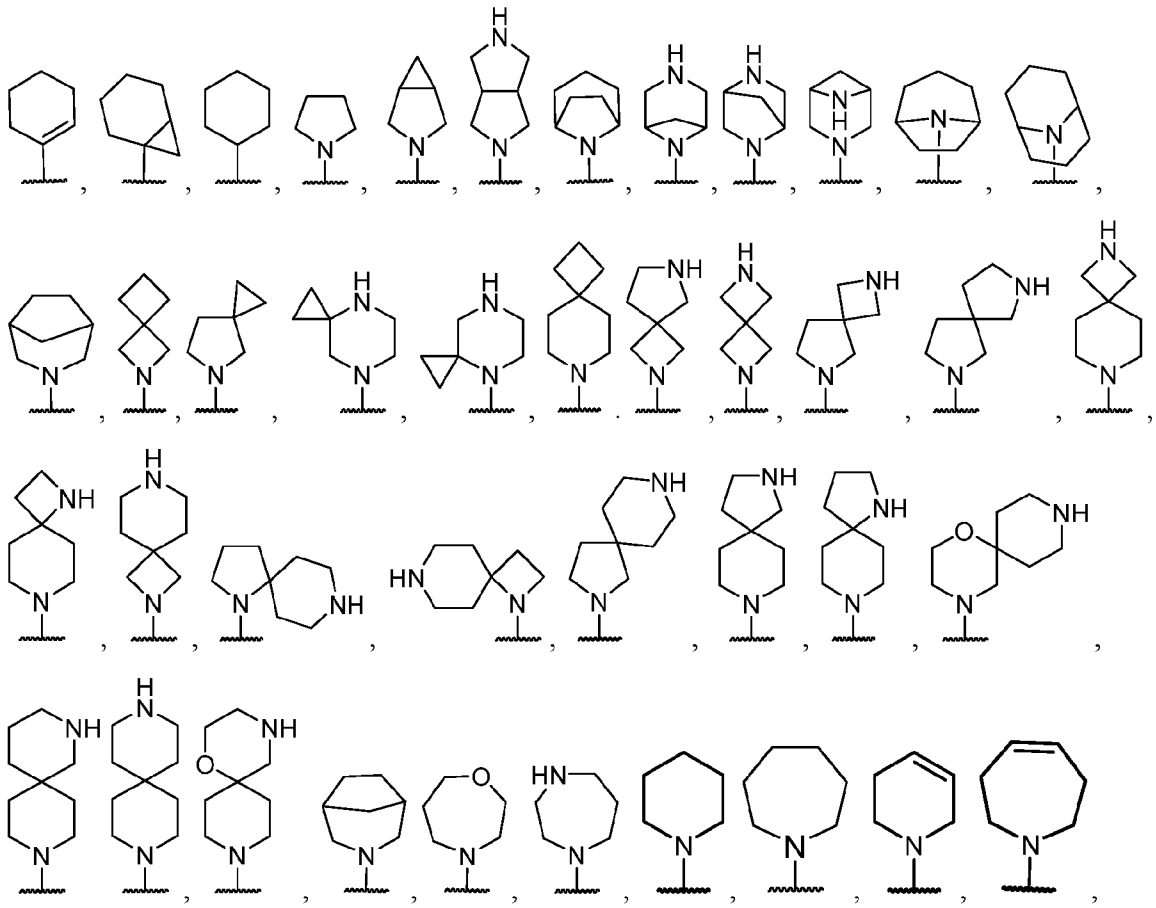
**[00221]** In some embodiments, for a compound or salt for Formula (I), $R^1$ is selected from a saturated 5- to 12-membered heterocycle, which is optionally substituted with one or more substituents. In some cases, the 5- to 12-membered heterocycle of $R^1$ is bridged. In some cases, the 5- to 12-membered heterocycle of $R^1$ is not bridged. In some cases, the 5- to 12-membered heterocycle is selected from 

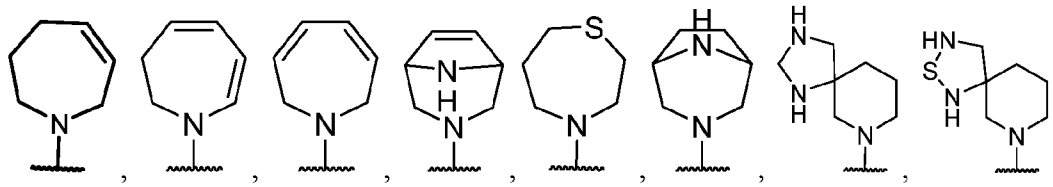
,

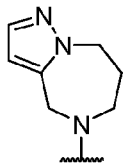


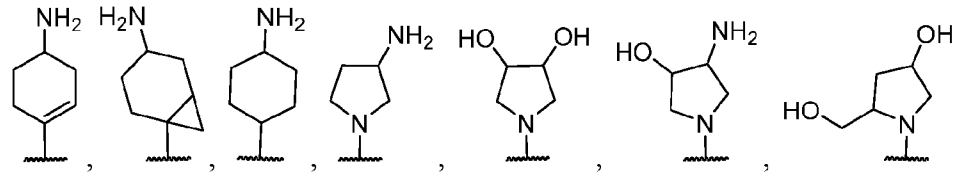
substituents.

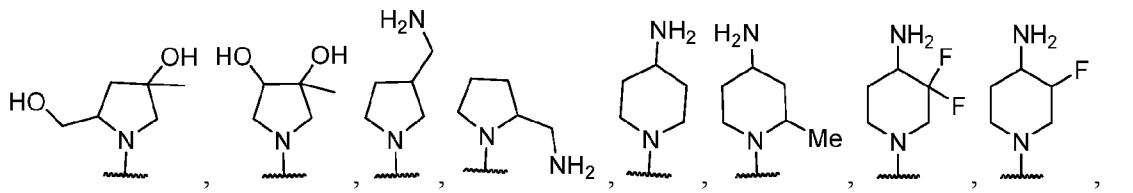
**[00222]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from

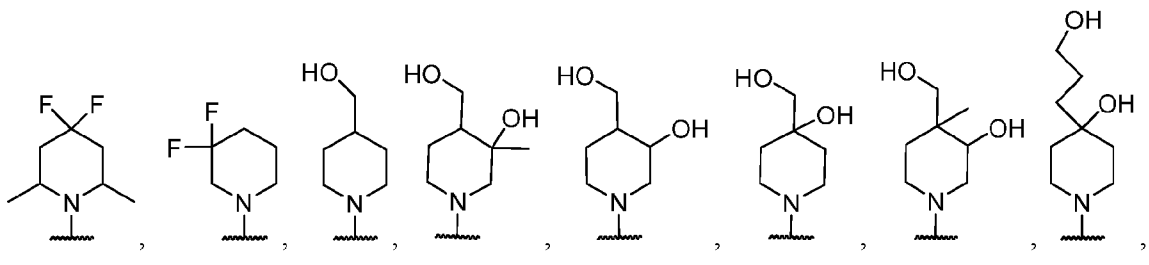


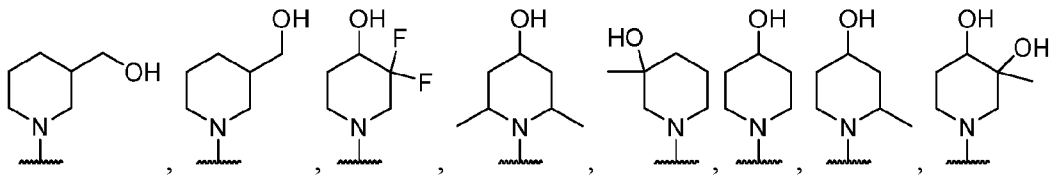

, and

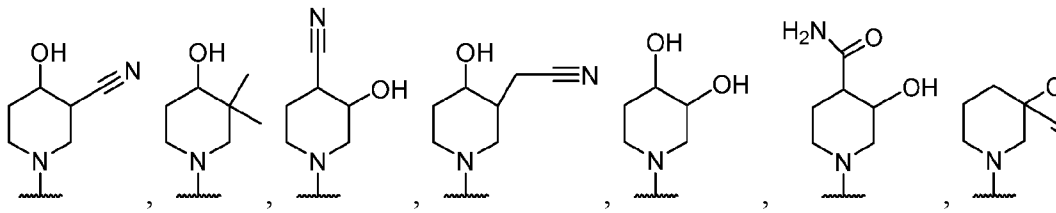

, each of which is optionally substituted with one or more substituents. In some cases, the one or more of the optional substituents are independently selected from halogen, -OH, -$N(R^{20})_2$, -$B(OH)_2$, -$C(O)N(R^{20})_2$, -NHCN, -$NO_2$, $C_{1-6}$ alkoxy, =O, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl. In some cases, $R^1$ is selected from

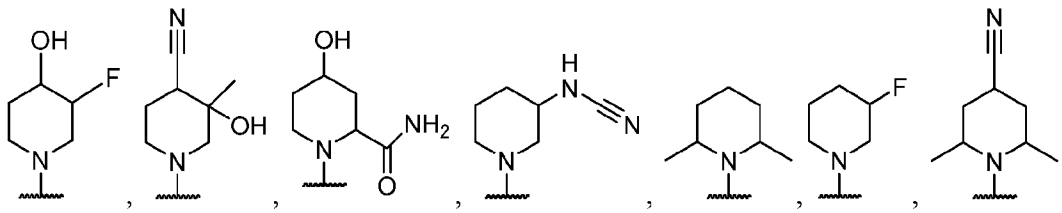

,

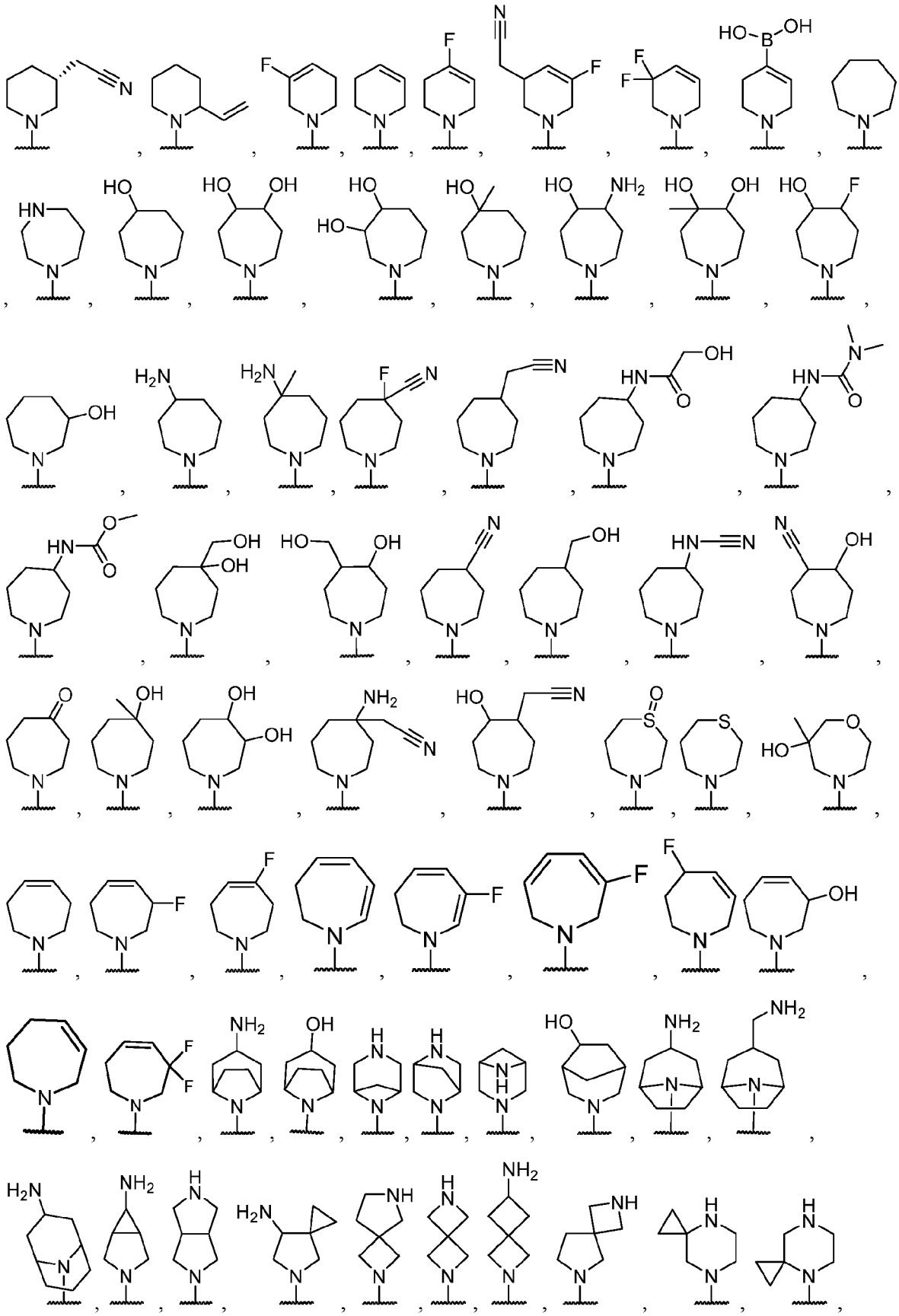

,

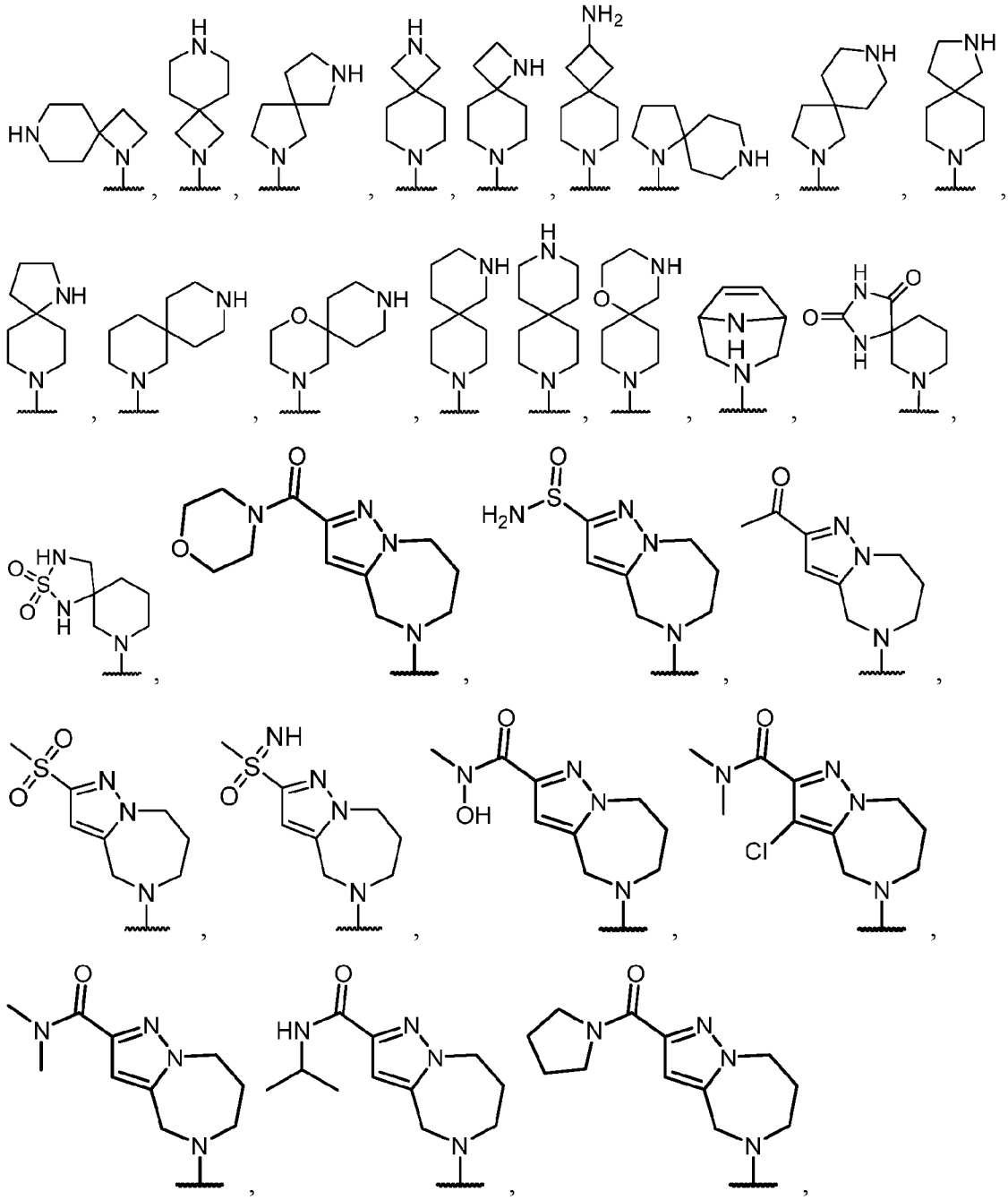

,

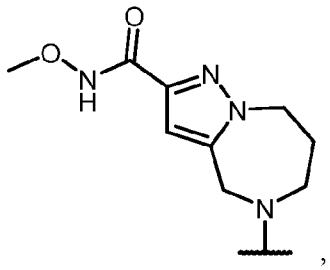
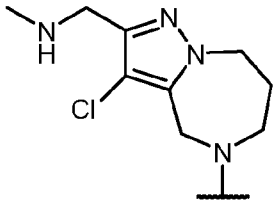
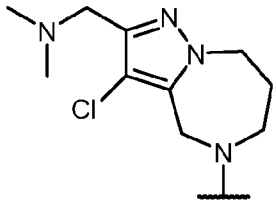
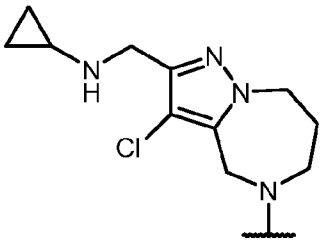

,


,


.






,

,

, and

.

**[00223]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 5- to 12-membered unsaturated heterocycle, wherein the heterocycle has as most one nitrogen atom. In some cases, the 5- to 12-membered unsaturated heterocycle has at least one nitrogen atom. In some cases, the 5- to 12-membered unsaturated heterocycle has at most one nitrogen atom.

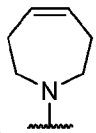
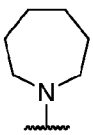
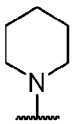
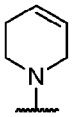
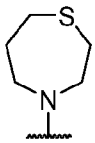
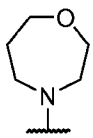
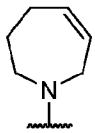
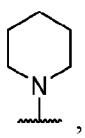
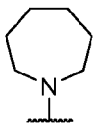
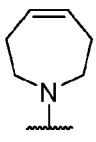
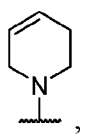
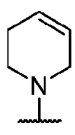
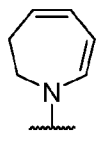
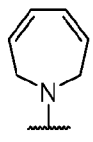
**[00224]** In some embodiments, for a compound or salt of Formula (I), the heterocycle of $R^1$ contains only 1 nitrogen atom and optionally one or more heteroatoms selected from oxygen, and sulfur. In some cases, the heterocycle is a fused heterocycle or a bridged heterocycle. In some cases, the heterocycle is a monocyclic heterocycle or a bridged heterocycle. In some cases, the heterocycle is a monocyclic heterocycle. In some cases, the heterocycle is a bridged heterocycle. In some cases, the heterocycle is selected from  and  . The heterocycle is optionally substituted as described elsewhere herein.

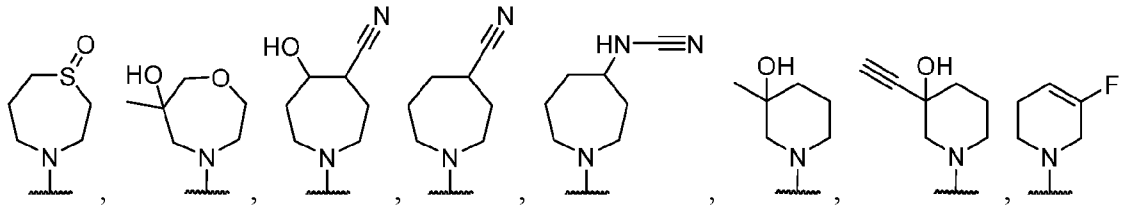
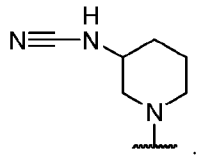
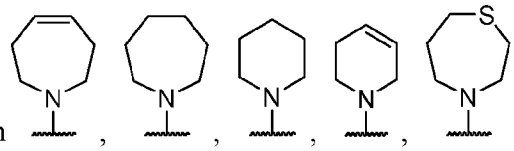
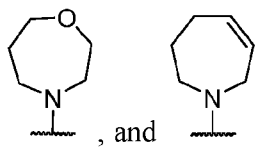
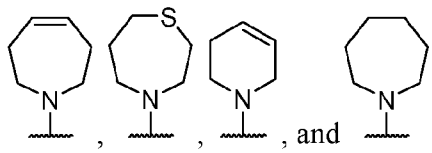
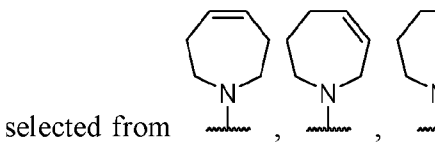
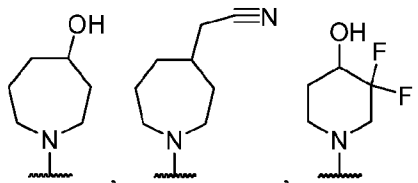
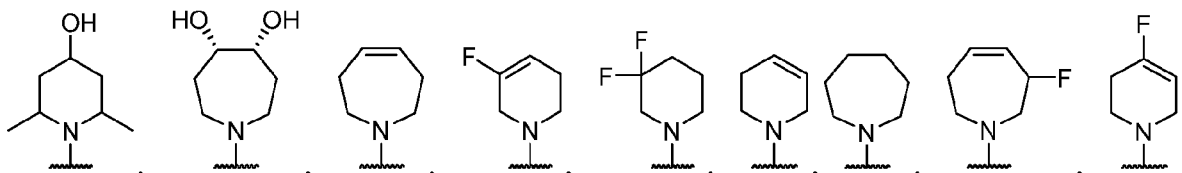
**[00225]** In some embodiments, for a compound or salt of Formula (I), the heterocycle of $R^1$ has at most 1 nitrogen atom. In some cases, the heterocycle of $R^1$ has only 1 nitrogen atom and optionally one or more other heteroatoms selected from oxygen and sulfur. In some cases, the heterocycle of $R^1$ has only 1 nitrogen atom and no other heteroatoms.

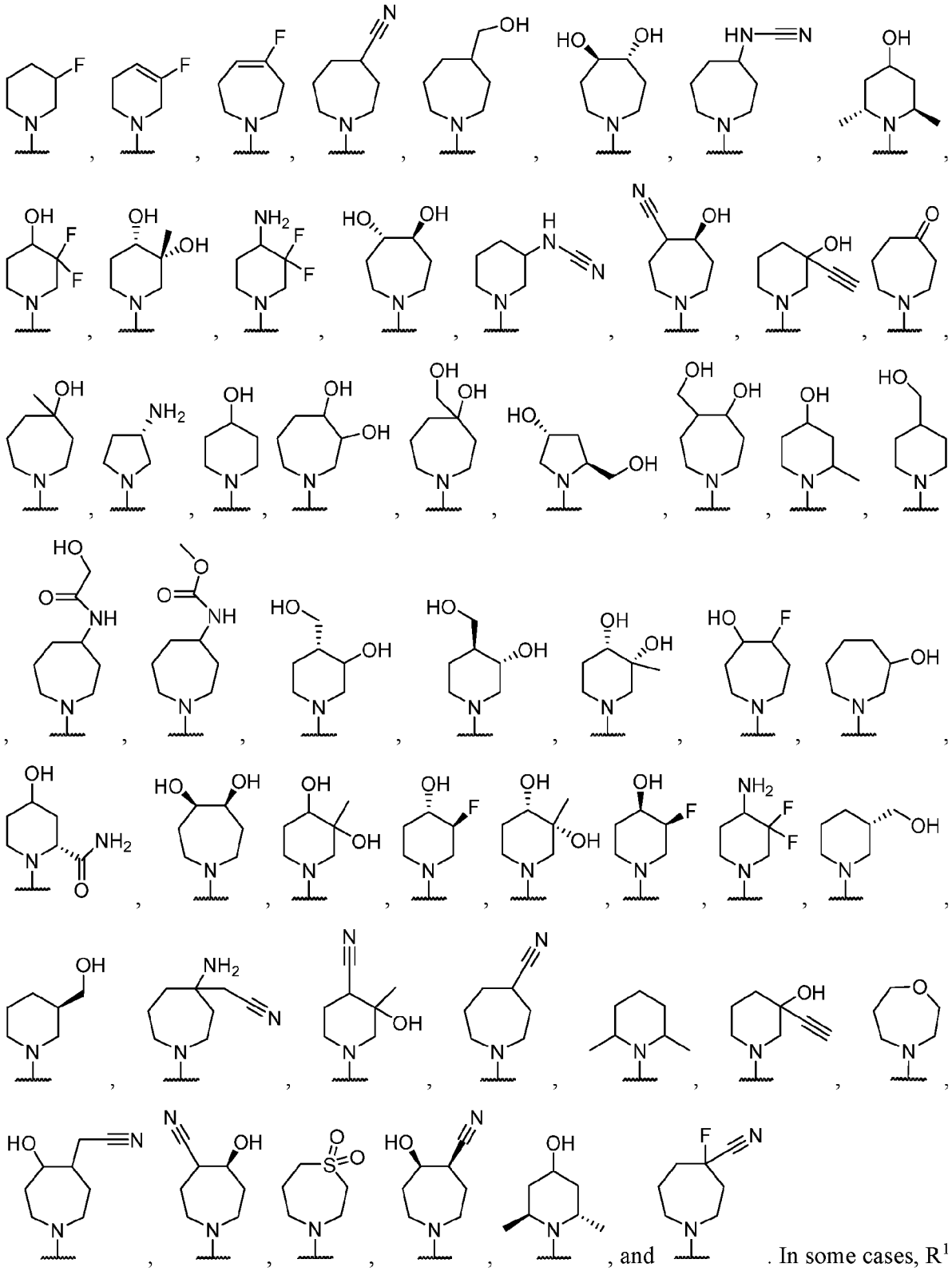
**[00226]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 5- to 12-membered saturated heterocycle, wherein the heterocycle has as most one nitrogen atom. In some cases, the 5- to 12-membered unsaturated heterocycle has at least one nitrogen atom. In some cases, the 5- to 12-membered unsaturated heterocycle has only one nitrogen atom and 0-2 other heteroatoms selected from nitrogen, oxygen, and sulfur. In some cases, the 5- to 12-membered unsaturated heterocycle has only one nitrogen atom and no further

heteroatoms. In some cases, the 5- to 12-membered unsaturated heterocycle has three nitrogen atoms and no further heteroatoms.

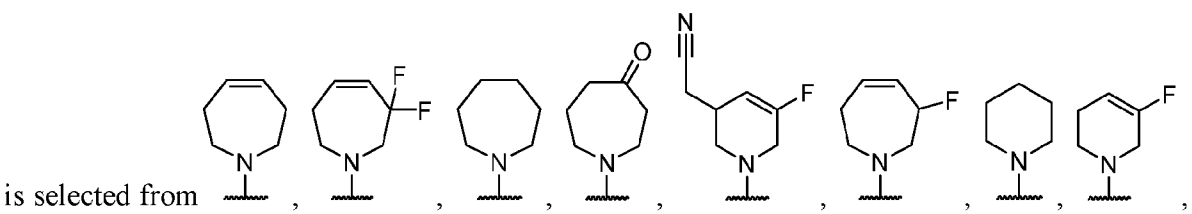
**[00227]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 5- to 12-membered unsaturated heterocycle, wherein the heterocycle has as most one nitrogen atom. In some cases, the 5- to 12-membered unsaturated heterocycle has at least one nitrogen atom. In some cases, the 5- to 12-membered unsaturated heterocycle has only one nitrogen atom and no further heteroatoms.

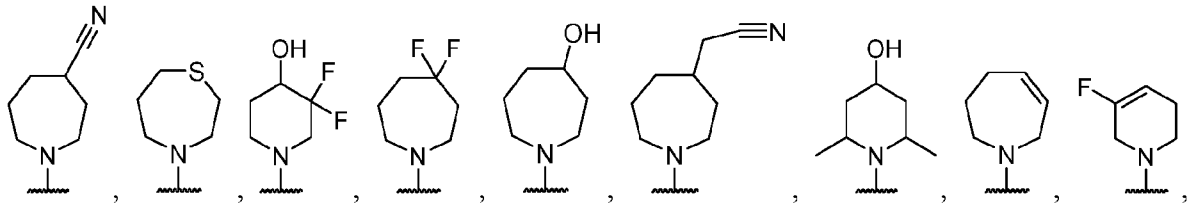
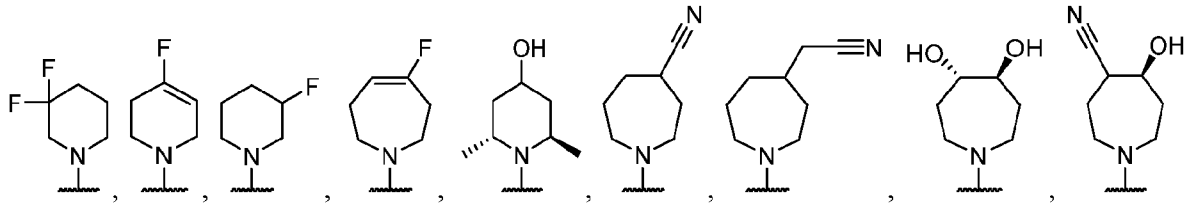
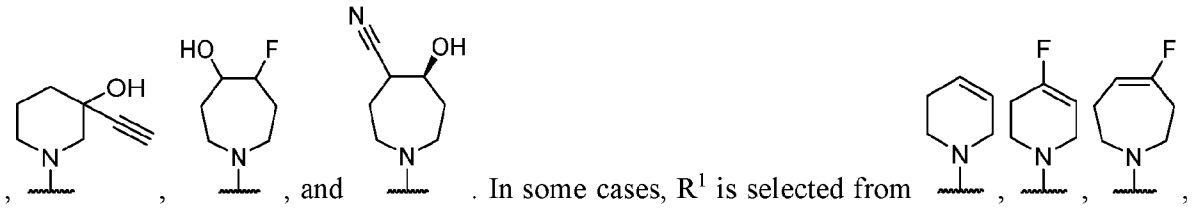
**[00228]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from 6- to 7-membered heterocycle. In some cases, $R^1$ is selected from 7-membered heterocycle. In some cases, $R^1$ is selected from 6-membered heterocycle. In some cases, the 6- to 7-membered heterocycle contains only 1 nitrogen atom and optionally one or more additional heteroatoms selected from oxygen, and sulfur. In some cases, the optionally one or more additional heteroatoms are selected from sulfur. In some cases, the optionally one or more additional heteroatoms are selected from oxygen. In some cases, the 6- to 7-membered heterocycle contains only 1 nitrogen atom and no further additional heteroatoms. In some cases, the 6- to 7-membered heterocycle is a non-aromatic 6- to 7-membered heterocycle. In some cases, the 6- to 7-membered heterocycle of $R^1$ is bound to Formula (I) via the only 1 nitrogen atom. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  , and  , each of which is substituted. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  , and  , each of which is substituted. In some cases, the substituents of $R^1$ are each selected from one or more halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, -NHCN, $-NO_2$, =O, -CN, $C_{1-6}$ fluoroalkyl, and $C_{2-6}$ alkynyl; and further optionally substituted with one or more substituents independently selected from $-C(O)N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkenyl. In some cases, the substituents of $R^1$ are each selected from one or more halogen, $-OR^{20}$, $-N(R^{20})_2$, -NHCN, =O, -CN, and $C_{2-6}$ alkynyl; and further optionally substituted with one or more substituents independently selected from $-C(O)N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, the substituents of $R^1$ are each selected from one or more halogen, -OH, -NHCN, =O, -CN, and $C_{2-6}$ alkynyl; and further optionally substituted with one or more substituents independently selected from $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from

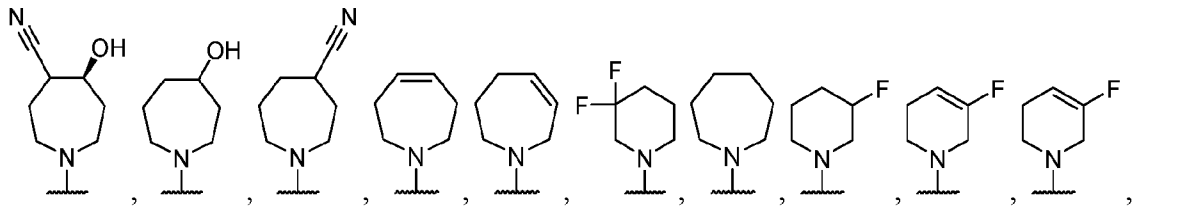
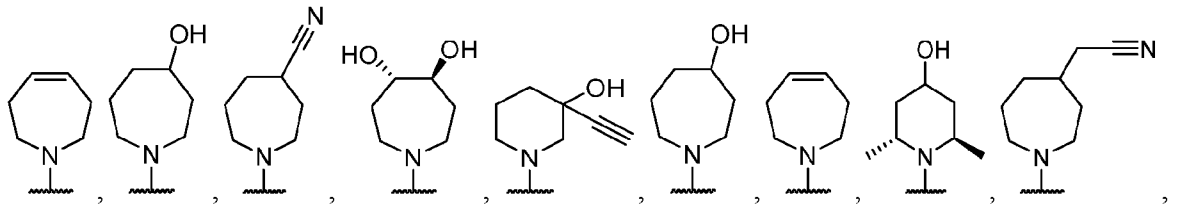

, and  . In some cases, $R^1$ is selected from  ,  , and , each of which is optionally substituted. In some cases, $R^1$ is selected from  , and  , each of which is optionally substituted. In some cases, $R^1$ is selected from , each of which is optionally substituted. In some cases, the one or more optional substituents of $R^1$ are each independently selected from fluorine, -OH, -C(O)$NH_2$, -NH-C(O)-($C_{1-6}$ alkoxy), -NH-C(O)-($C_{1-6}$ hydroxyalkyl), -$NH_2$, -NH(CN), =O, -CN, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of $R^1$ are each independently selected from halogen, -OH, -CN, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of $R^1$ are each independently selected from halogen, -OH, and -CN. In some cases, the one or more optional substituents of $R^1$ are each independently selected from fluorine, -OH, -CN, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, oxo, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of $R^1$ are each independently selected from fluorine, -OH, -CN, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, $R^1$ is selected from  ,  ,

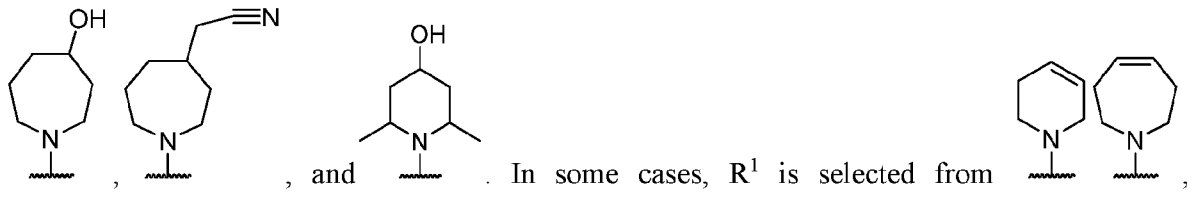


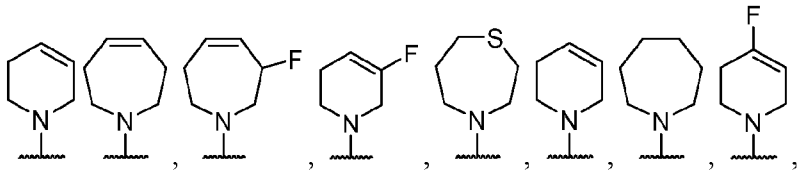
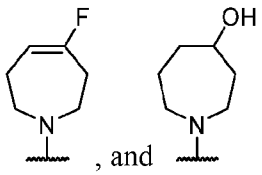
. In some cases, $R^1$ is selected from

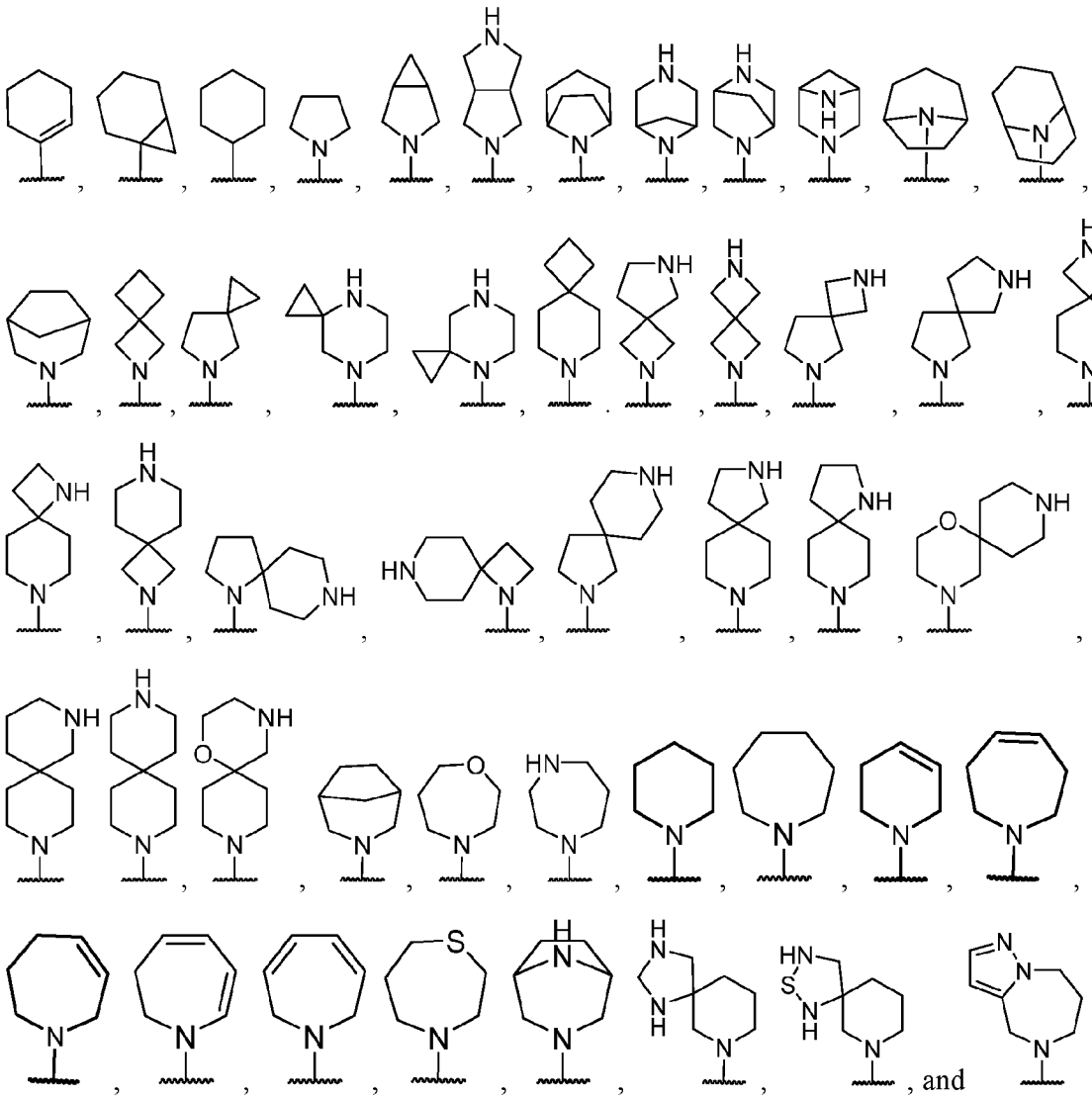


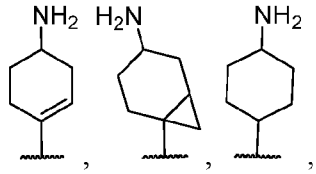
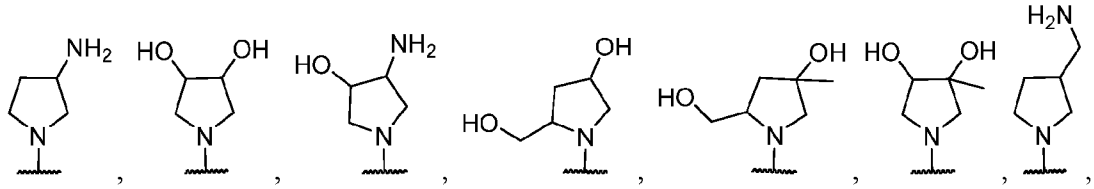
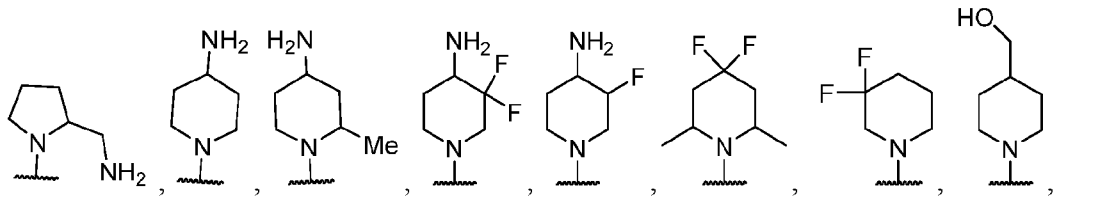
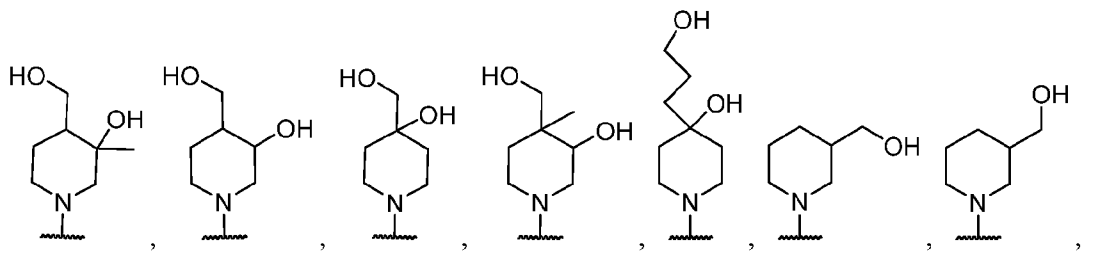
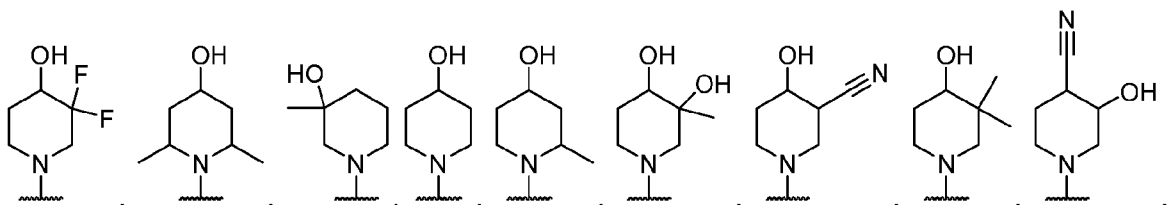
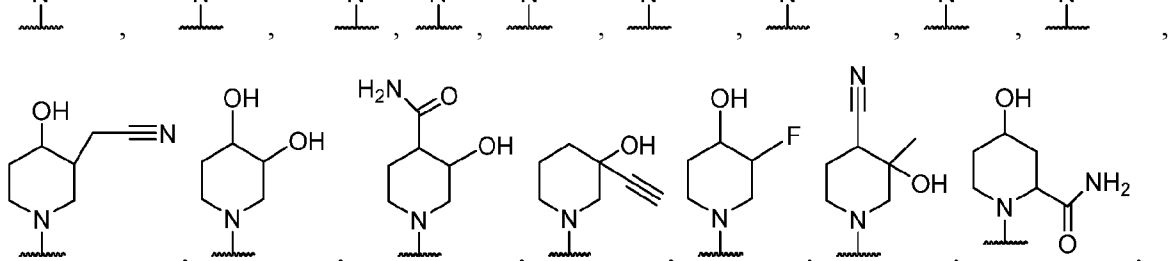
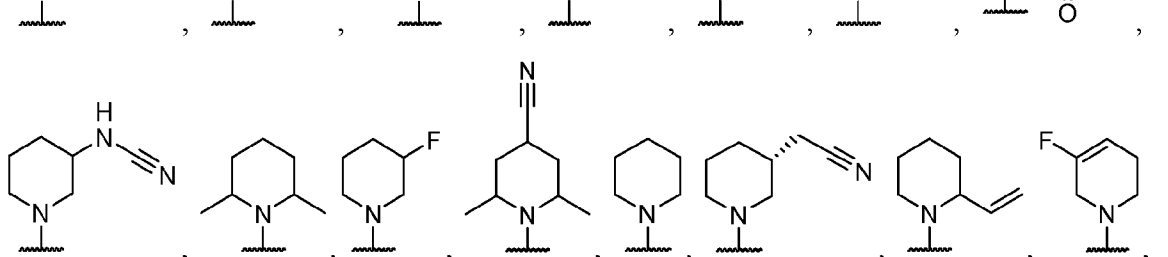
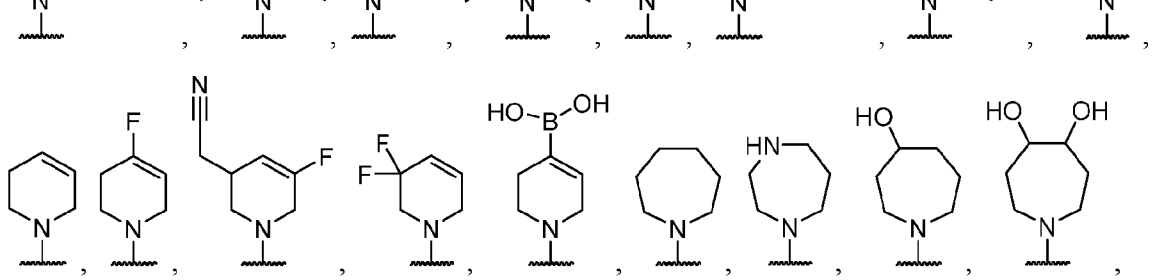
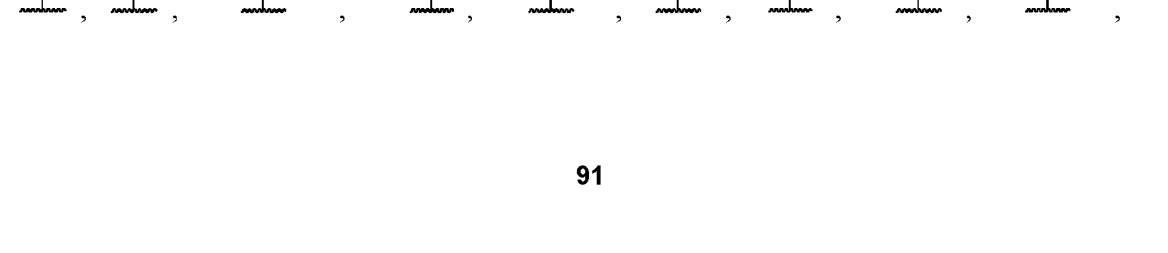



, and . In some cases, $R^1$ is selected from

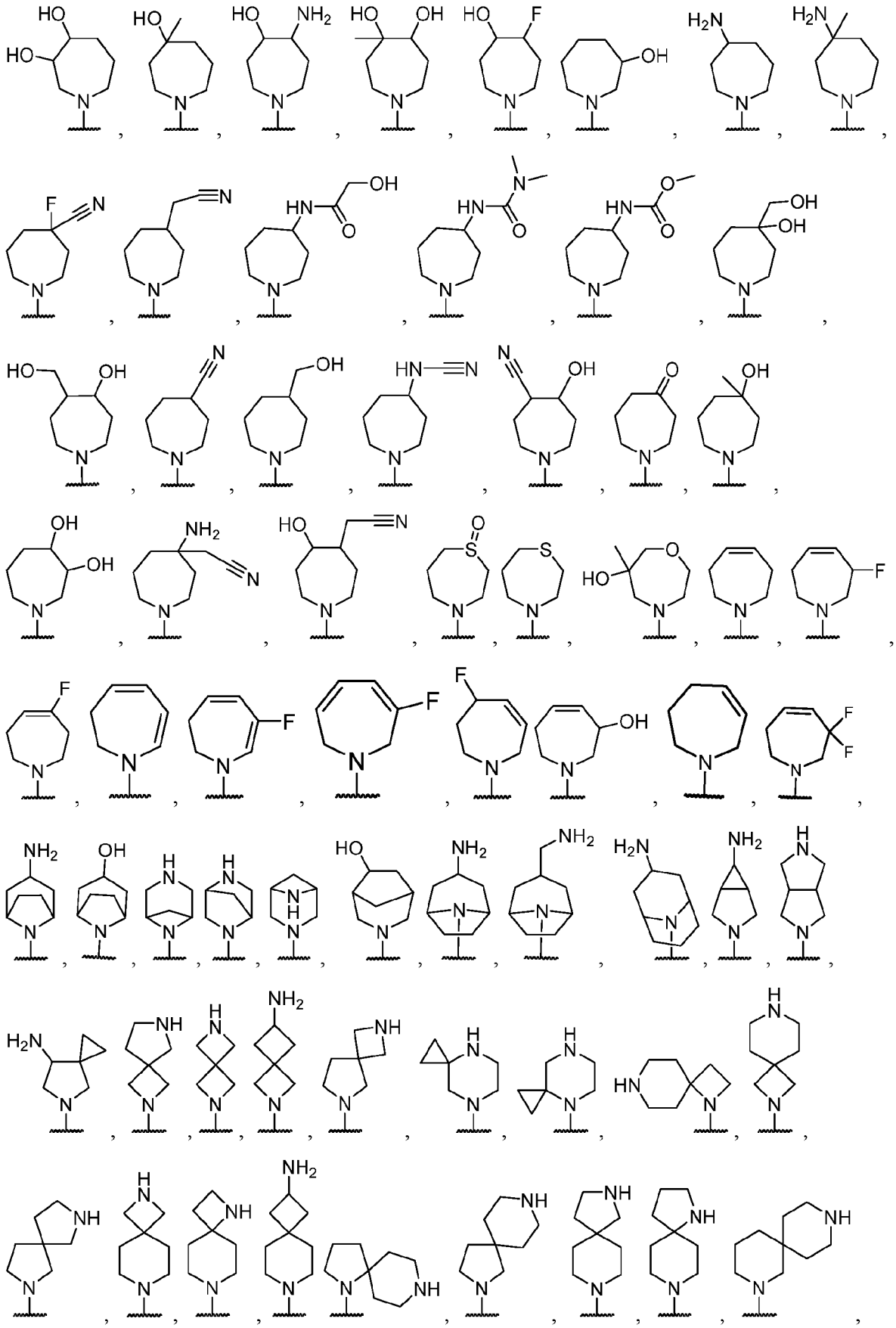


, and . In some cases, $R^1$ is selected from

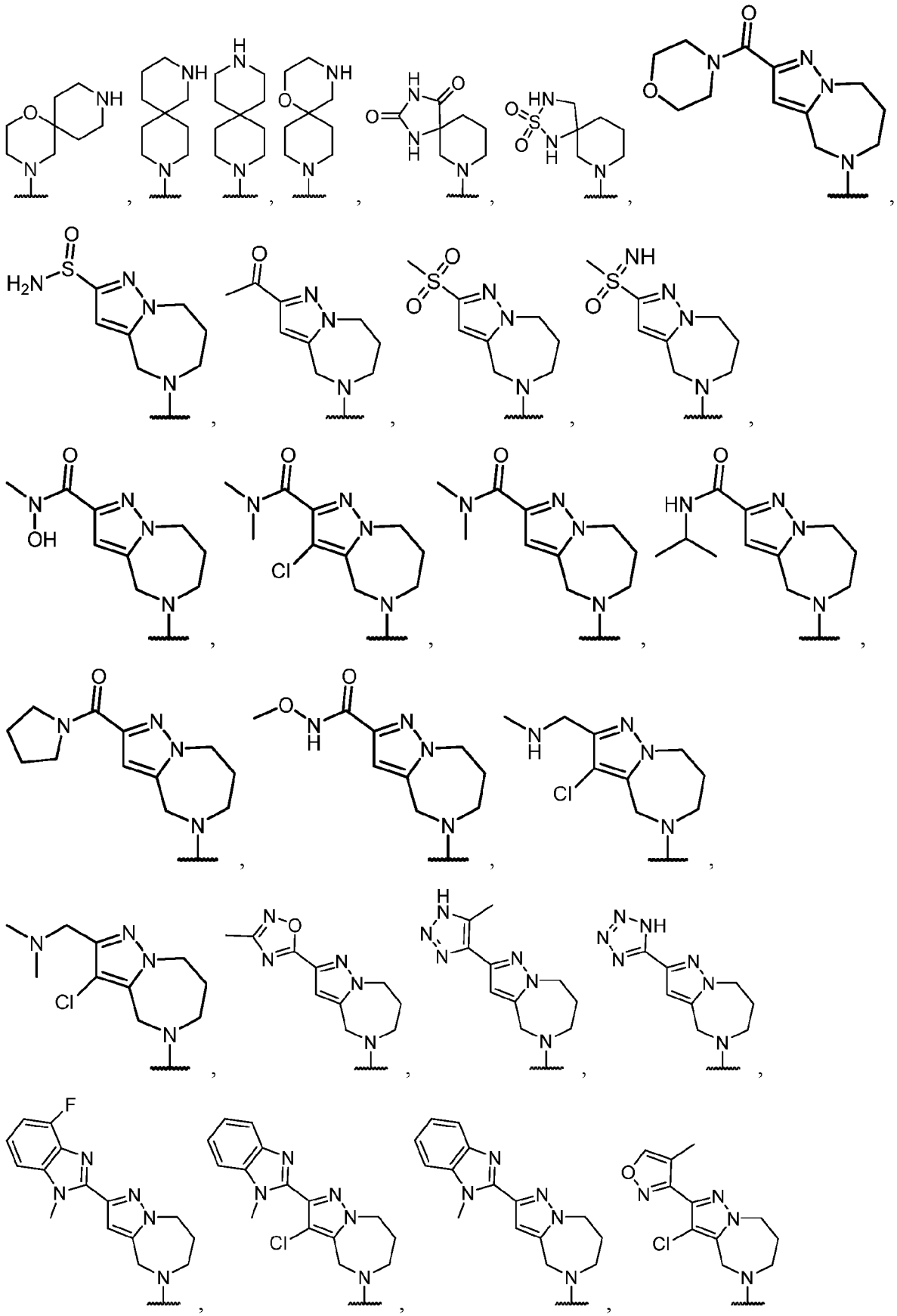

, and . In

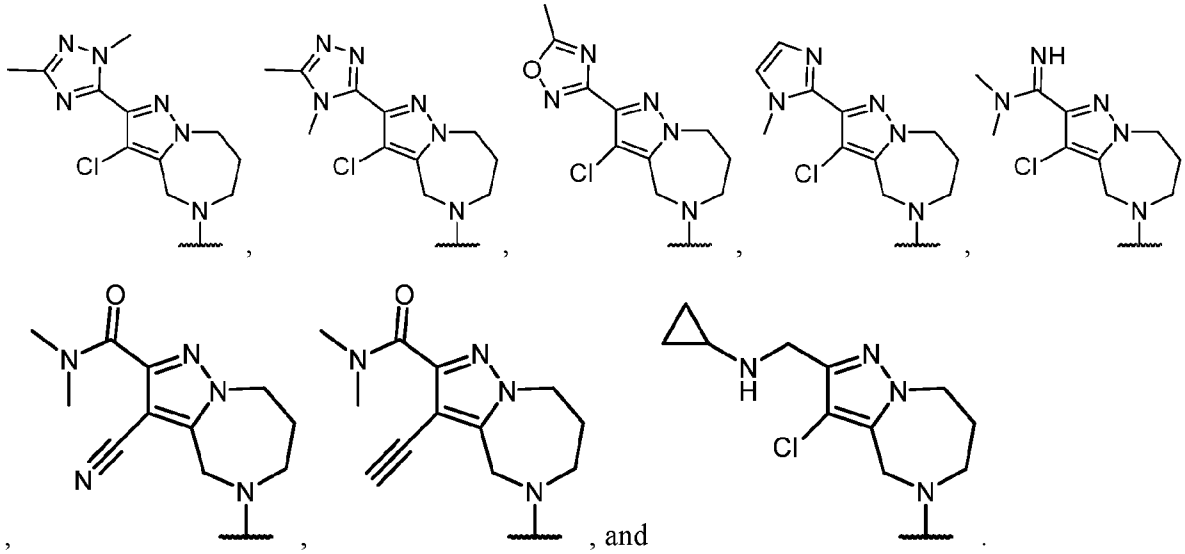
some cases, $R^1$ is selected from  ,  , and .

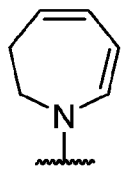
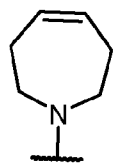
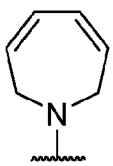
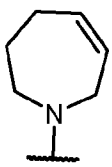
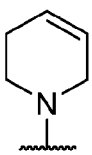
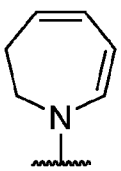
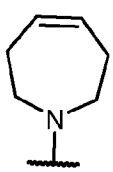
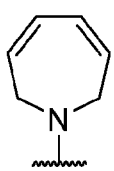
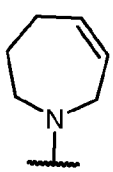
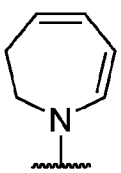
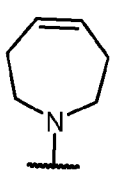
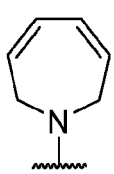
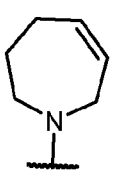
**[00229]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from  , and , each of which is optionally substituted with one or more substituents. In some cases, the one or more of the optional substituents are independently selected from halogen, -OH, $-N(R^{20})_2$, $-B(OH)_2$, $-C(O)N(R^{20})_2$, -NHCN, $-NO_2$, $C_{1-6}$ alkoxy, =O, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{1-6}$ aminoalkyl, $C_{1-6}$

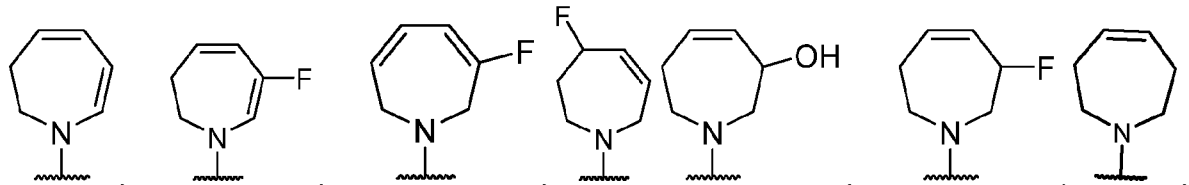
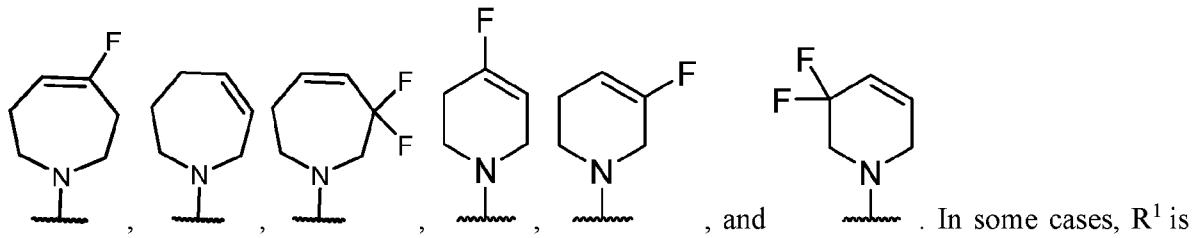
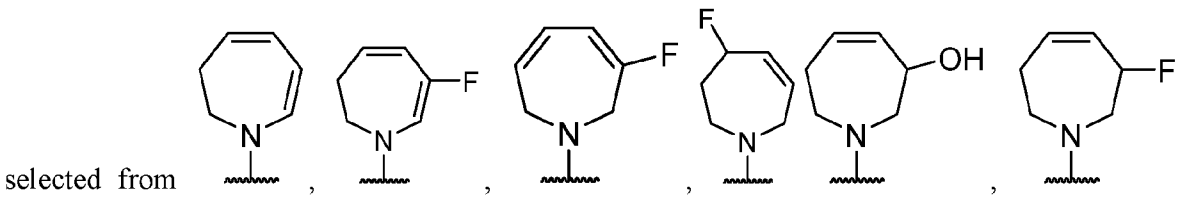
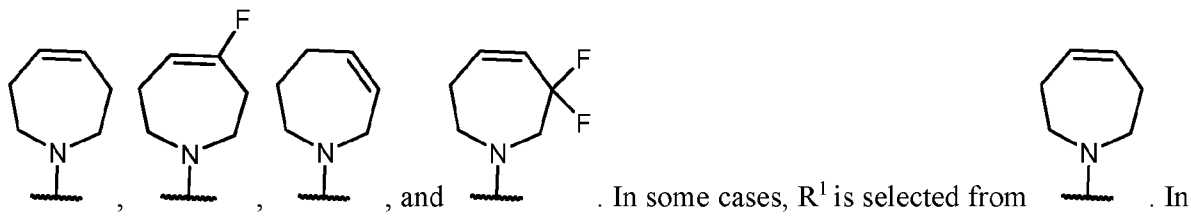
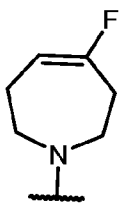
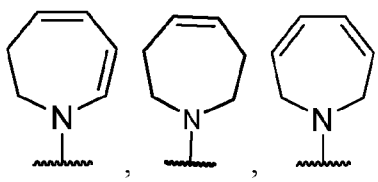
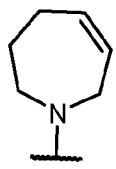
hydroxyalkyl, and $C_{1-6}$ haloalkyl. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  .



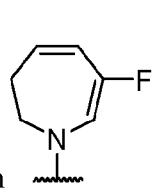
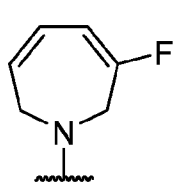
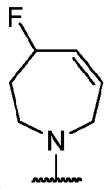
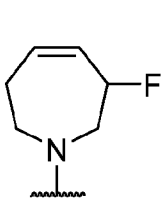
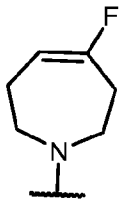
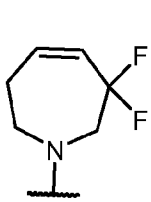
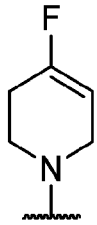
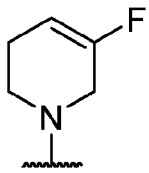
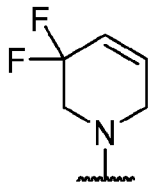
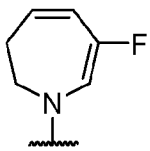
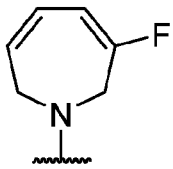
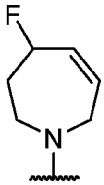
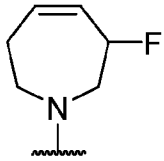
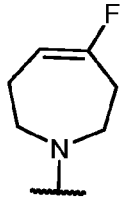
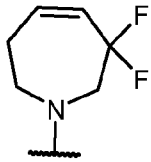
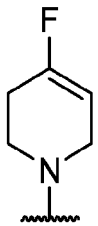
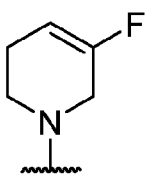
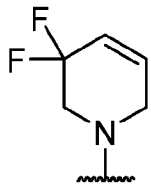
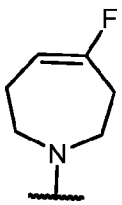
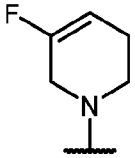
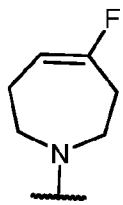
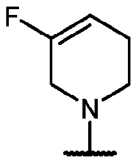
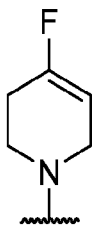


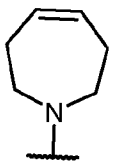
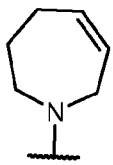


**[00230]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted unsaturated 6- to 8-membered heterocycle. In some cases, $R^1$ is selected from an optionally substituted unsaturated 6-membered heterocycle. In some cases, $R^1$ is selected from an optionally substituted unsaturated 7-membered heterocycle. In some cases, the heterocycle has 1 or 2 double bonds. In some cases, the heterocycle has only 1 double bond. In some cases, the heterocycle has only 2 double bonds. In some cases, $R^1$ is selected from  ,  ,  ,  , and  wherein each is optionally substituted with one or more substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from  ,  ,  , and  wherein each is optionally substituted with one or more substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from  ,  ,  , and  , wherein each is optionally substituted with one or more substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$

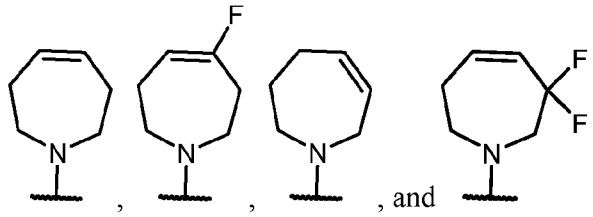
alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from  ,  , and . In some cases, $R^1$ is selected from  ,  , and . In some cases, $R^1$ is selected from . In some cases, $R^1$ is  . In some cases, $R^1$ is selected from  , and  , wherein each is substituted with one or more substituents independently selected from halogen.

**[00231]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an unsaturated 6- to 7-membered heterocycle, wherein the unsaturated 6- to 7-membered heterocycle is substituted with one or more substituents selected from halogen. In some cases, the unsaturated 6- to 7-membered heterocycle is substituted with at least one halogen. In some cases, the unsaturated 6- to 7-membered heterocycle is substituted with at only one halogen. In some cases, the unsaturated 7-membered heterocycle is substituted with one fluorine. In some cases, $R^1$ is selected from an unsaturated 6-membered heterocycle, substituted with at least one halogen. In some cases, $R^1$ is selected from an unsaturated 7-membered heterocycle, substituted with at least

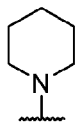
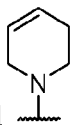
one halogen. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, $R^1$ is selected from  ,  ,  ,  ,  , and  . In some cases, $R^1$ is selected from  ,  , and  . In some cases, $R^1$ is selected from  and  . In some cases, $R^1$ is  . In some cases, $R^1$ is  . In some cases, $R^1$ is  .

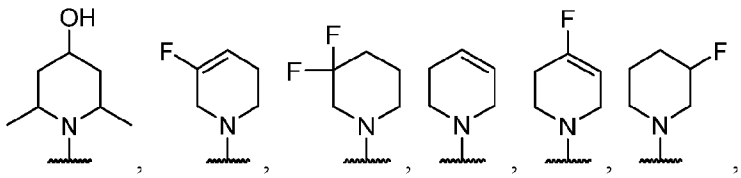
**[00232]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted unsaturated 6- to 8-membered heterocycle. In some cases, $R^1$ is selected from an optionally substituted unsaturated 7-membered heterocycle. In some cases, $R^1$ is selected from  , and  , wherein each is optionally substituted with one or more substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$

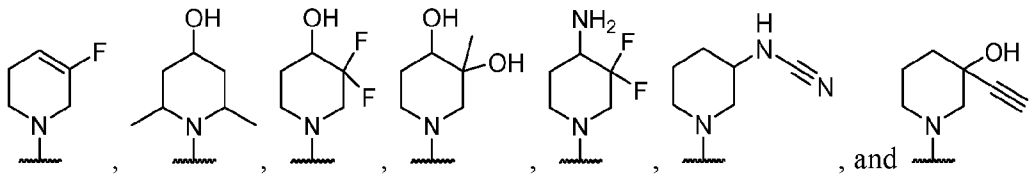
alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from




, , , and .

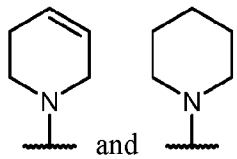
**[00233]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 6-membered heterocycle. In some cases, the 6-membered heterocycle contains only 1 nitrogen atom. In some cases, the 6-membered heterocycle of $R^1$ is bound to Formula (I) via the only 1 nitrogen atom. In some cases, $R^1$ is selected from  and  , any of which is optionally substituted. In some cases, the one or more optional substituents of $R^1$ are each independently selected from halogen, $-OR^{20}$, $-N(R^{20})_2$, =O, -CN, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of $R^1$ are each independently selected from fluorine, -OH, $-NH_2$, -NH(CN), =O, -CN, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of $R^1$ are each independently selected from fluorine, -OH, $-NH_2$, -NH(CN), =O, -CN, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the 6-membered heterocycle is a partially unsaturated 6-membered heterocycle or a saturated 6-membered heterocycle. In some cases, the 6-membered heterocycle is partially unsaturated. In some cases, the 6-membered heterocycle is a saturated 6-membered heterocycle. In some cases, the 6-membered heterocycle is a monocyclic 6-membered heterocycle. In some cases, the 6-membered heterocycle is not a bridged heterocycle.

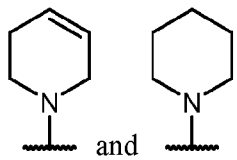
In some cases, $R^1$ is selected from 

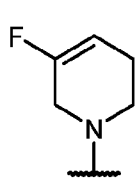
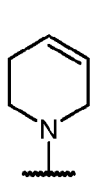
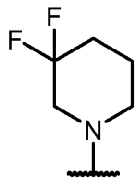

, , , , , , 

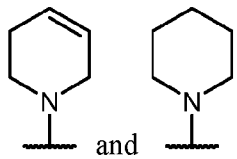

, , , , , , , and .

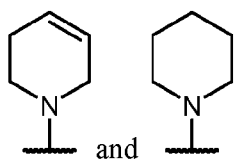
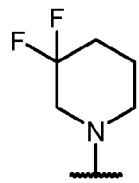
**[00234]** In some embodiments, for a compound of Formula (I), $R^1$ is selected from an optionally substituted 6-membered unsaturated heterocycle and 6-membered saturated heterocycle.

**[00235]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from  and , wherein each is optionally substituted with one or more substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

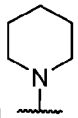
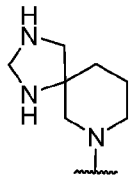
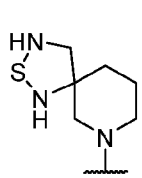
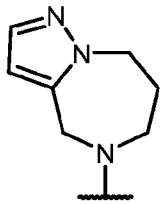
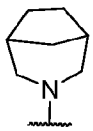
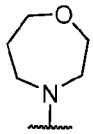
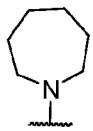
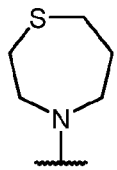
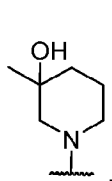
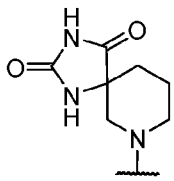
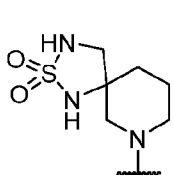
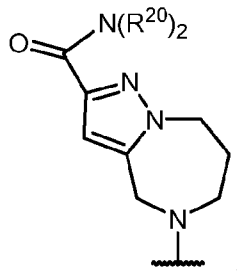
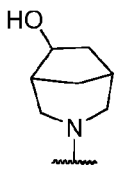
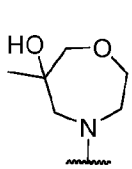
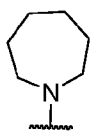
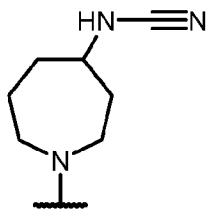
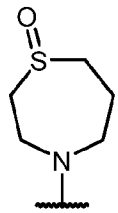
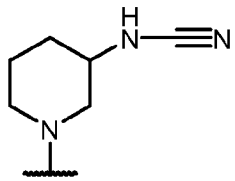
**[00236]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from  and , wherein each is optionally substituted with one or more substituents independently selected from halogen, and $C_{1-6}$ haloalkyl.

**[00237]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from  ,  , and  .

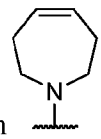
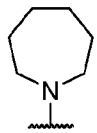
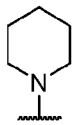
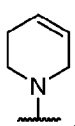
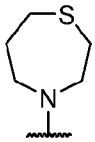
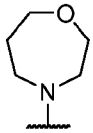
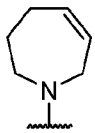
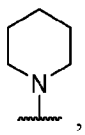
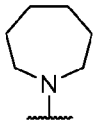
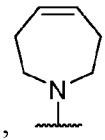
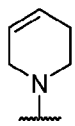
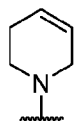
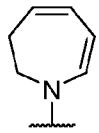
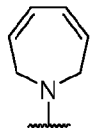
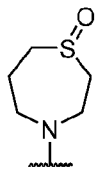
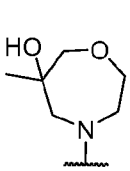
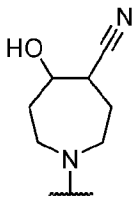
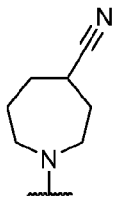
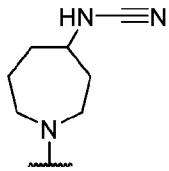
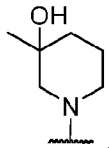
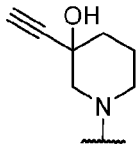
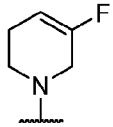
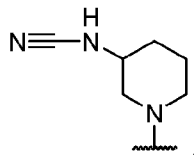
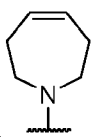
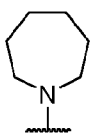
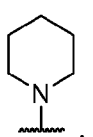
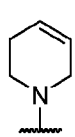
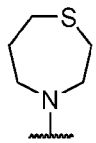
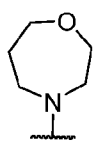
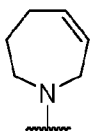
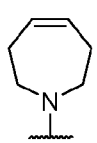
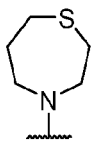
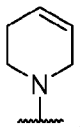
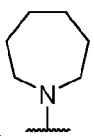
**[00238]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from  and , wherein each is optionally substituted two substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

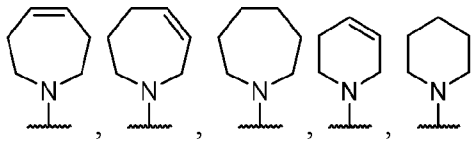
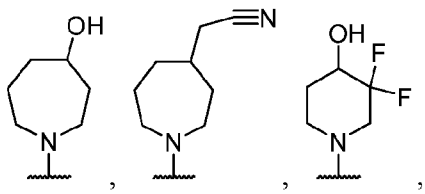
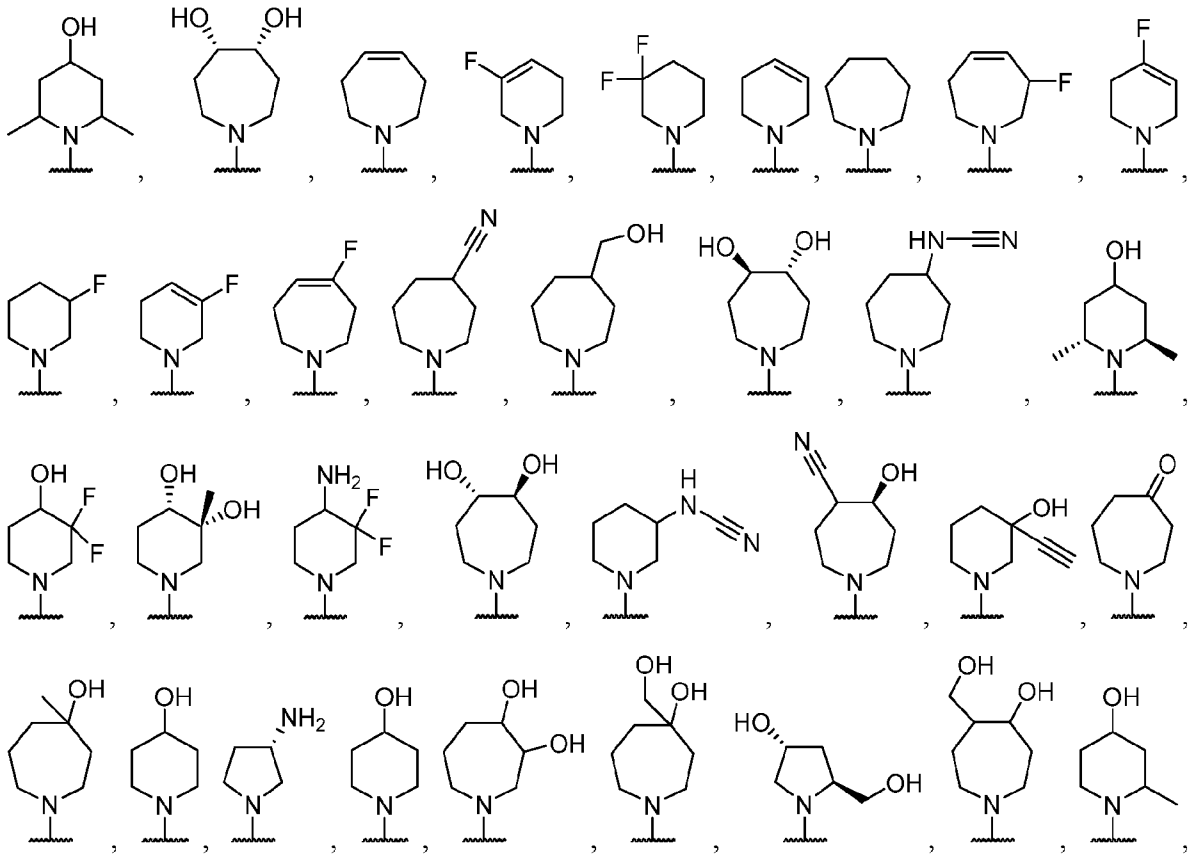
**[00239]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from  and , wherein each is optionally substituted with two substituents independently selected from halogen, and $C_{1-6}$ haloalkyl. In some cases, $R^1$ is  .

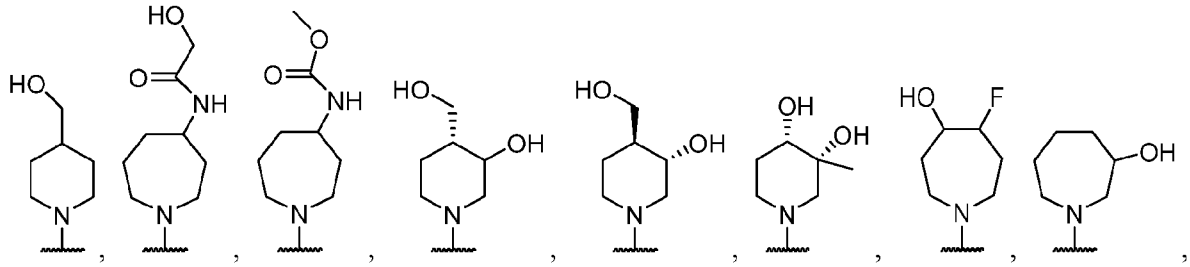
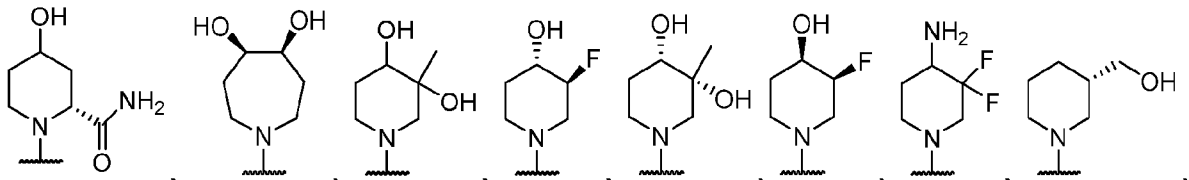
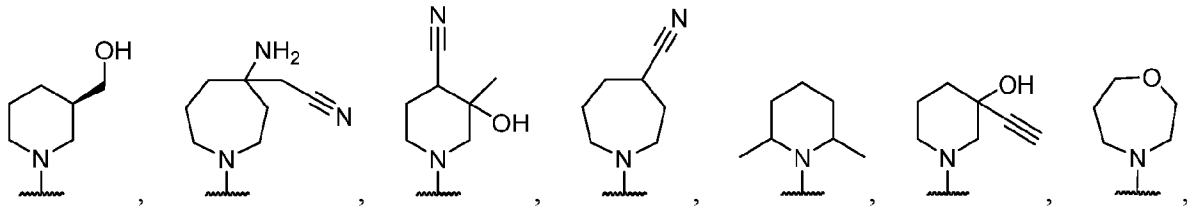
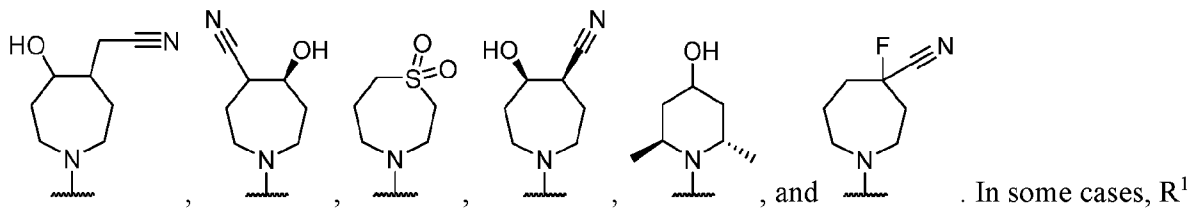
**[00240]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 6- to 10-membered heterocycle. In some cases, the 6- to 10-membered

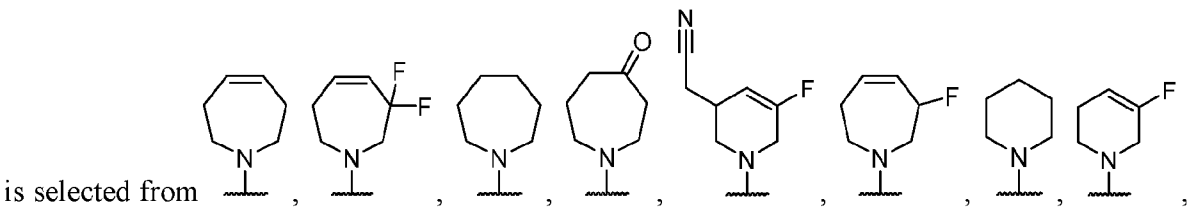
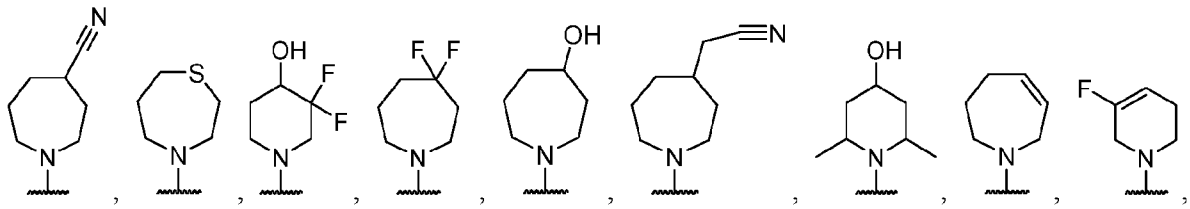
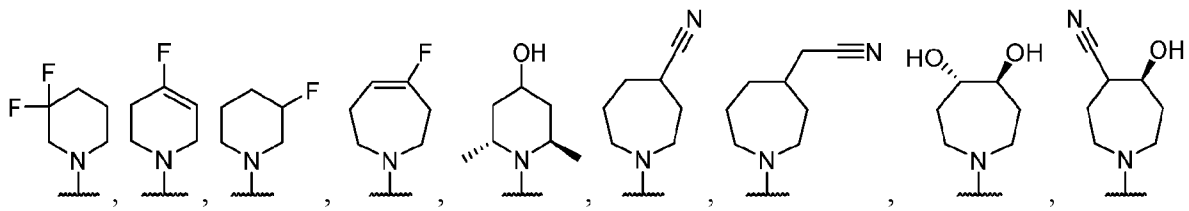
heterocycle contains at least 1 nitrogen atom. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted with one or more substituents independently selected from halogen, =O, -OH, -CN, -NHCN, -C(O)N($R^{20}$)$_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

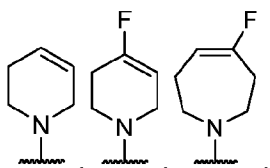
**[00241]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from 6- to 7-membered heterocycle. In some cases, $R^1$ is selected from 7-membered heterocycle. In some cases, $R^1$ is selected from 6-membered heterocycle. In some cases, the 6- to 7-membered heterocycle contains only 1 nitrogen atom and optionally one or more additional heteroatoms selected from oxygen, and sulfur. In some cases, the optionally one or more additional heteroatoms are selected from sulfur. In some cases, the optionally one or more additional heteroatoms are selected from oxygen. In some cases, the 6- to 7-membered heterocycle contains only 1 nitrogen atom and no further additional heteroatoms. In some cases, the 6- to 7-membered heterocycle is a

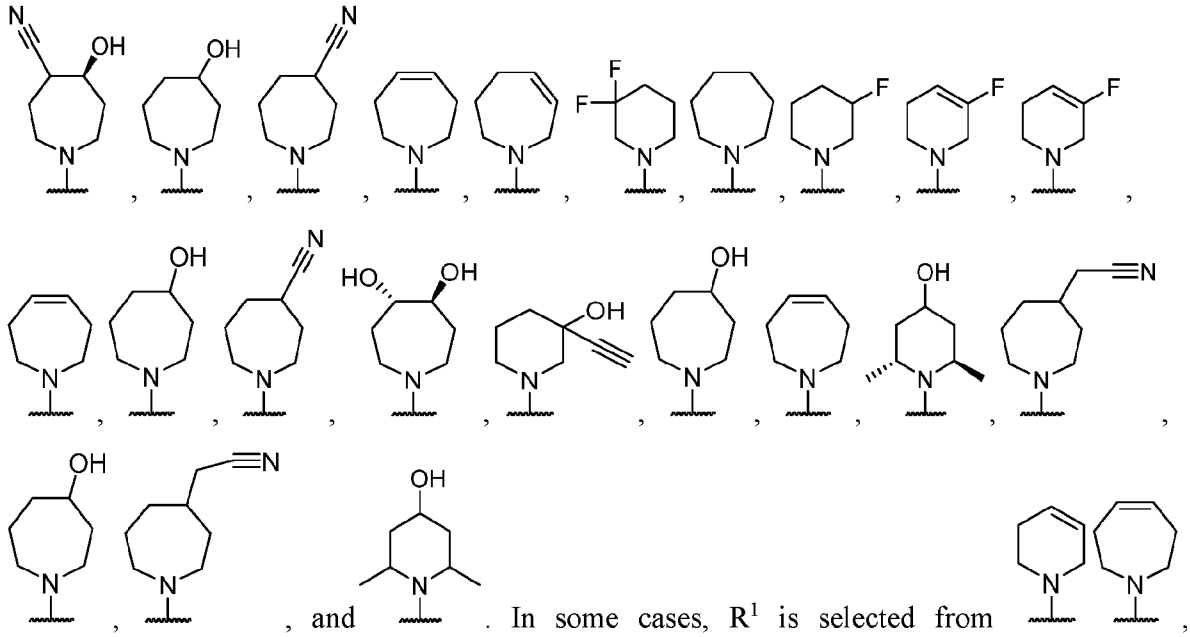
non-aromatic 6- to 7-membered heterocycle. In some cases, the 6- to 7-membered heterocycle of $R^1$ is bound to Formula (I) via the only 1 nitrogen atom. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  , and  , each of which is substituted. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  , and  , each of which is substituted. In some cases, the substituents of $R^1$ are each selected from one or more halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, -NHCN, $-NO_2$, =O, -CN, $C_{1-6}$ fluoroalkyl, and $C_{2-6}$ alkynyl; and further optionally substituted with one or more substituents independently selected from $-C(O)N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkenyl. In some cases, the substituents of $R^1$ are each selected from one or more halogen, $-OR^{20}$, $-N(R^{20})_2$, -NHCN, =O, -CN, and $C_{2-6}$ alkynyl; and further optionally substituted with one or more substituents independently selected from $-C(O)N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, the substituents of $R^1$ are each selected from one or more halogen, -OH, -NHCN, =O, -CN, and $C_{2-6}$ alkynyl; and further optionally substituted with one or more substituents independently selected from $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted. In some cases, $R^1$ is selected from  ,  ,  , and  , each of which is optionally substituted. In some cases, $R^1$ is

selected from  each of which is optionally substituted. In some cases, the one or more optional substituents of $R^1$ are each independently selected from fluorine, -OH, -C(O)$NH_2$, -NH-C(O)-($C_{1-6}$ alkoxy), -NH-C(O)-($C_{1-6}$ hydroxyalkyl), -$NH_2$, -NH(CN), =O, -CN, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of $R^1$ are each independently selected from halogen, -OH, -CN, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of $R^1$ are each independently selected from halogen, -OH, and -CN. In some cases, the one or more optional substituents of $R^1$ are each independently selected from fluorine, -OH, -CN, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, oxo, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of $R^1$ are each independently selected from fluorine, -OH, -CN, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, $R^1$ is selected from  , 

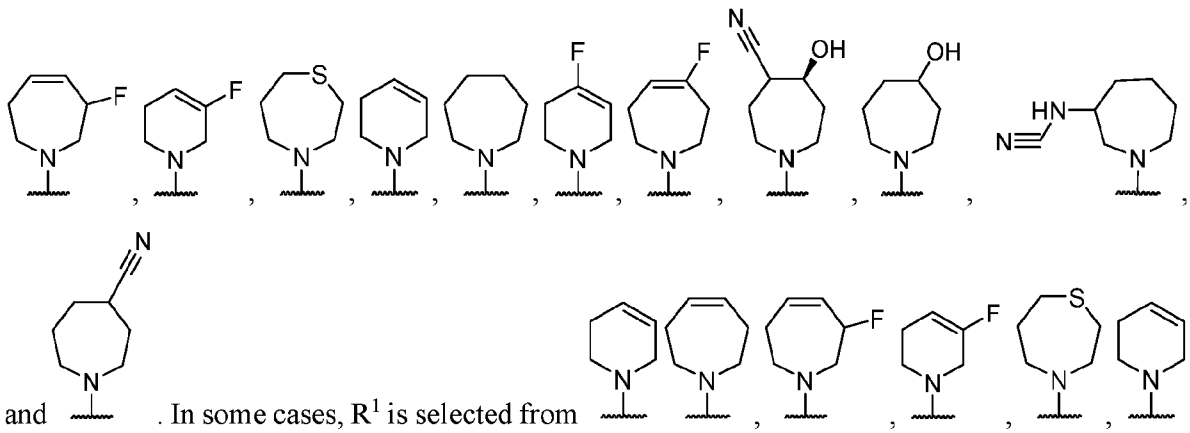




, and . In some cases, $R^1$ is selected from




, and . In some cases, $R^1$ is selected from


.



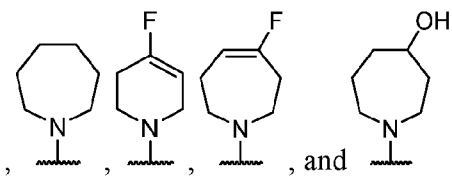
. In some cases, $R^1$ is selected from



and



. In some cases, $R^1$ is selected from

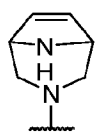


, and



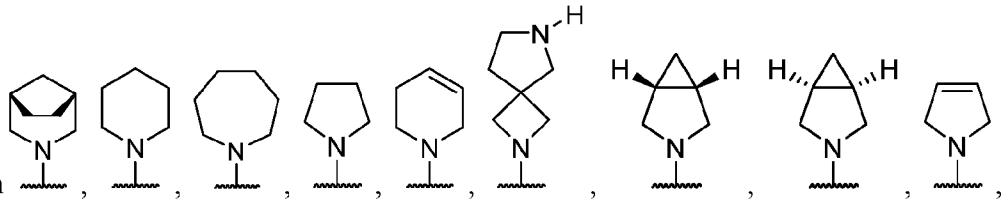
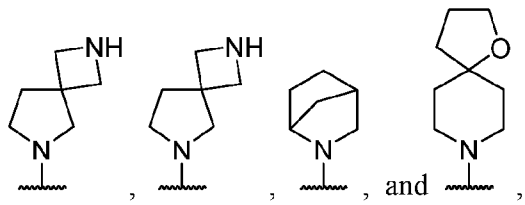
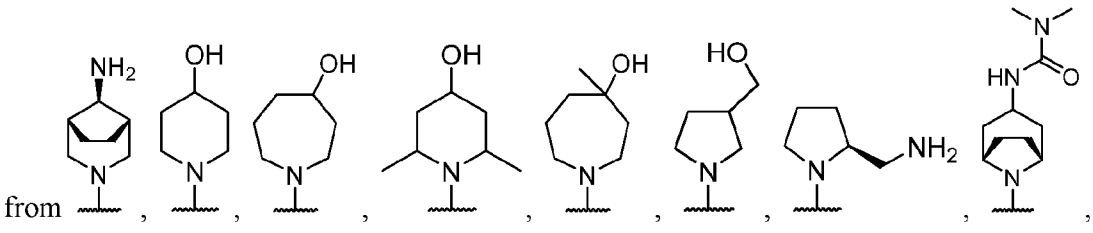
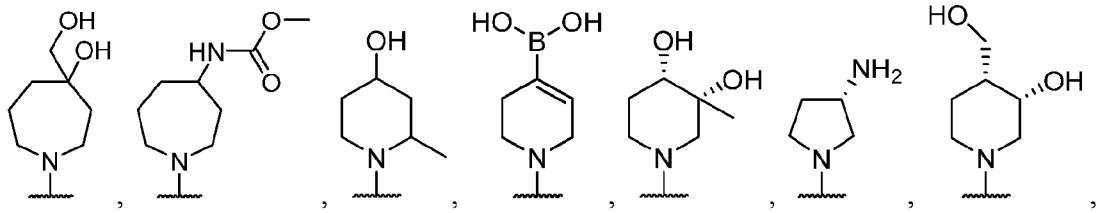
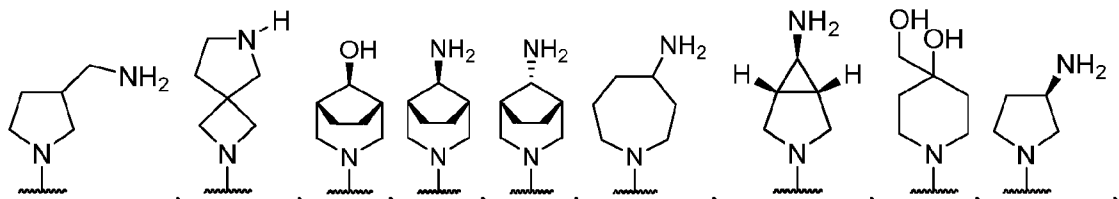
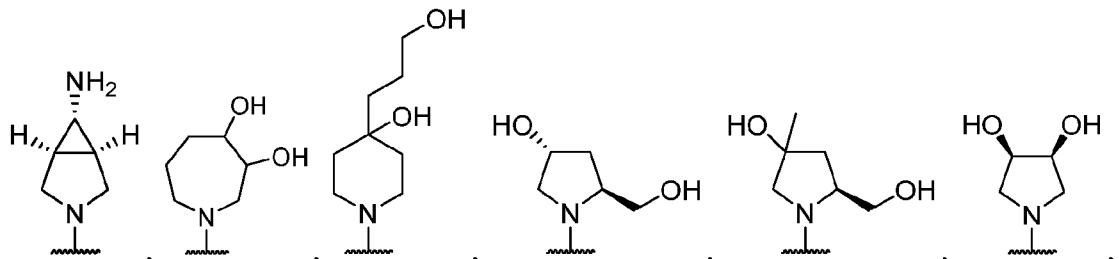
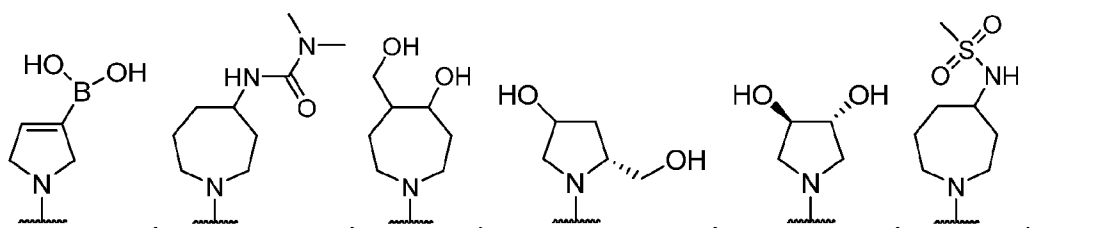
.

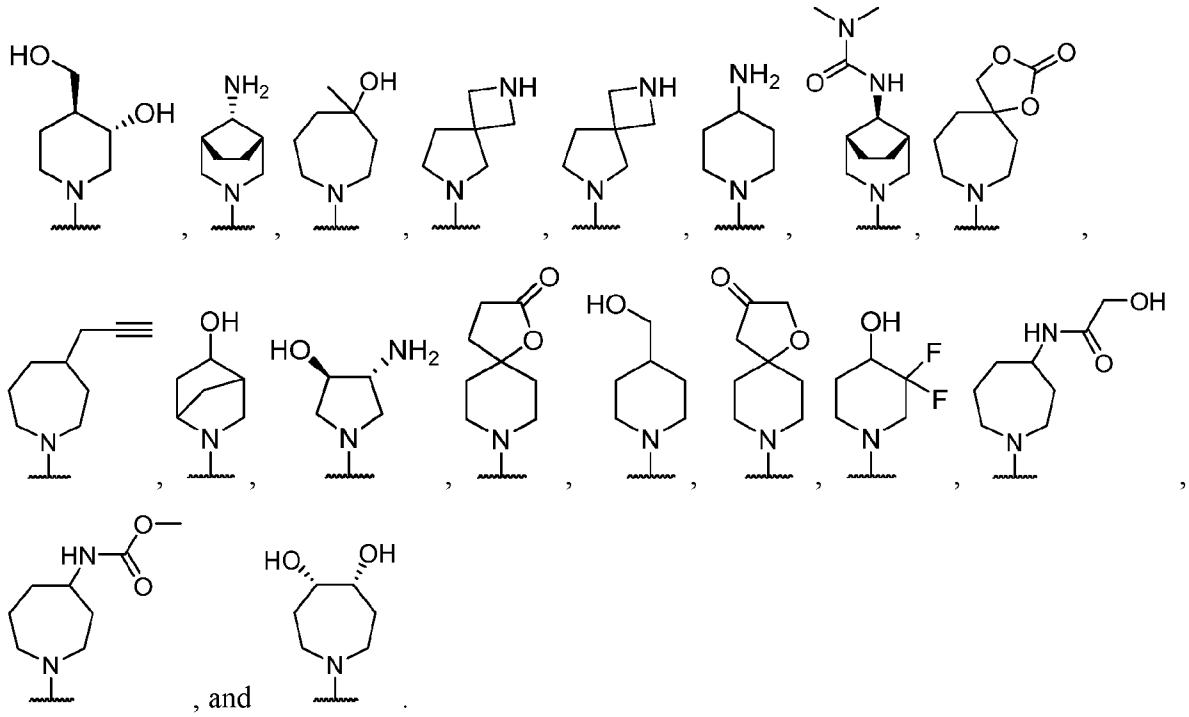
**[00242]** In some embodiments, for a compound or salt of Formula (I), the 5- to 12-membered heterocycle of $R^1$ is unsaturated and a bridged heterocycle. In some cases, $R^1$ is selected from an optionally substituted 7- to 8-membered unsaturated and bridged heterocycle. In some cases, $R^1$ is selected from



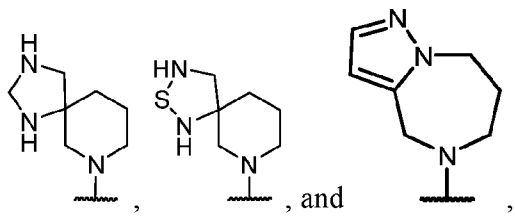
.

**[00243]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from 5- to 10-membered heterocycle, 7-, 8-, 10-, 11-membered spiro heterocycle, and 6-, 9-, 10-, 11-, and 12-membered fused heterocycle, and wherein each are optionally substituted with one or more substituents independently selected from halogen, $-N(R^{20})_2$, $C_{1-6}$ alkyl, $-OR^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-B(OR^{20})_2$, $C_{1-6}$ cyanoalkyl, $-N(R^{20})C(O)N(R^{20})_2$, =O, $C_{1-6}$ hydroxyalkyl,

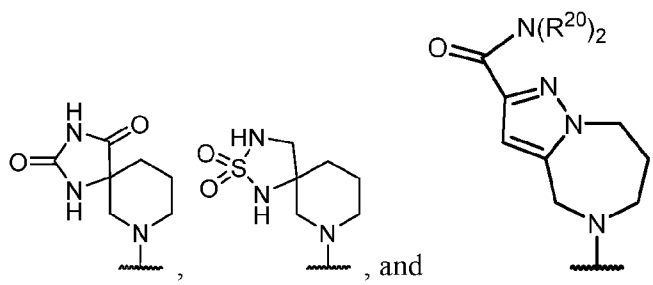
halogen, -N($R^{20}$)C(O)$R^{20}$, -N($R^{20}$) S(O)$_2$($R^{20}$), and $C_{1-6}$ aminoalkyl. In some cases, $R^1$ is selected from  ,  , and , wherein each is optionally substituted with one or more substituents independently selected from halogen, -N($R^{20}$)$_2$, $C_{1-6}$ alkyl, -O$R^{20}$, -N($R^{20}$)C(O)N($R^{20}$)$_2$, -B(O$R^{20}$)$_2$, $C_{1-6}$ cyanoalkyl, -N($R^{20}$)C(O)N($R^{20}$)$_2$, =O, $C_{1-6}$ hydroxyalkyl, halogen, -N($R^{20}$)C(O)$R^{20}$, -N($R^{20}$) S(O)$_2$($R^{20}$), and $C_{1-6}$ aminoalkyl. In some cases, $R^1$ is selected from  ,  ,  ,  ,  .



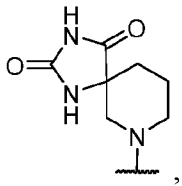
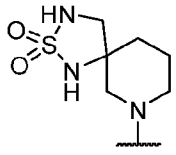
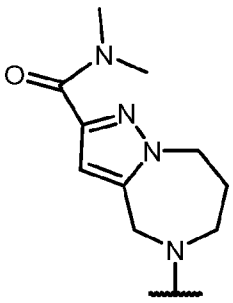
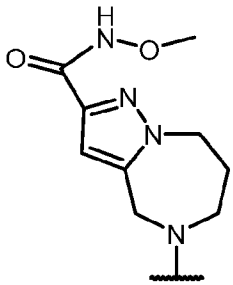
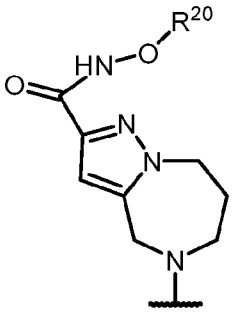
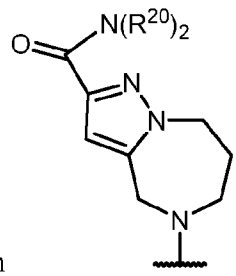
**[00244]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 10-membered heterocycle. In some cases, the 10-membered heterocycle is a bicyclic heterocycle. In some cases, the 10-membered heterocycle is a spiro heterocycle. In some cases, the 10-membered heterocycle is a fused heterocycle. In some cases, the 10-membered heterocycle is a saturated heterocycle. In some cases, the 10-membered heterocycle is a non-aromatic heterocycle. In some cases, the 10-membered heterocycle contains at least 1 nitrogen atom. In some cases, the 10-membered heterocycle contains at least 2 nitrogen atoms. In some cases, the 10-membered heterocycle contains at least 3 nitrogen atoms. In some cases, the 10-membered heterocycle contains at least 1 sulfur atom. In some cases, $R^1$ is selected from

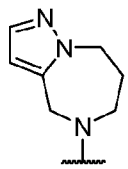
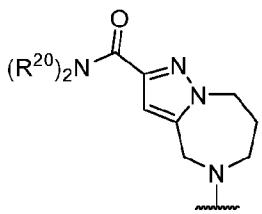


, each of which is optionally substituted with one or more substituents independently selected from halogen, =O, -OH, -CN, -NHCN, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from

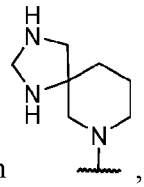
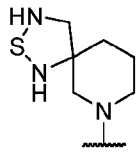
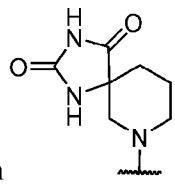
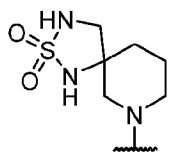
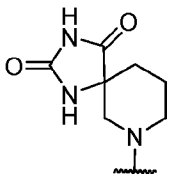
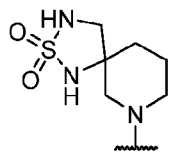


. In some cases,

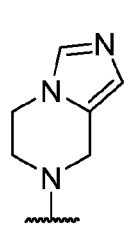
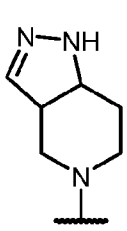
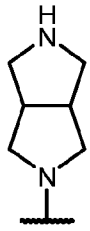
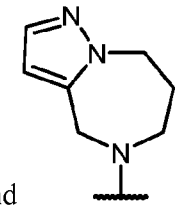
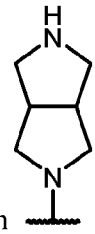
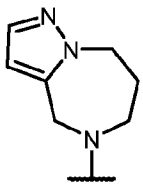
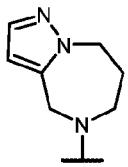
$R^1$ is selected from  , and  . In some cases, $R^1$ is selected from  and  . In some cases, $R^1$ is selected from  . In some cases, $R^1$ is selected from  , which is optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-SR^{20}$, $-N(R^{20})_2$, $-NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl.

**[00245]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted unsaturated 9- to 11-membered heterocycle. In some cases, $R^1$ is selected from an optionally substituted unsaturated 10-membered heterocycle. In some cases, $R^1$ is selected from an optionally substituted unsaturated 10-membered fused heterocycle. In some cases, $R^1$ is  , which is optionally substituted. In some cases, the one or more optional substituents are selected from halogen, -OH, $-C(O)N(R^{20})_2$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, $R^1$ is  , optionally substituted with one or more substituents selected from $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$

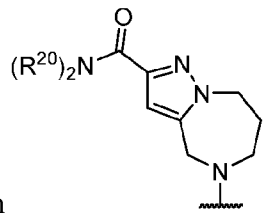
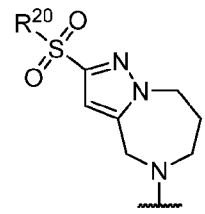
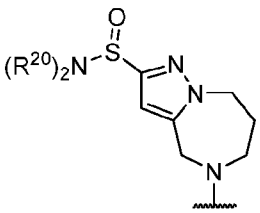
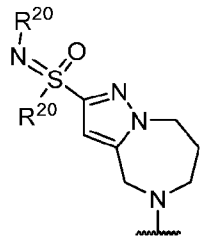
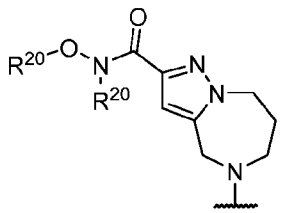
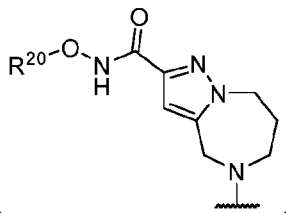
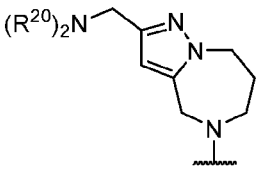
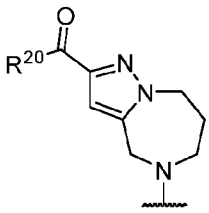
hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and $C_{3-12}$ carbocycle, and each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle.

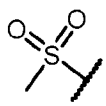
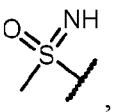
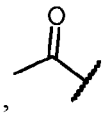
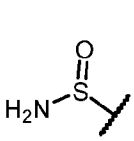
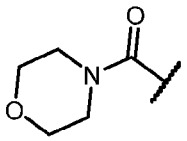
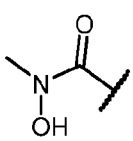
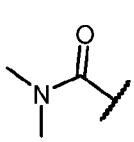
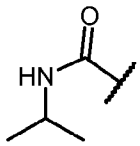
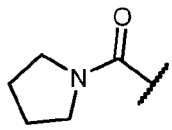
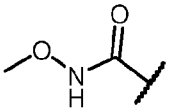
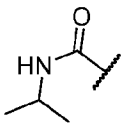
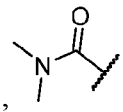
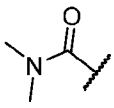
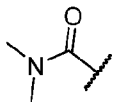
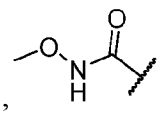
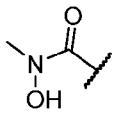
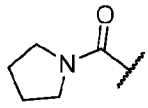
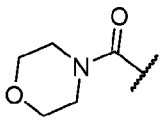
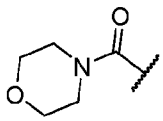
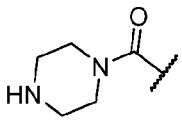
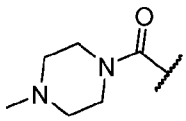
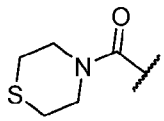
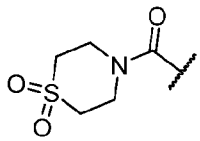
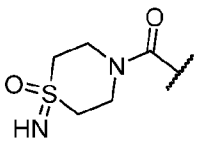
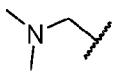
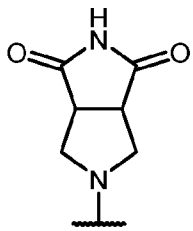
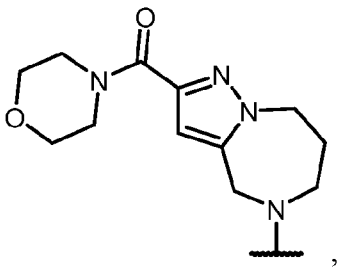
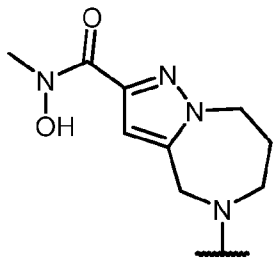
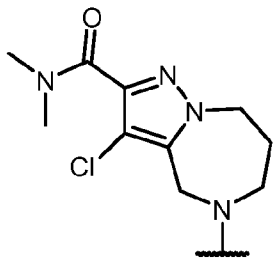
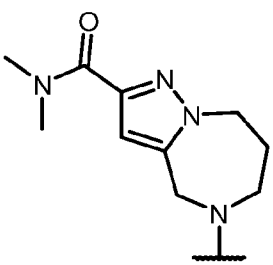
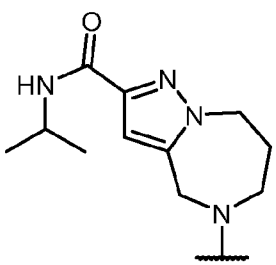
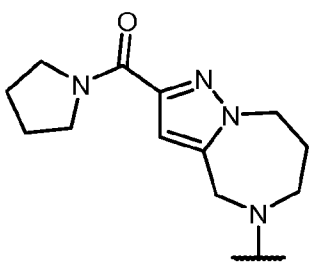
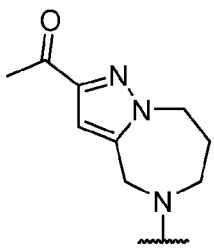
**[00246]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from a 7- to 11-membered spiro heterocycle. In some cases, $R^1$ is selected from a 10-membered spiro heterocycle. In some cases, the spiro heterocycle has at least 3 nitrogen atoms. In some cases, the spiro heterocycle has at least 1 sulfur atom. In some cases, $R^1$ is selected from  , and  , each of which is optionally substituted. In some cases, the one or more optional substituents are independently selected from halogen, -OH, $-N(R^{20})_2$, $-NO_2$, =O, -CN, -NHCN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl. In some cases, $R^1$ is selected from  , and  . In some cases, $R^1$ is  . In some cases, $R^1$ is  .

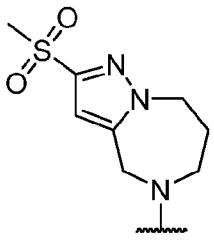
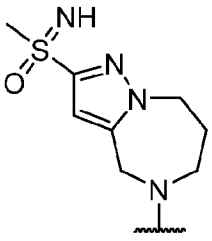
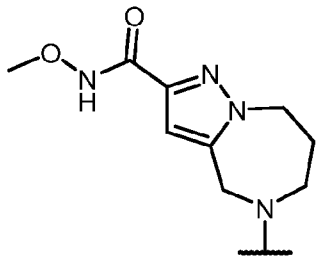
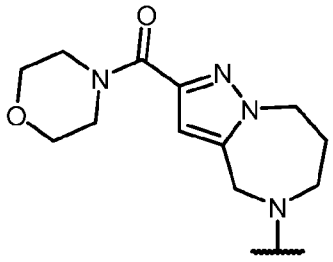
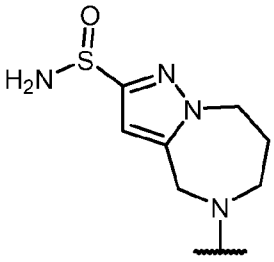
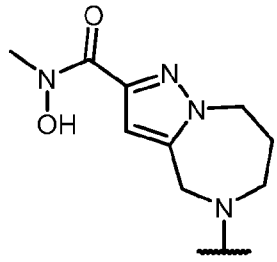
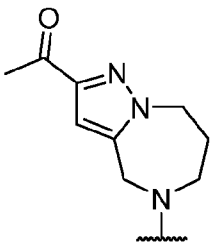
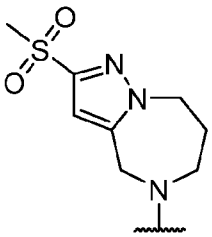
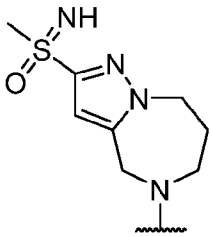
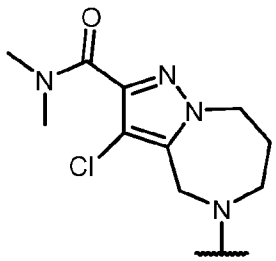
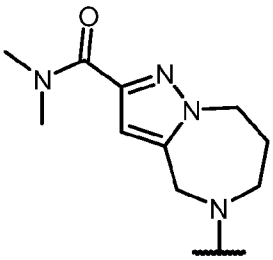
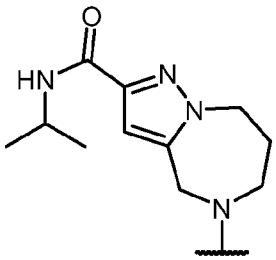
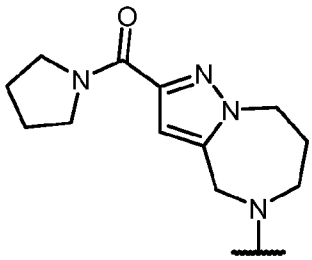
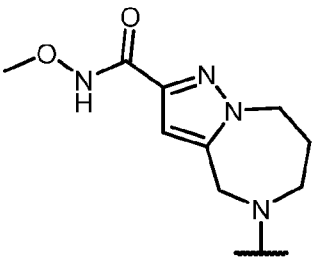
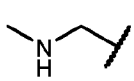
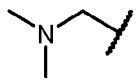
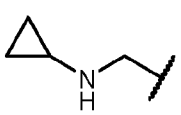
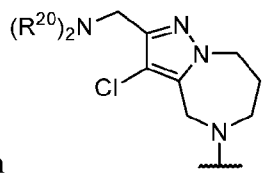
**[00247]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 8- to 10-membered fused heterocycle. In some cases, the 8- to 10-membered fused heterocycle is a bicyclic heterocycle. In some cases, the 8- to 10-membered fused heterocycle is a saturated heterocycle. In some cases, the 8- to 10-membered fused heterocycle is an unsaturated heterocycle. In some cases, the 8- to 10-membered heterocycle is a non-aromatic heterocycle. In some cases, $R^1$ is selected from an optionally substituted 10-membered fused heterocycle. In some cases, the 10-membered fused heterocycle is a bicyclic heterocycle. In some cases, the 10-membered fused heterocycle is a saturated heterocycle. In some cases, the 10-membered heterocycle is a non-aromatic heterocycle. In some cases, the fused heterocycle has one saturated ring and one aromatic ring. In some cases, the fused

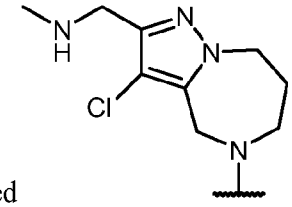
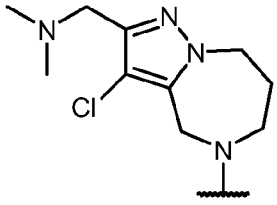
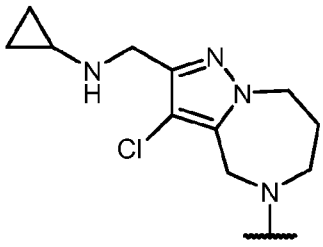
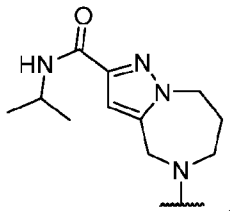
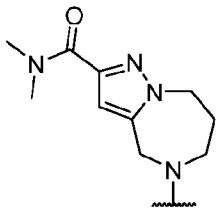
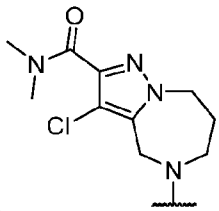
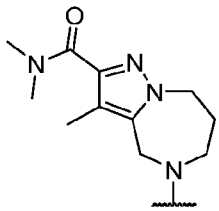
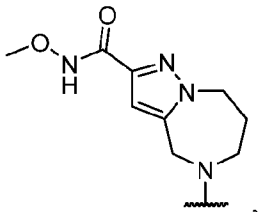
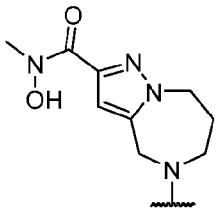
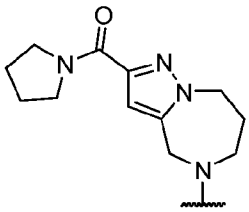
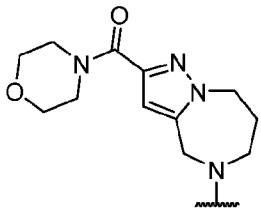
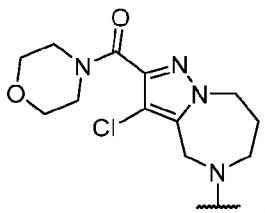
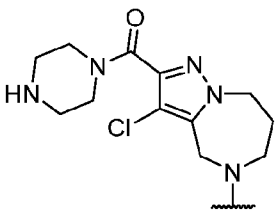
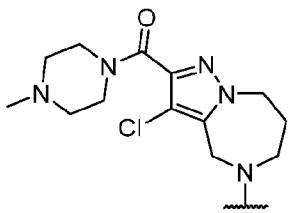
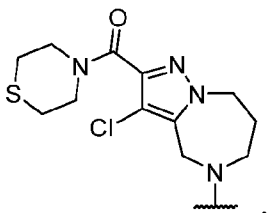
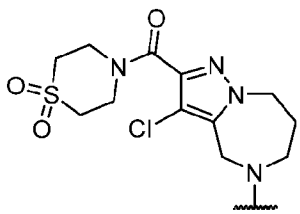
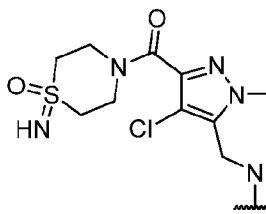
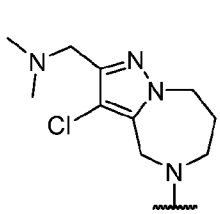
heterocycle has one saturated ring and one unsaturated ring. In some cases, the fused heterocycle has two saturated rings. In some cases, the 10-membered heterocycle contains at least 1 nitrogen atom. In some cases, the 10-membered heterocycle contains at least 2 nitrogen atoms. In some cases, the 10-membered heterocycle contains at least 3 nitrogen atoms. In some cases, $R^1$ is selected from  ,  ,  , and  , each of which is optionally substituted with one or more substituents. In some cases, $R^1$ is selected from  and  , each of which is optionally substituted with one or more substituents. In some cases, $R^1$ is  , which is optionally substituted with one or more substituents. In some cases, the one or more optional substituents of $R^1$ are independently selected from halogen, -OH, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$C(O)N(R^{20})_2$, -$C(O)NHOR^{20}$, -$N(R^{20})_2$, -$C(O)R^{20}$, -$NO_2$, =O, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the optional one or more substituents are independently selected from halogen, =O, -OH, -CN, -NHCN, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$C(O)R^{20}$, -$C(O)N(R^{20})_2$, -$C(O)NR^{20}OR^{20}$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, the optional one or more substituents are independently selected from halogen, =O, $C_{1-6}$ alkyl-$N(R^{20})_2$, -$S(O)_2(R^{20})$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$C(O)R^{20}$, -$C(O)N(R^{20})_2$, and -$C(O)NR^{20}OR^{20}$. In some cases, the optional one or more substituents are independently selected from halogen, =O, -$S(O)_2(R^{20})$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$C(O)R^{20}$, -$C(O)N(R^{20})_2$, and -$C(O)NR^{20}OR^{20}$. In some cases, the optional one or more substituents are independently selected from -$C(O)R^{20}$, -$C(O)N(R^{20})_2$, and -$C(O)NR^{20}OR^{20}$. In some cases, the optional one or more substituents are independently selected

from -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$. In some cases, the optional one or more substituents are independently selected from -$S(O)N(R^{20})_2$. In some cases, the optional one or more substituents are independently selected from $S(O)_2(R^{20})$. In some cases, the optional one or more substituents are independently selected from $S(O)R^{20}(=NR^{20})$. In some cases, the optional one or more substituents are independently selected from -$C(O)R^{20}$. In some cases, the optional one or more substituents are independently selected from -$C(O)N(R^{20})_2$. In some cases, the optional one or more substituents are independently selected from -$C(O)NR^{20}OR^{20}$. In some cases, $R^1$ is selected from

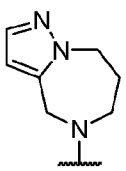

,

,

,

,

,

,

, and

, each of which is further optionally substituted. In some cases, the further one or more optional substituents are selected from halogen, -OH, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the further one or more optional substituents are selected from halogen and $C_{1-6}$ alkyl. In some cases, the further one or more optional substituents are selected from halogen. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and 3- to 12-membered heterocycle. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and 3- to 12-membered saturated heterocycle. In some cases, each $R^{20}$ is independently selected from 5- to 6-membered saturated heterocycle. In some cases, the heterocycle of $R^{20}$ has at least one nitrogen atom. In some cases, the heterocycle of $R^{20}$ has at least one sulfur atom. In some cases, the heterocycle of $R^{20}$ has at least one oxygen atom. In some cases, the heterocycle of $R^{20}$ contains only 1 heteroatom. In some cases, the heterocycle of $R^{20}$ has at least two heteroatoms. In some cases, the heterocycle of $R^{20}$ contains only 2 heteroatoms. In some cases, the optional one or

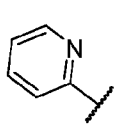
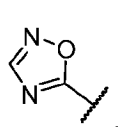
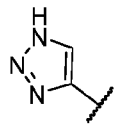
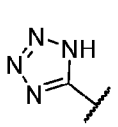
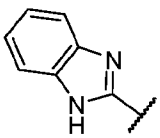
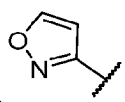
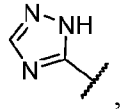
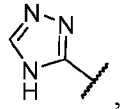
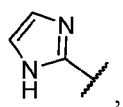
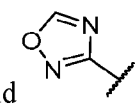
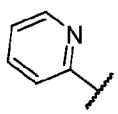
more substituents of $R^1$ are independently selected from halogen,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, the optional one or more substituents of $R^1$ are independently selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,

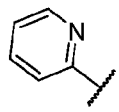
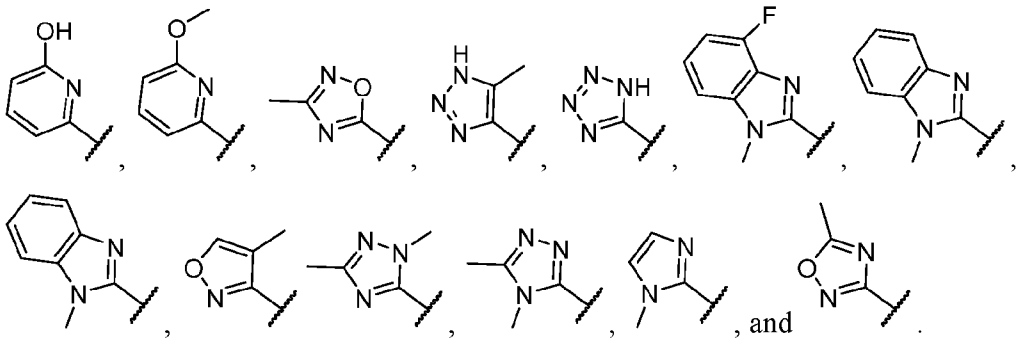

,

, and

. In some cases, $R^1$ is selected from

,

,

,

,

,

,

,

,

,

, and

. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen, and $C_{1-6}$ alkyl-$N(R^{20})_2$. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen,

,

, and

. In some cases, $R^1$ is selected from

. In some cases, each $R^{20}$ is independently selected from hydrogen, $C_{1-6}$ alkyl, and $C_{3-6}$ carbocycle. In some cases, $R^1$ is

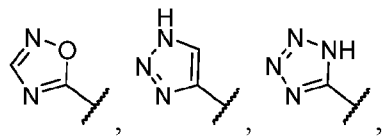
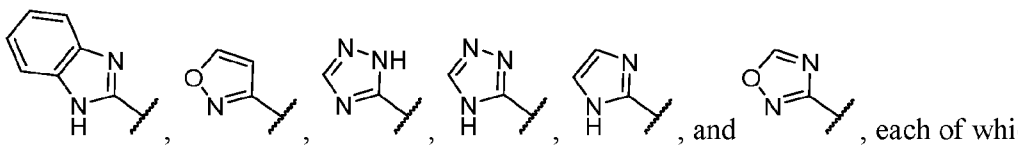
selected  ,  , and  . In some cases, $R^1$ is selected  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

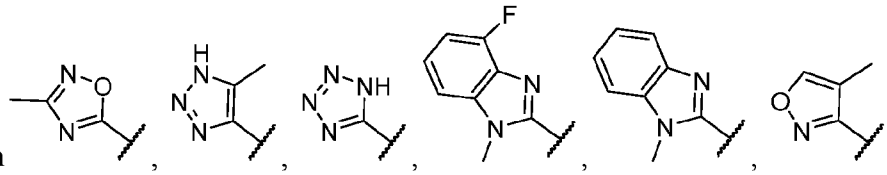
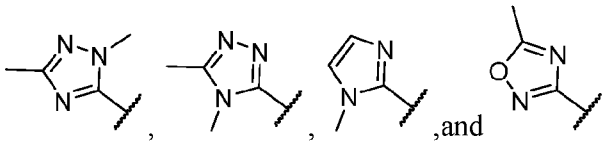
**[00248]** In some embodiments, for a compound or salt of Formula (I), when $R^1$ is substituted with $-C(O)R^{20}$, $R^{20}$ is selected from a 5- to 12-membered heterocycle.

**[00249]** In some embodiments, for a compound or salt of Formulas (I), (I-A), or (I-B)$R^1$ is  , and the one or more optional substituents of $R^1$ are independently selected from halogen, -OH, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(=NR^{20})N(R^{20})_2$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, and optionally substituted 5- to 12-membered heterocycle. In some cases, the one or more optional substituents of $R^1$ are independently selected from halogen, -OH, -

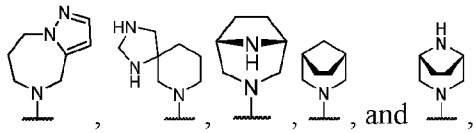
$S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(=NR^{20})N(R^{20})_2$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, and optionally substituted 5- to 12-membered heterocycle. In some cases, the one or more optional substituents of $R^1$ are independently selected from halogen, -CN, $C_{2-6}$ alkynyl, $-C(=NR^{20})N(R^{20})_2$, and optionally substituted 5- to 12-membered heterocycle. In some cases, the one or more optional substituents of $R^1$ are independently selected from halogen, $-C(=NR^{20})N(R^{20})_2$, and optionally substituted 5- to 12-membered heterocycle. In some cases, the one or more optional substituents of $R^1$ are independently selected from $-C(=NR^{20})N(R^{20})_2$, and optionally substituted 5- to 12-membered heterocycle. In some cases, the one or more optional substituents of $R^1$ are independently selected from optionally substituted 5- to 12-membered heterocycle. In some cases, the one or more optional substituents of $R^1$ are independently selected from a 5-membered heterocycle and 9-membered heterocycle, each of which is optionally substituted independently with one or more $R^{1*}$. In some cases, $R^1$ is substituted with at least one halogen atom and optionally substituted with one or more substituents are independently selected from -CN, $C_{2-6}$ alkynyl, $-C(=NR^{20})N(R^{20})_2$, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted independently with one or more $R^{1*}$. In some cases, the heterocycle has at least one nitrogen atom. In some cases, the heterocycle has at least oxygen atom. In some cases, the heterocycle has at least one nitrogen atom and at least one oxygen atom. In some cases, heterocycle has at least two heteroatoms. In some cases, the heterocycle has at least three heteroatoms. In some cases, the heterocycle has at least four heteroatoms. In some cases, the heterocycle of the one or more optional substituents of $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted with one or more $R^{1*}$. In some cases, the heterocycle of the one or more optional substituents of $R^1$ is selected from  , which is optionally substituted with one or more $R^{1*}$.. In some cases, each $R^{1*}$ is independently selected from halogen, $-OR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-}$

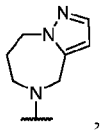
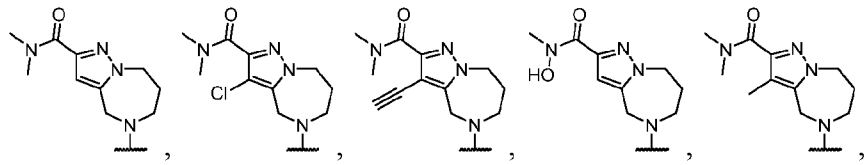
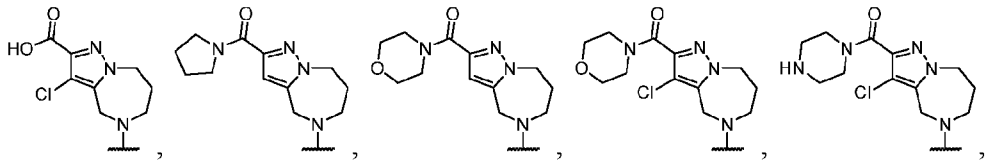
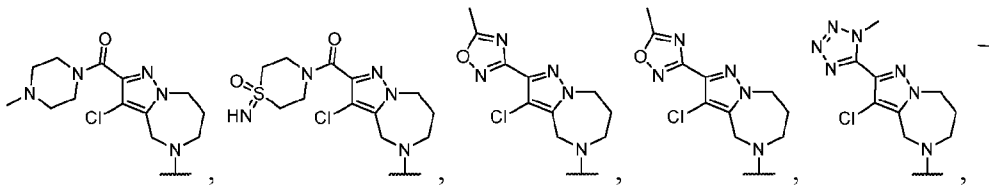
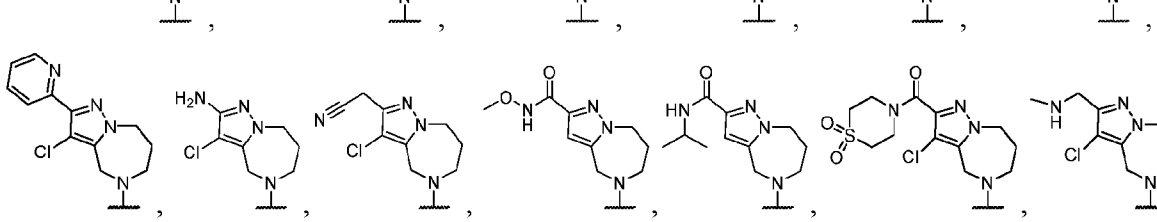
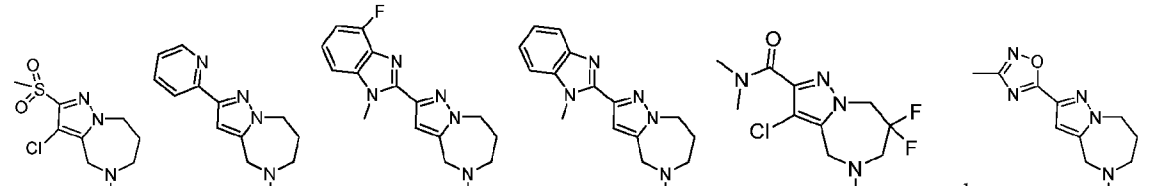
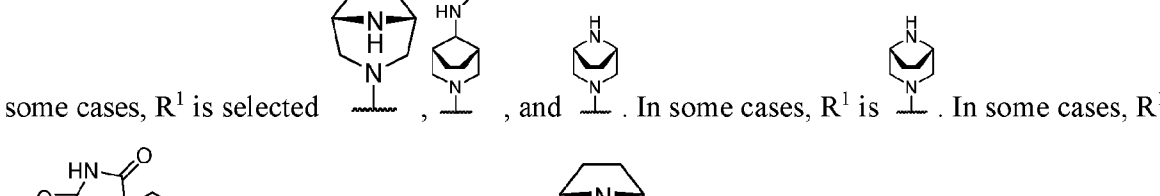
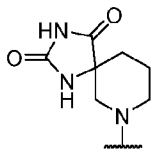
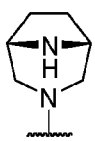
$_{6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, $-OR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen. In some cases, each $R^{1*}$ is independently selected from $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from $-OR^{20}$. In some cases, each $R^{1*}$ is independently selected from -OH. In some cases, each $R^{1*}$ is independently selected from -OMe. In some cases, the heterocycle of the one or more optional substituents of $R^1$ is selected from  ,  , and .

**[00250]** In some embodiments, for a compound or salt of Formulas (I), (I-A), or (I-B), the one or more optional substituents of $R^1$ are independently selected from $-C(=NR^{20})N(R^{20})_2$, and optionally substituted 5- to 12-membered heterocycle. In some cases, the one or more optional substituents of $R^1$ are independently selected from optionally substituted 5- to 12-membered heterocycle. In some cases, the heterocycle is selected from  ,  , and , each of which is optionally substituted with one or more $R^{1*}$. In some cases, the one or more optional substituents

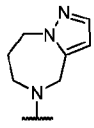
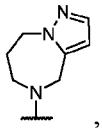
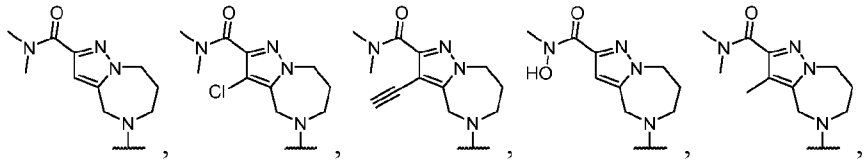
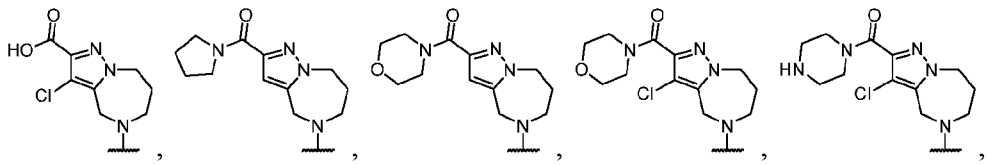
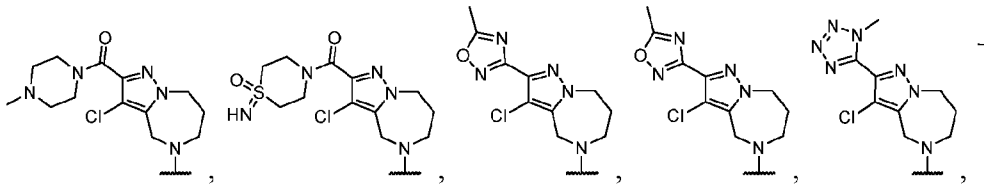
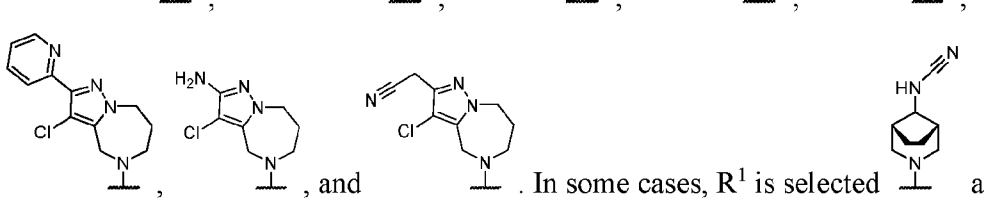
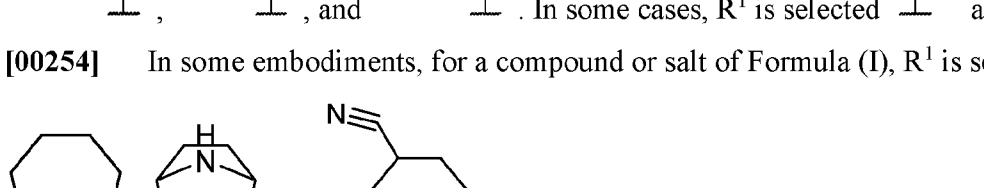
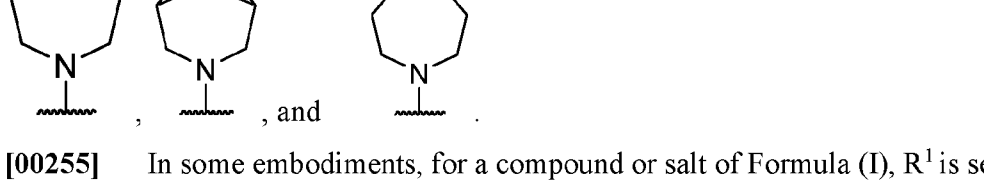
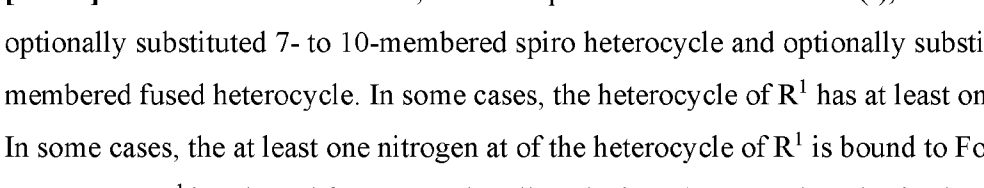
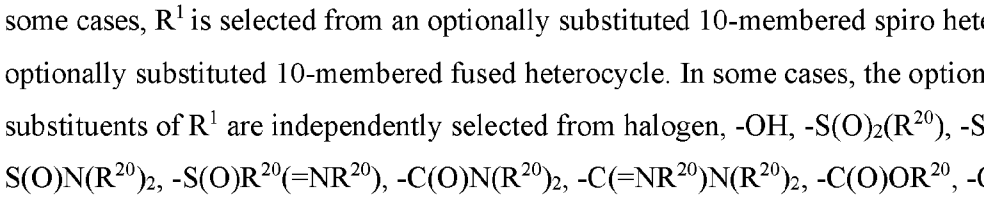
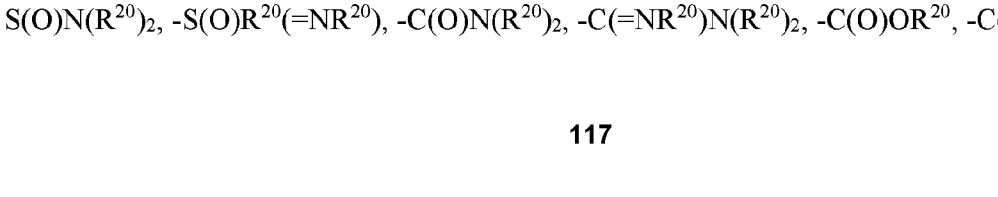
of $R^1$ is selected from  ,  ,and .

**[00251]** In some embodiments, for a compound or salt of Formulas (I), (I-A), or (I-B), each $R^{1*}$ is independently selected from halogen, $-OR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, $-OR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen, and $C_{1-6}$ alkyl. In some cases, each $R^{1*}$ is independently selected from halogen. In some cases, each $R^{1*}$ is independently selected from $C_{1-6}$ alkyl.

**[00252]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from 5- to 15-membered heterocycle (preferably 8- to 10-membered heterocycle or preferably 10-membered heterocycle), each of which are optionally substituted with one or more substituents independently selected from halogen, oxo, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-SO_2R^{20}$, -NHCN, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{2-6}$ alkynyl, and 5- to 12-membered heterocycle (preferably 5- to 9-membered heterocycle), wherein the 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$; each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, the 8- to 10-membered heterocycle is bicyclic. In some cases, the 10-membered heterocycle is substituted. In some cases, $R^1$ is selected  , each of which is

optionally substituted. In some cases, $R^1$ is selected  , which is optionally substituted. In some cases, $R^1$ is selected  ,  ,  ,  , ,  ,  , and . In some cases, $R^1$ is selected , , and . In some cases, $R^1$ is  . In some cases, $R^1$ is selected  .

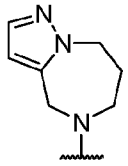
**[00253]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from 5- to 15-membered heterocycle (preferably 8- to 10-membered heterocycle or preferably 10-membered heterocycle or preferably 8-membered heterocycle), each of which are optionally substituted with one or more substituents independently selected from halogen, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, -NHCN, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, and 5- to 12-membered heterocycle (preferably 5- to 6-membered heterocycle), wherein the 5- to 12-membered heterocycle are each optionally substituted independently with one or

more $R^{1*}$; each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, the 8- to 10-membered heterocycle is bicyclic. In some cases, the 10-membered heterocycle is substituted. In some cases, $R^1$ is selected  ,  , and  , each of which is optionally substituted. In some cases, $R^1$ is selected  , which is optionally substituted. In some cases, $R^1$ is selected  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, $R^1$ is selected  and  .

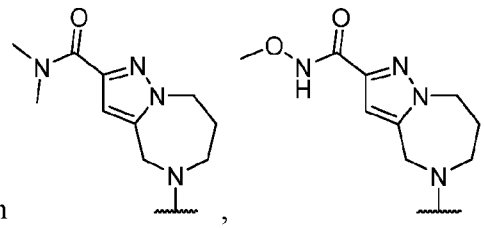
**[00254]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from  ,  , and  .

**[00255]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 7- to 10-membered spiro heterocycle and optionally substituted 7- to 10-membered fused heterocycle. In some cases, the heterocycle of $R^1$ has at least one nitrogen atom. In some cases, the at least one nitrogen at of the heterocycle of $R^1$ is bound to Formula (I). In some cases, $R^1$ is selected from an optionally substituted 10-membered spiro heterocycle and optionally substituted 10-membered fused heterocycle. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen, -OH, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(=NR^{20})N(R^{20})_2$, $-C(O)OR^{20}$, $-C(O)NHOR^{20}$, -

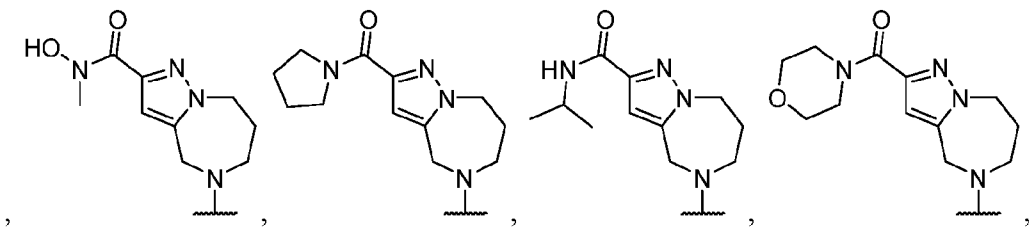
$N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted with one or more substituents selected from halogen, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from



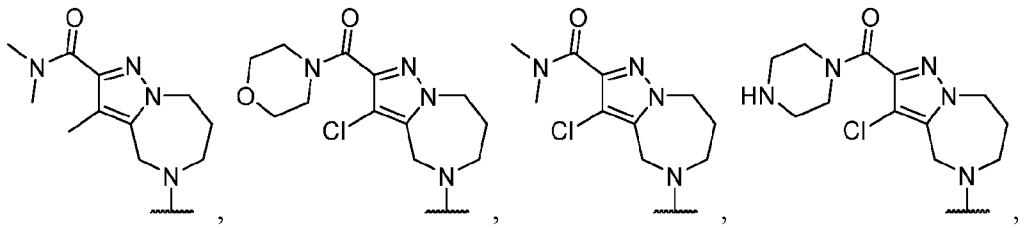
, which is substituted with one or more substituents independently selected from halogen, -OH, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(=NR^{20})N(R^{20})_2$, $-C(O)OR^{20}$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted with one or more substituents selected from halogen, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from



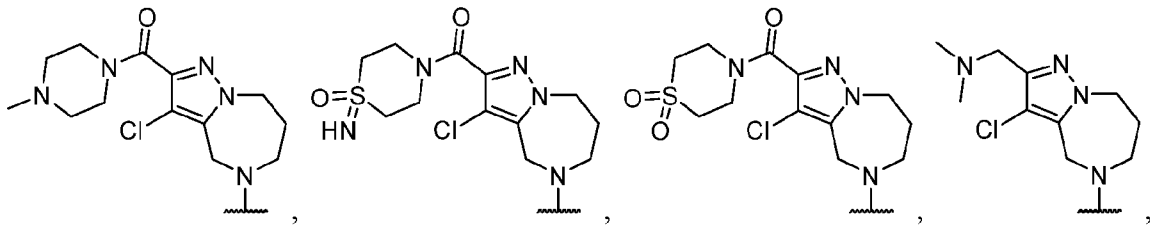
,



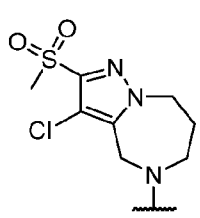
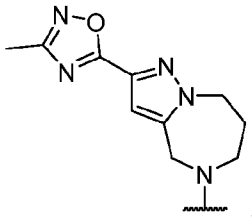
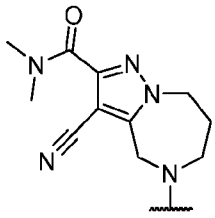
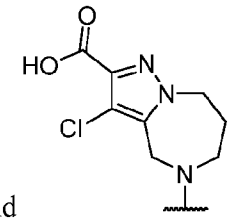
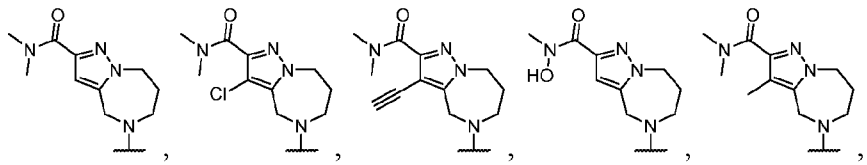
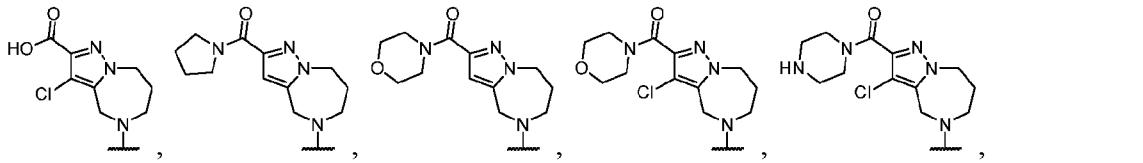
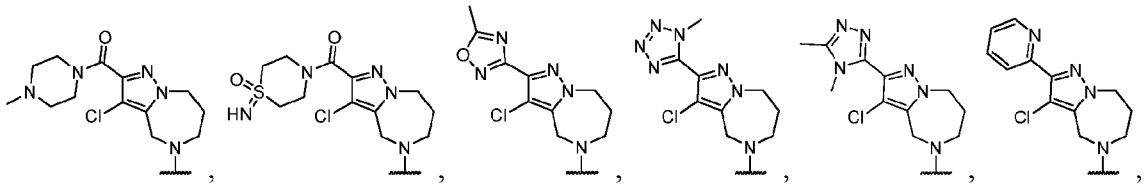
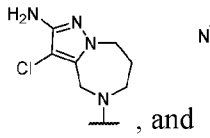
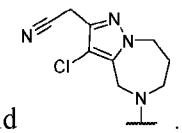
,



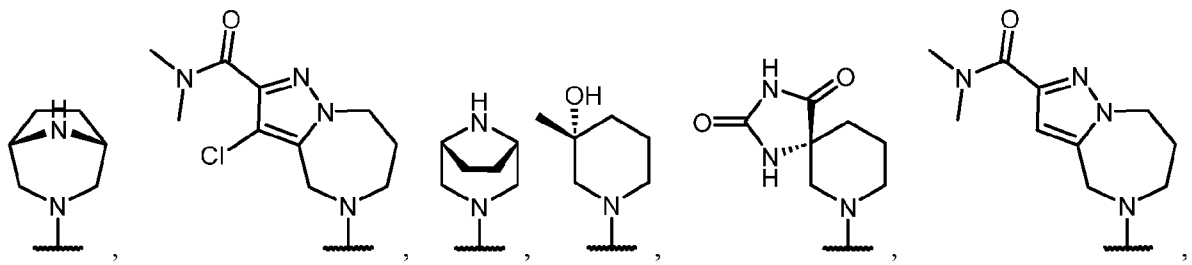
,

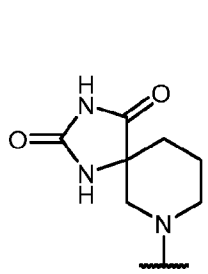
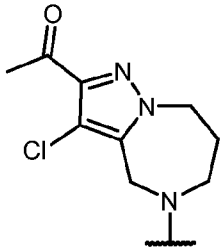
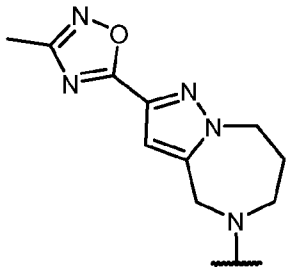
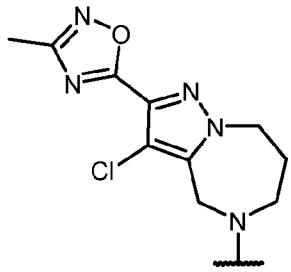
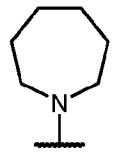
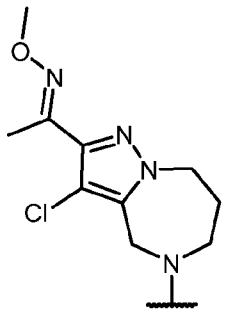
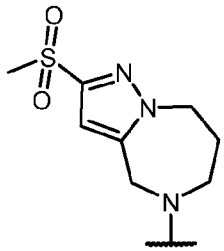
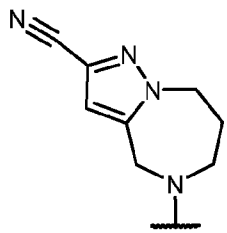
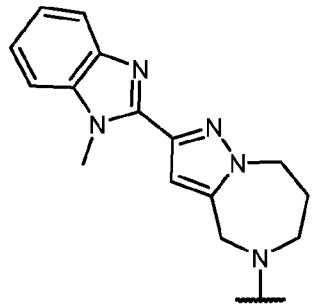
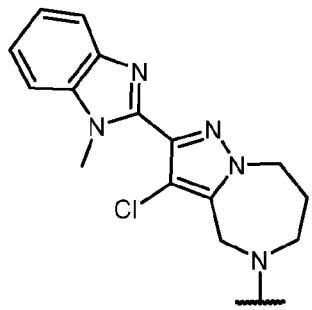
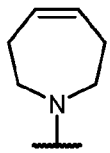
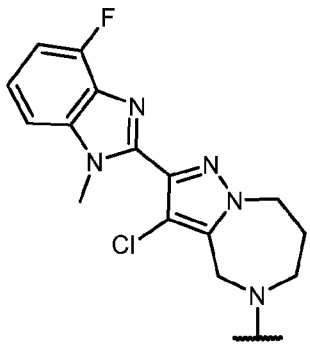
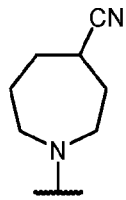
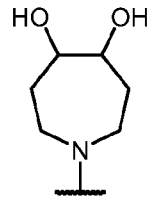
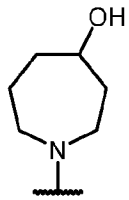
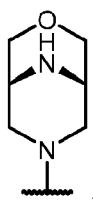
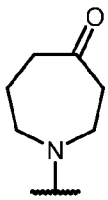
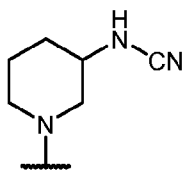
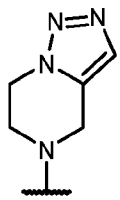
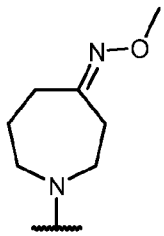
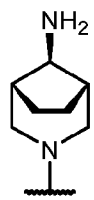
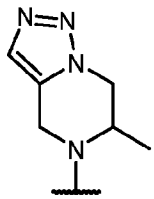
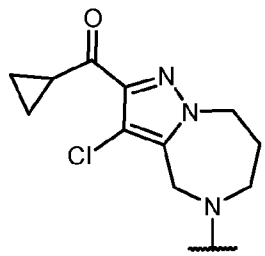
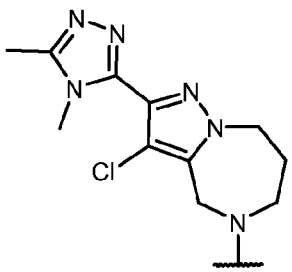
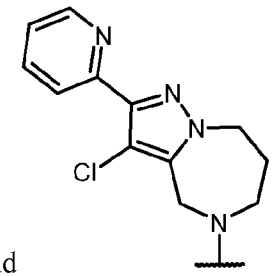
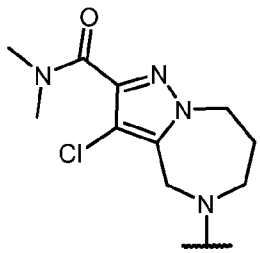


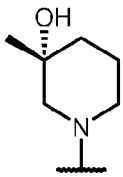
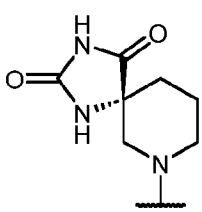
,

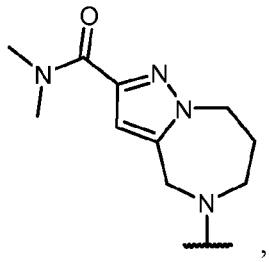
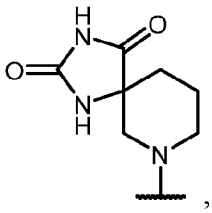
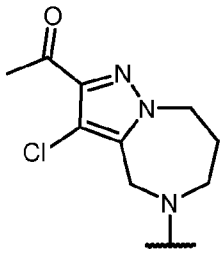
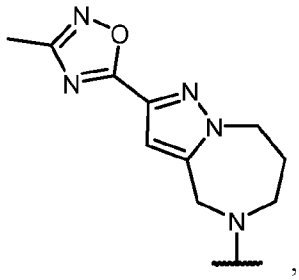
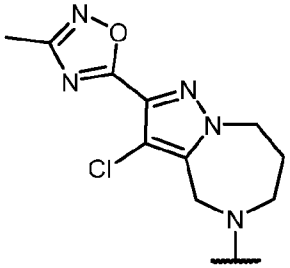
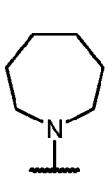
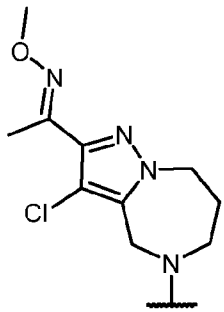
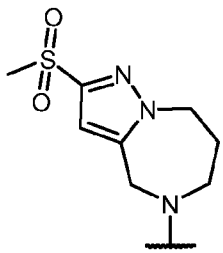
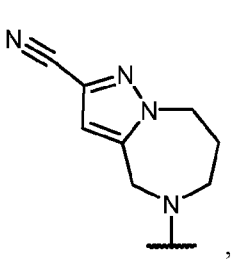
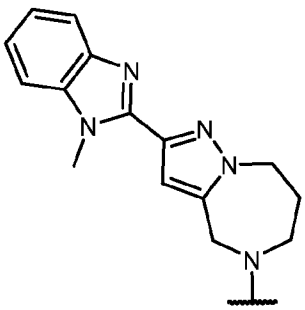
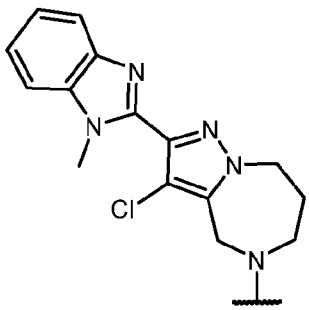
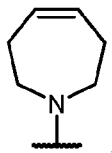
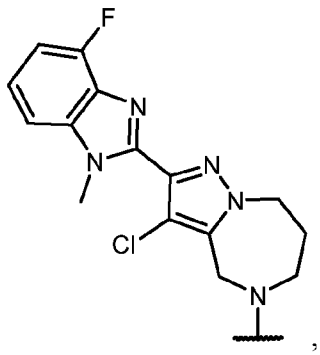
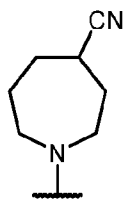
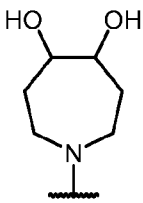
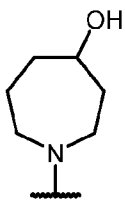
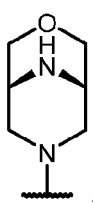
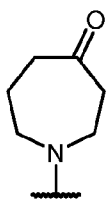
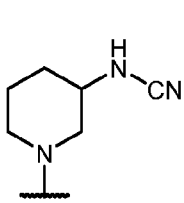
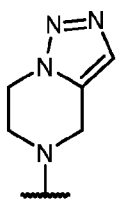
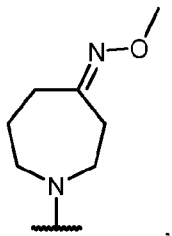



, and  . In some cases, $R^1$ is selected 



, and  .

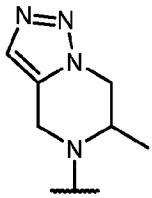
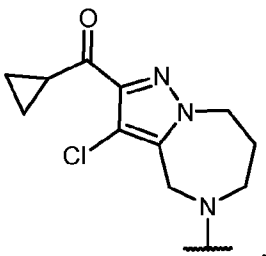
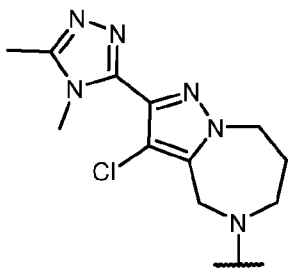
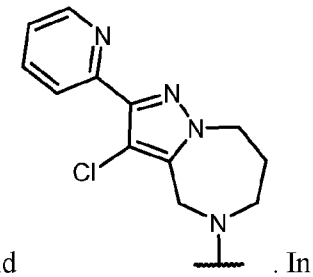
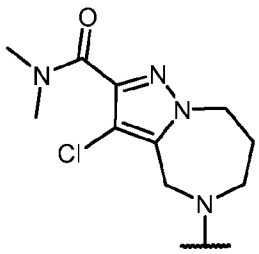
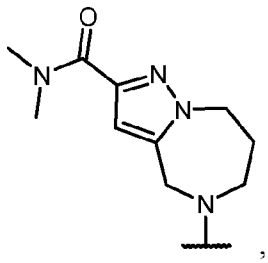
**[00256]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 6- to 11-membered heterocycle, wherein the 6- to 11-membered heterocycle has at least one nitrogen atom. In some cases, the one or more optional substituents of $R^1$ is selected from halogen, $-OR^{20}$, $-C(O)N(R^{20})_2$, $-C(O)R^{20}$, $-S(O)_2R^{20}$, =O, $-C_{1-6}$ alkyl(=$NOR^{20}$), =$NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted independently with one or more $R^{1*}$; and wherein each $R^{1*}$ is independently selected from halogen, and $C_{1-6}$ alkyl. In some embodiments, $R^1$ is selected from

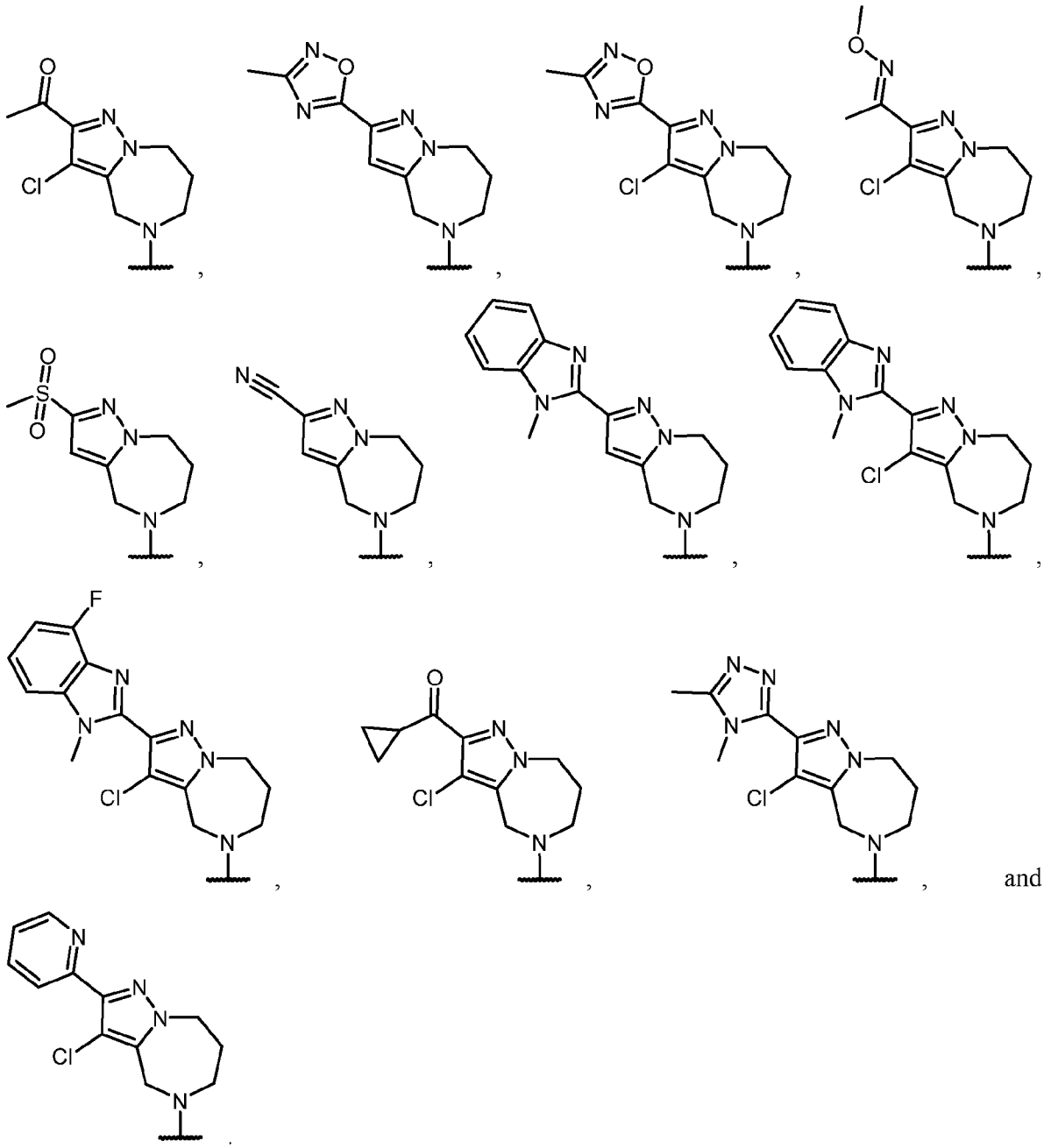


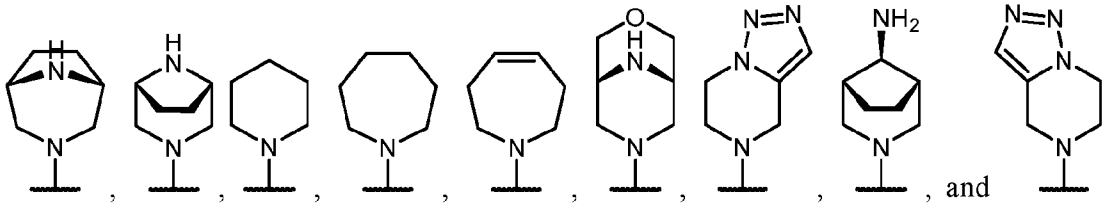

























, and . In some cases, $R^1$ is selected from hydrogen, 


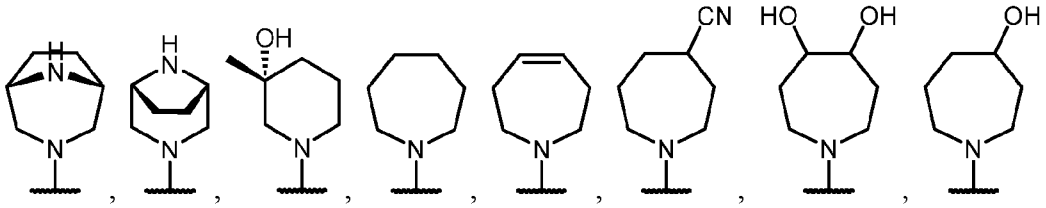
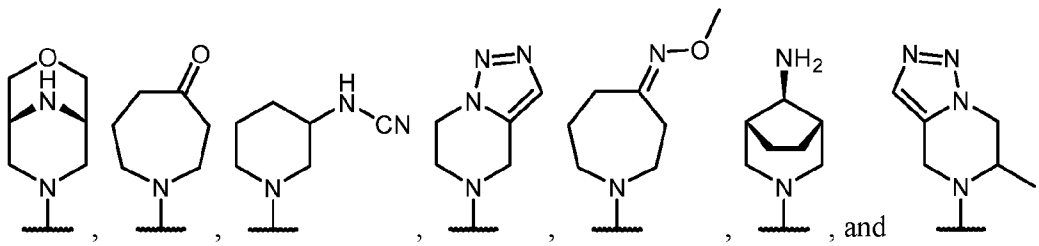



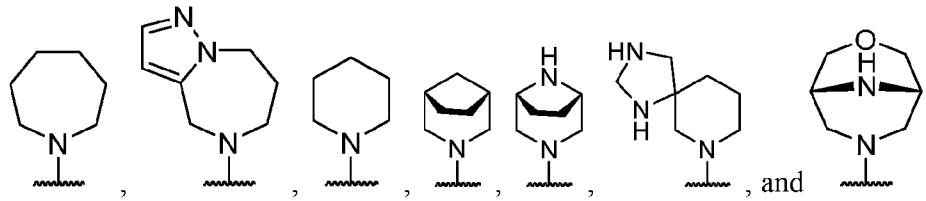
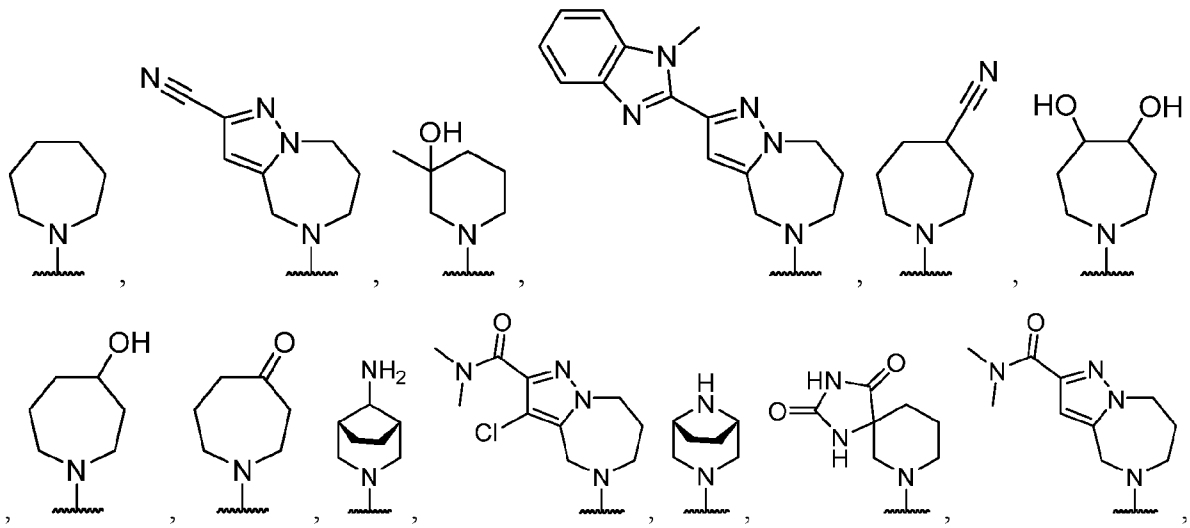

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

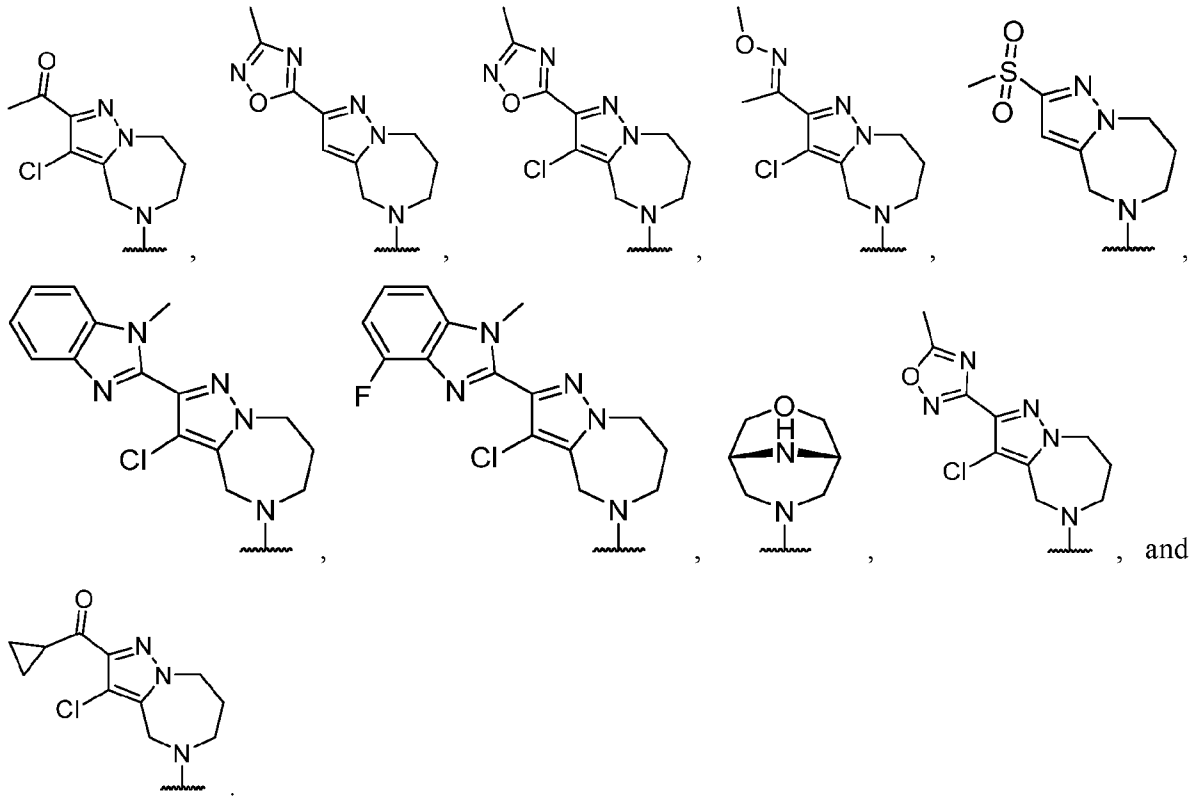
,

,

,

, and

. In some cases, $R^1$ is selected from hydrogen,

,

,

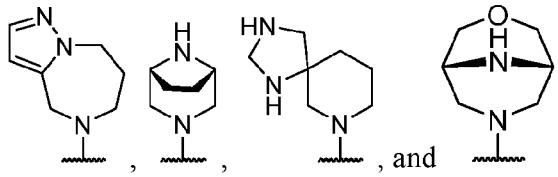
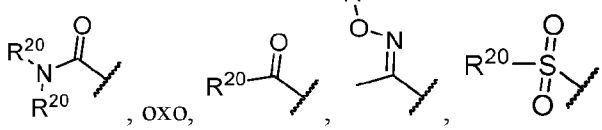
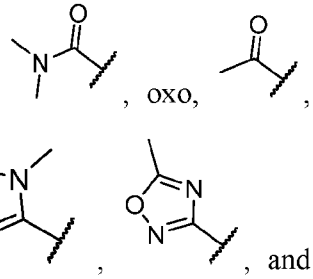


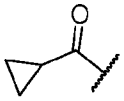
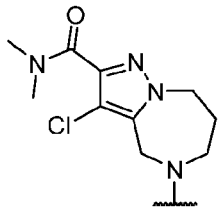
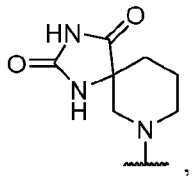
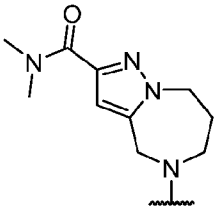
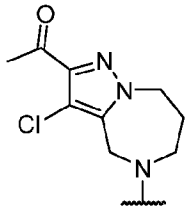
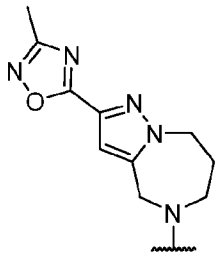
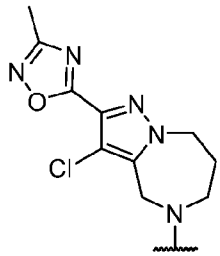
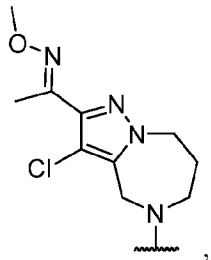
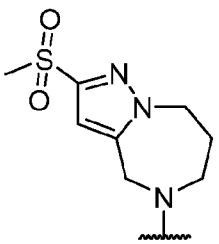
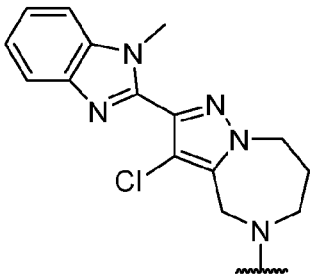
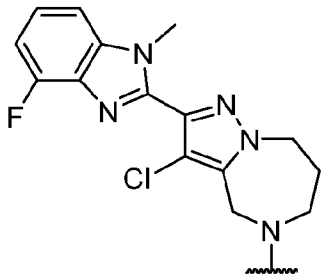
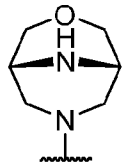
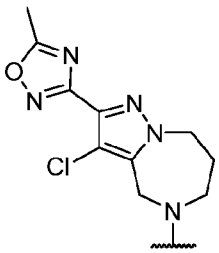
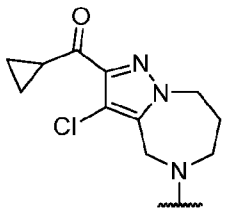
**[00257]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from hydrogen and optionally substituted 5- to 15-membered heterocycle. In some cases, $R^1$ is selected from  , each of which is optionally substituted. In some cases, the optional one or more substituents of $R^1$ is selected from -OH, =NO($R^{20}$), -NHCN, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from

hydrogen,  ,  , and .

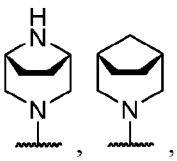
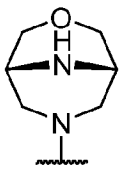
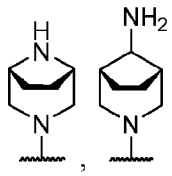
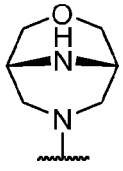
**[00258]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from hydrogen and optionally substituted 7- to 10-membered heterocycle. In some cases, $R^1$ is selected from hydrogen  , and , each of which is optionally substituted. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen, $-NH_2$, $-S(O)_2(R^{20})$, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, $=O$,$=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted independently with one or more $R^{1*}$; and wherein each $R^{1*}$ is independently selected from halogen, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from hydrogen,  .



**[00259]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 8- to 10-membered heterocycle. In some cases, the heterocycle is bicyclic. In some cases, the heterocycle has at least one nitrogen atom. In some cases, the heterocycle has at least two nitrogen atoms. In some cases,  each of which is optionally substituted. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen,  , and 5- to 9-membered heteroaryl, wherein the 5- to 9-membered heteroaryl is substituted with at least one $R^{1*}$, wherein the $R^{1*}$ is selected from halogen, and $C_{1-6}$ alkyl. In some cases, the optional one or more substituents of $R^1$ are independently selected from chlorine, 

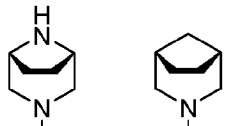
 . In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and .

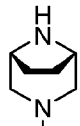
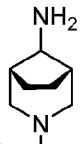
**[00260]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted bridged 8- to 9-membered heterocycle. In some cases, the heterocycle of $R^1$ is selected from

 , , and  , each of which is optionally substituted. In some cases, the one or more substituents of $R^1$ are selected from halogen, $C_{1-6}$ alkyl, $-N(R^{20})_2$, and $C_{1-6}$ aminoalkyl. In some cases, $R^1$ is selected  , , and  .

**[00261]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted bridged 8-membered heterocycle, wherein the heterocycle contains heteroatoms selected from nitrogen. In some cases, the one or more substituents of $R^1$ are selected

from $C_{1-6}$ alkyl, $-N(R^{20})_2$, and $C_{1-6}$ aminoalkyl. In some cases, the heterocycle of $R^1$ is selected from

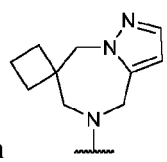
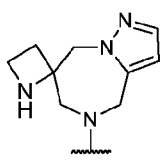

, and

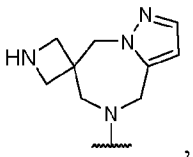
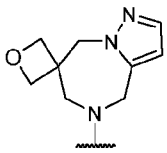
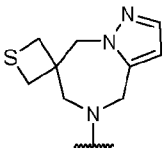
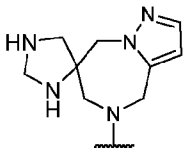
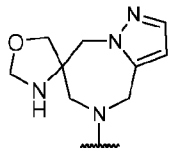
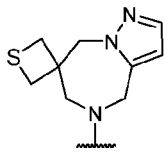
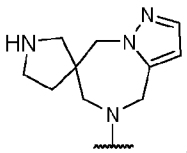
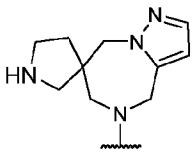
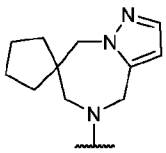
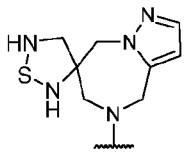
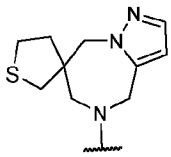
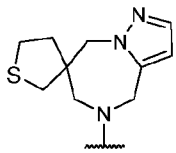
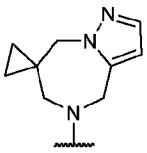
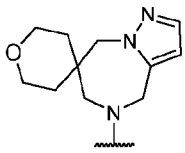
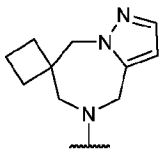
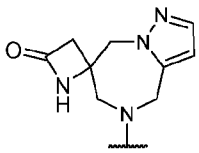
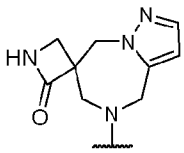
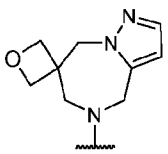
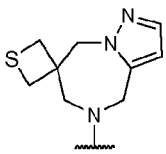
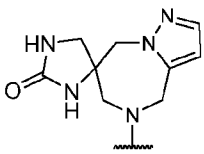
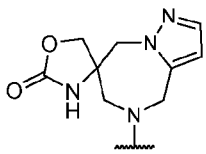
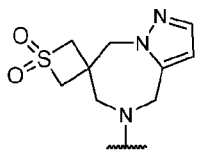
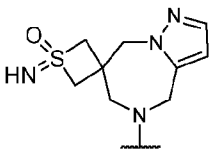
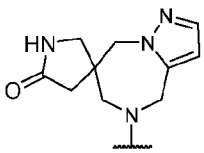
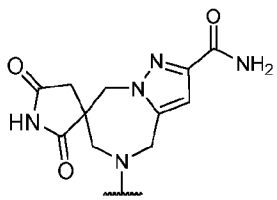
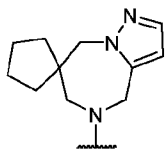
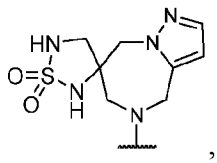
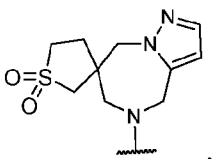
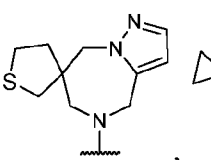
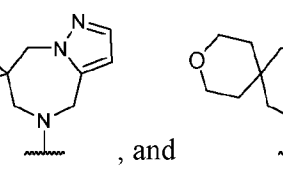
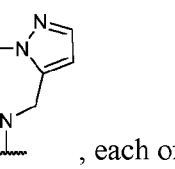
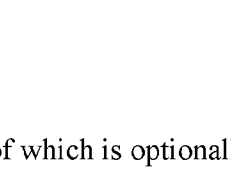
, each of which is optionally substituted. In some cases, $R^1$ is selected

and

. In some cases, $R^1$ is

. In some cases, $R^1$ is

.

**[00262]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is hydrogen.

**[00263]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is an optionally substituted 12- to 15-membered heterocycle. In some cases, $R^1$ is an optionally substituted 12-membered heterocycle. In some cases, $R^1$ is an optionally substituted 13-membered heterocycle. In some cases, $R^1$ is an optionally substituted 14-membered heterocycle. In some cases, $R^1$ is an optionally substituted 15-membered heterocycle. In some cases, the heterocycle of $R^1$ is tricyclic. In some cases, the heterocycle of $R^1$ contains a fused heterocycle. In some cases, the heterocycle of $R^1$ contains a spiro-heterocycle. In some cases, the heterocycle of $R^1$ contains a fused and spiro-heterocycle. In some cases, the heterocycle of $R^1$ is an unsaturated heterocycle. In some cases, the heterocycle of $R^1$ is a non-aromatic heterocycle. In some cases, the heterocycle of $R^1$ has at least one double bond. In some cases, the heterocycle of $R^1$ has at least two double bonds. In some cases, the heterocycle of $R^1$ has at least 2 heteroatoms. In some cases, the heterocycle of $R^1$ has at least 3 heteroatoms. In some cases, the heterocycle of $R^1$ has at least 4 heteroatoms. In some cases, the heterocycle of $R^1$ has at least 5 heteroatoms. In some cases, the heterocycle of $R^1$ has at least 6 heteroatoms. In some cases, the heterocycle of $R^1$ has at least 7 heteroatoms. In some cases, the heteroatoms are selected from oxygen, nitrogen, and sulfur. In some cases, the heterocycle of $R^1$ has at least 3, 4, or 5 nitrogen atoms, and at least 1 sulfur atom. In some cases, the heterocycle of $R^1$ has at least 3, 4, or 5 nitrogen atoms, and at least 1 oxygen atom. In some cases, the heterocycle of $R^1$ has at least 3, 4, or 5 nitrogen atoms. In some cases, the heterocycle of $R^1$ has at least 3, 4, or 5 nitrogen atoms and no other heteroatoms. In some cases, the heteroatoms are selected from nitrogen and sulfur. In some cases, the heteroatoms are selected from nitrogen and oxygen. In some cases, $R^1$ is selected from

,

,

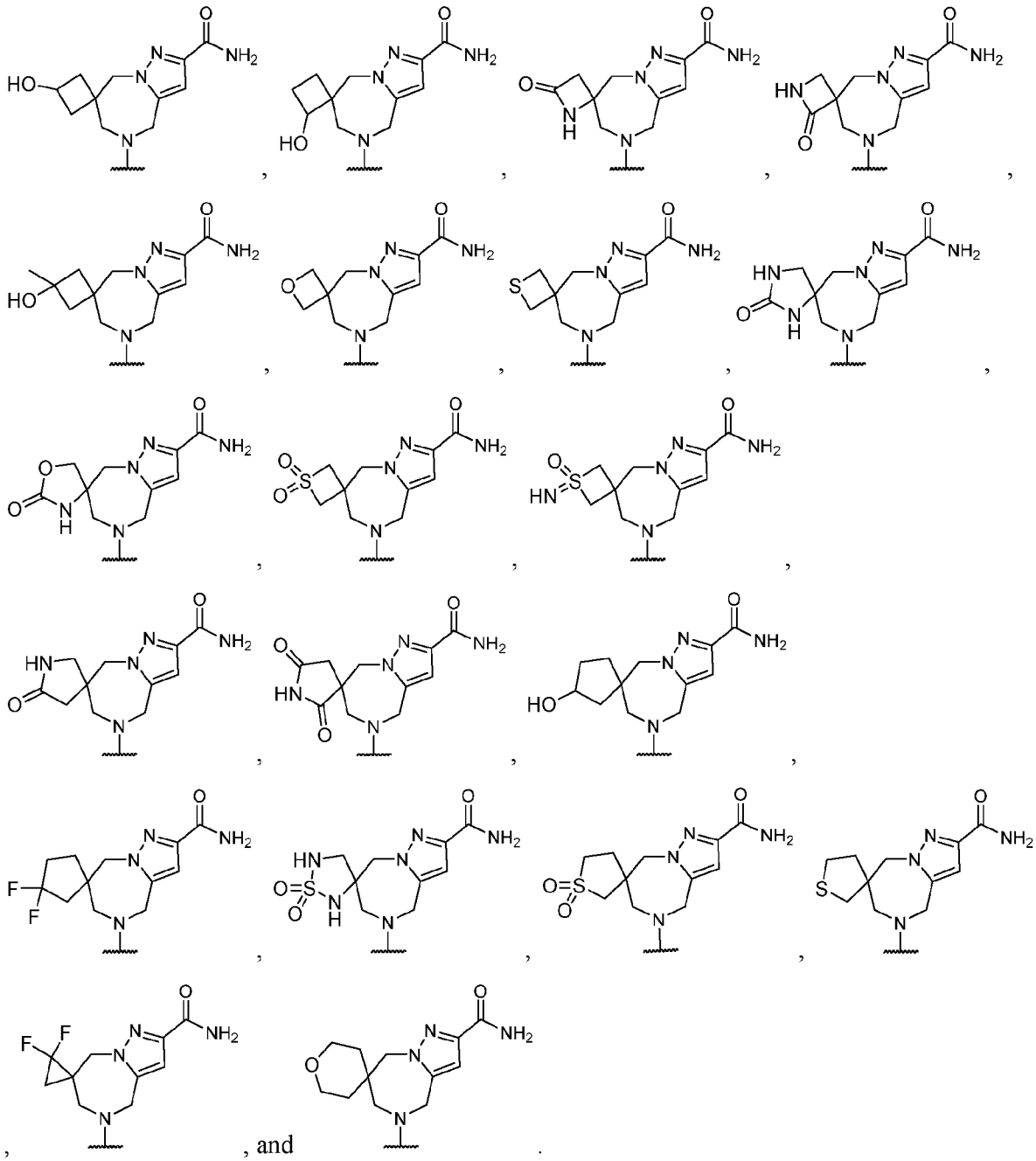

,

,

,

,

,

,

,

,

,

,

,

,

, and

, each of which is optionally substituted with one or more substituents. In some cases, $R^1$ is selected from

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

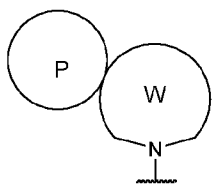
,

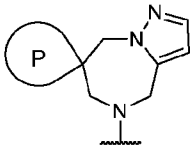
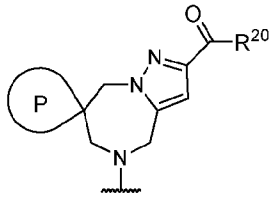
, and

, each of which is optionally substituted with one or more substituents. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen, -OH, -NHCN, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, =NH, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen, -OH, -NHCN, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen, -OH, $C_{1-6}$ alkyl, and $-C(O)N(R^{20})_2$. In some cases, $R^1$ is selected from

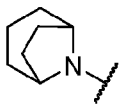
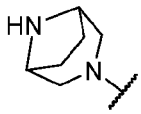
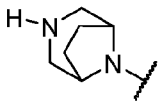
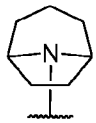
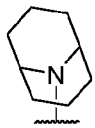
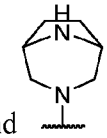
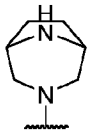


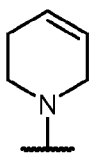
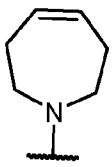
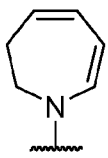
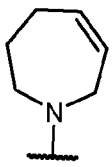
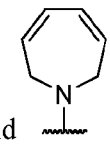
, and .

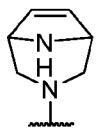
**[00264]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is an optionally substituted 12- to 15-membered heterocycle. In some cases, $R^1$ is  , wherein Ring W is an optionally substituted heterocycle and Ring P is an optionally substituted carbocycle or optionally substituted heterocycle, wherein Ring P forms a spirocycle with Ring W. In some cases, Ring W is an optionally substituted fused heterocycle. In some cases, Ring P and Ring W combine to form a heterocycle having at least 12 atoms and most 15 atoms. In some cases, Ring P and Ring W have in total at least 12 atoms and most 15 atoms. In some cases, Ring

W is an optionally substituted 10-membered fused heterocycle. In some cases, $R^1$ is  , wherein Ring P is an optionally substituted carbocycle or optionally substituted heterocycle. In some cases, $R^1$ is  . In some cases, Ring P is an optionally substituted carbocycle. In some cases, Ring P is an optionally substituted heterocycle. In some cases, Ring P forms an optionally substituted $C_3$-$C_6$ carbocycle or optionally substituted 4-to 6-membered heterocycle. In some cases, Ring P forms an optionally substituted $C_3$ carbocycle. In some cases, Ring P forms an optionally substituted $C_4$ carbocycle. In some cases, Ring P forms an optionally substituted $C_5$ carbocycle. In some cases, Ring P forms an optionally substituted 4-membered heterocycle. In some cases, Ring P forms an optionally substituted 5-membered heterocycle. In some cases, Ring P forms an optionally substituted 5-membered heterocycle. In some cases, Ring P has at least 1, 2, or 3 heteroatoms. In some cases, the heteroatoms are selected from oxygen, nitrogen, and sulfur. In some cases, Ring P has 1 sulfur atom. In some cases, Ring P has 1 nitrogen atom. In some cases, Ring P has 1 oxygen atom. In some cases, the one or more optional substituents of Ring P are independently selected from halogen, -OH, -NHCN, =O, $=NR^{20}$, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of Ring P are independently selected from halogen, -OH, =O, =NH, -CN, and $C_{1-6}$ alkyl. In some cases, the one or more optional substituents of Ring W are independently selected from halogen, -OH, -NHCN, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents of Ring W are independently selected from halogen, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, and $C_{1-6}$ alkyl. In some cases, the one or more optional substituents of Ring W are independently selected from $-C(O)R^{20}$. In some cases, Ring P is substituted. In some cases, Ring W is substituted.

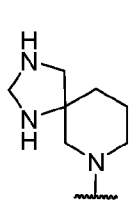
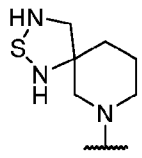
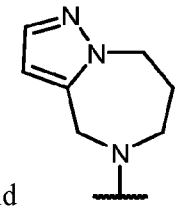
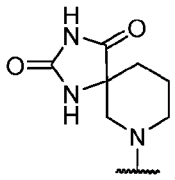
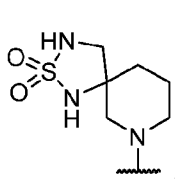
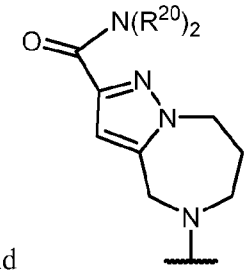
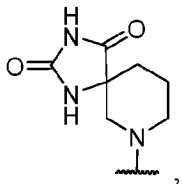
**[00265]** In some embodiments, for a compound or salt for Formula (I), $R^1$ is selected from a 5- to 12-membered bridged heterocycle, which is optionally substituted with one or more substituents. In some cases, $R^1$ is selected from an 8-membered bridged heterocycle, which is

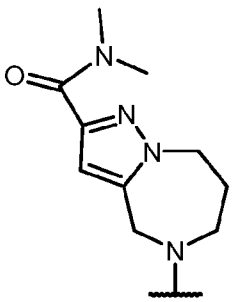
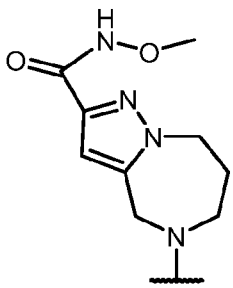
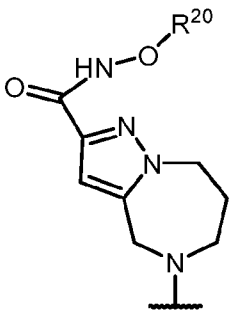
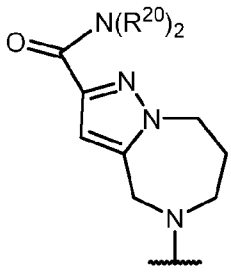
optionally substituted with one or more substituents. In some cases, the bridged heterocycle has at least 1 heteroatom. In some cases, the bridged heterocycle has at least 2 heteroatoms. In some cases, the bridged heterocycle has at least 1 nitrogen atom. In some cases, the bridged heterocycle has at least 2 nitrogen atoms. In some cases, the bridged heterocycle has 2 nitrogen atoms. In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  and , which are each optionally substituted with one or more substituents. In some cases, $R^1$ is selected from  , which is optionally substituted with one or more substituents.

**[00266]** In some embodiments, for a compound or salt for Formula (I), $R^1$ is selected from an unsaturated 5- to 12-membered heterocycle, which is optionally substituted with one or more substituents. In some cases, the unsaturated 5- to 12-membered heterocycle is selected from  ,  ,  ,  , and  , each of which is optionally substituted with one or more substituents.

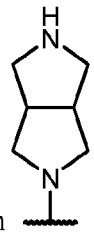
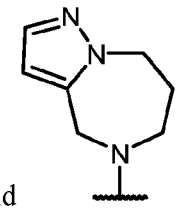
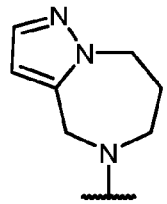
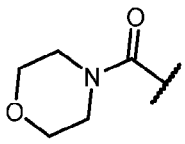
**[00267]** In some embodiments, for a compound or salt of Formula (I), wherein the 5- to 12-membered heterocycle of $R^1$ is unsaturated and a bridged heterocycle. In some cases, $R^1$ is selected from an optionally substituted 7- to 8-membered unsaturated and bridged heterocycle. In some cases, $R^1$ is selected from  .

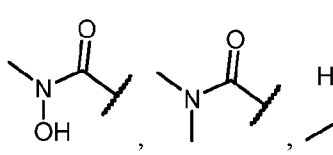
**[00268]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 10-membered heterocycle. In some cases, the 10-membered heterocycle is a bicyclic heterocycle. In some cases, the 10-membered heterocycle is a spiro heterocycle. In some cases, the 10-membered heterocycle is a fused heterocycle. In some cases, the 10-membered heterocycle is a saturated heterocycle. In some cases, the 10-membered heterocycle is a non-aromatic heterocycle. In some cases, the 10-membered heterocycle contains at least 1 nitrogen atom. In some cases, the 10-membered heterocycle contains at least 2 nitrogen atoms. In some cases, the 10-membered heterocycle contains at least 3 nitrogen atoms. In some cases, the 10-membered heterocycle contains at least 1 sulfur atom. In some cases, $R^1$ is selected from

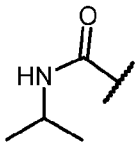
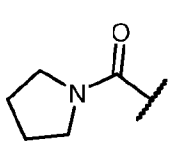
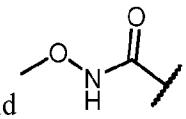
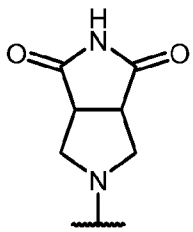
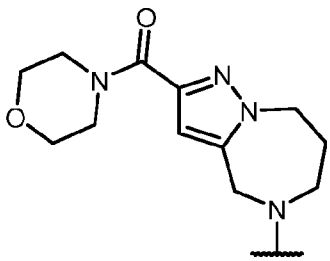
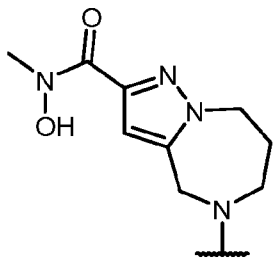
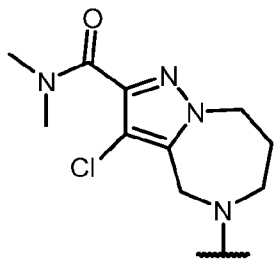
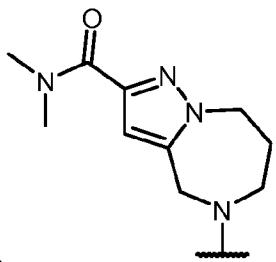
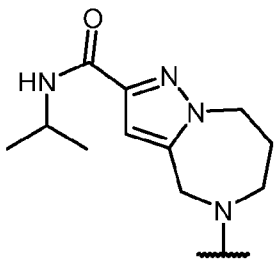
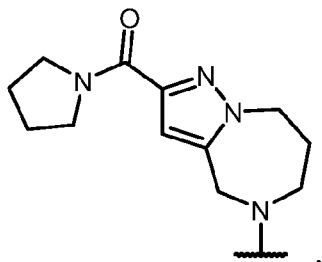
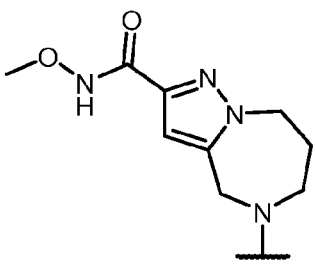
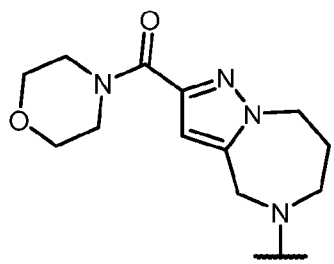
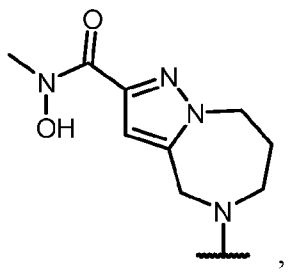
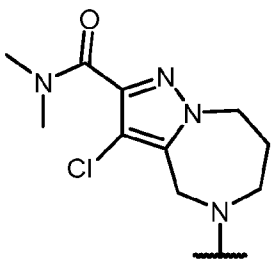
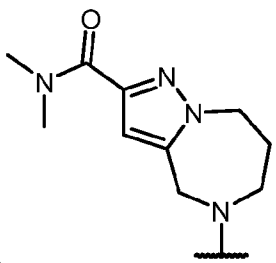
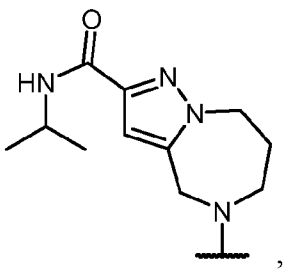
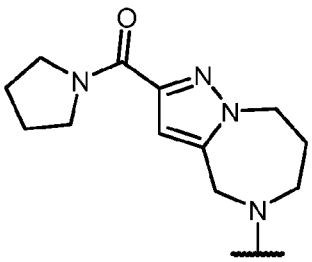
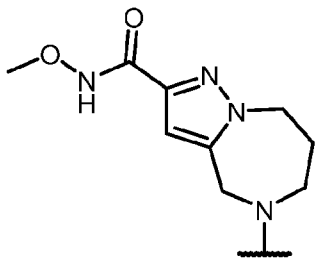



, , and , each of which is optionally substituted with one or more substituents independently selected from halogen, =O, -OH, -CN, -NHCN, -C(O)N($R^{20}$)$_2$, -C(O)N$R^{20}$O$R^{20}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from 


, , and . In some cases, $R^1$ is selected from 

, and . In some cases, $R^1$ is selected from 

and . In some cases, $R^1$ is selected from 
. In some cases, $R^1$ is selected from 
, which is optionally substituted with one or more substituents independently selected from halogen, -O$R^{20}$, -S$R^{20}$, -N($R^{20}$)$_2$, -$NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl.

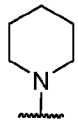
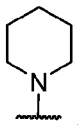
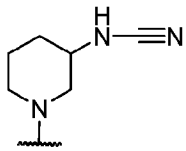
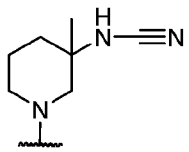
**[00269]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 8- to 10-membered fused heterocycle. In some cases, the 8- to 10-membered fused heterocycle is a bicyclic heterocycle. In some cases, the 8- to 10-membered

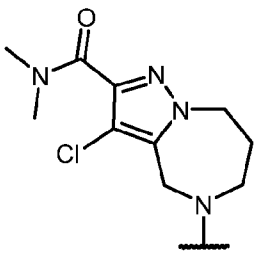
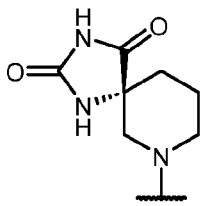
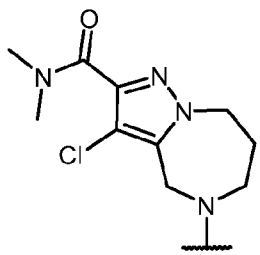
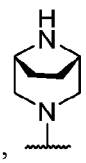
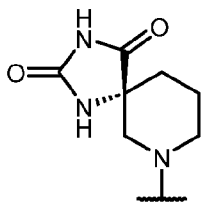
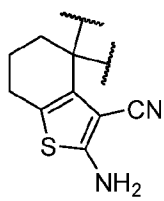
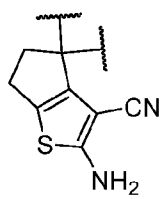
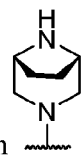
fused heterocycle is a saturated heterocycle. In some cases, the 8- to 10-membered heterocycle is a non-aromatic heterocycle. In some cases, $R^1$ is selected from an optionally substituted 10-membered fused heterocycle. In some cases, the 10-membered fused heterocycle is a bicyclic heterocycle. In some cases, the 10-membered fused heterocycle is a saturated heterocycle. In some cases, the 10-membered heterocycle is a non-aromatic heterocycle. In some cases, the fused heterocycle has one saturated ring and one aromatic ring. In some cases, the fused heterocycle has one saturated ring and one unsaturated ring. In some cases, the fused heterocycle has two saturated rings. In some cases, the 10-membered heterocycle contains at least 1 nitrogen atom. In some cases, the 10-membered heterocycle contains at least 2 nitrogen atoms. In some cases, the 10-membered heterocycle contains at least 3 nitrogen atoms. In some cases, $R^1$ is selected from  and  , each of which is optionally substituted with one or more substituents. In some cases, $R^1$ is  , which is optionally substituted with one or more substituents. In some cases, the optional one or more substituents are independently selected from halogen, =O, -OH, -CN, -NHCN, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, the optional one or more substituents are independently selected from halogen, =O, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, and $-C(O)NR^{20}OR^{20}$. In some cases, the optional one or more substituents are independently selected from $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, and $-C(O)NR^{20}OR^{20}$. In some cases, the optional one or more substituents are independently selected from $-C(O)R^{20}$. In some cases, the optional one or more substituents are independently selected from $-C(O)N(R^{20})_2$. In some cases, the optional one or more substituents are independently selected from $-C(O)NR^{20}OR^{20}$. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and 3- to 12-membered heterocycle. In some cases, each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and 3- to 12-membered saturated heterocycle. In some cases, the optional one or more substituents of $R^1$ are independently selected from  ,

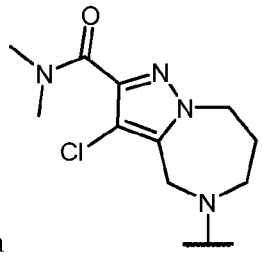


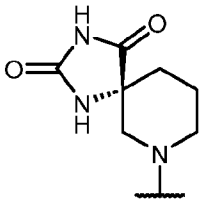
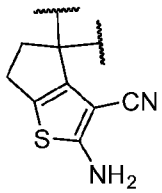
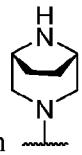
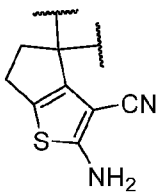
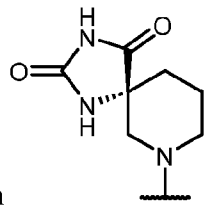
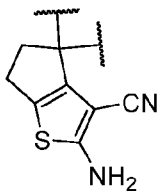
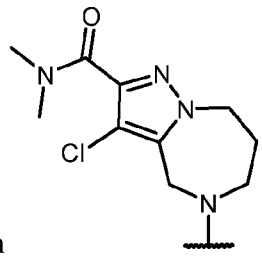
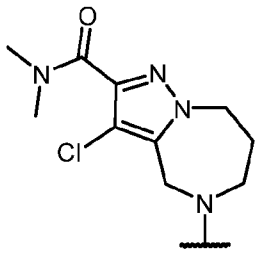
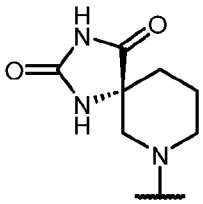


, and  . In some cases, $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, $R^1$ is selected from  ,  ,  ,  ,  , and  .

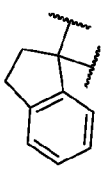
**[00270]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted saturated 6- to 7-membered heterocycle. In some cases, $R^1$ is selected from an optionally substituted saturated 6-membered heterocycle. In some cases, $R^1$ is selected from

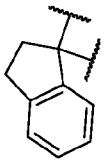
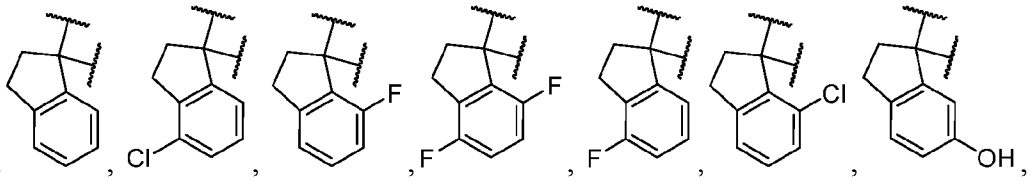
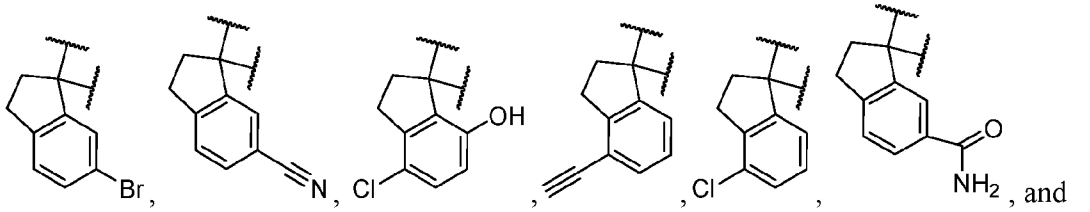
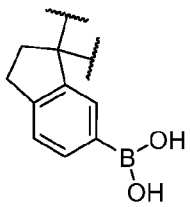
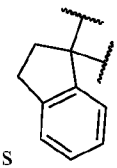
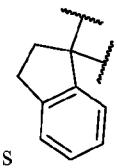
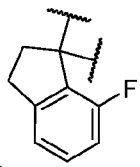
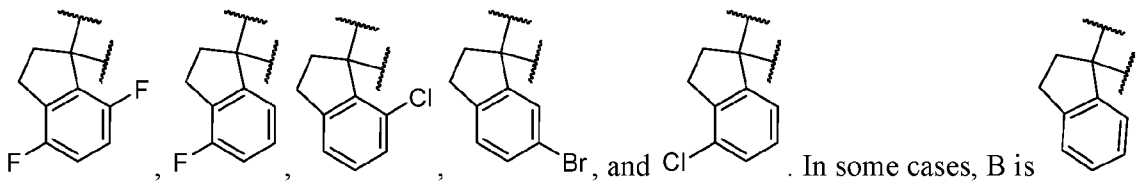
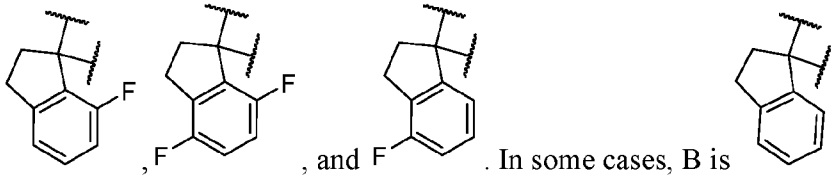

, which is optionally substituted. In some cases, the optional one or more substituents are independently selected from halogen, -CN, -NHCN, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, the optional one or more substituents are independently selected from -CN, -NHCN, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, the optional one or more substituents are independently selected from -CN, -NHCN, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, the optional one or more substituents are independently selected from -NHCN, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from 
, which is substituted with one or more substituents selected from -NHCN, and $C_{1-6}$ alkyl. In some cases, $R^1$ is selected from 
, and 
.

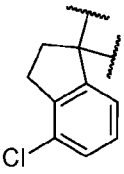
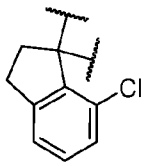
**[00271]** In some embodiments, for a compound or salt of Formula (I), $R^3$ is -CN, and $R^1$ is selected from 
, 
, and 
; and B is an optionally substituted 8- to 9-membered fused heterocycle, wherein the 8- to 9-membered fused heterocycle has at least one sulfur atom. In some cases, $R^3$ is -CN, and $R^1$ is selected from 
, 
, and 
; and B is selected from 
, and 
. In some cases, $R^3$ is -CN, and $R^1$ is selected from 
. In some cases, $R^3$ is -CN,

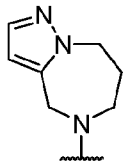
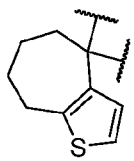
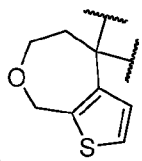
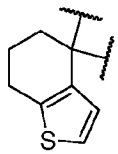
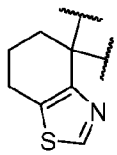
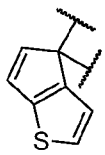
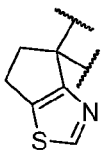
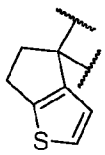
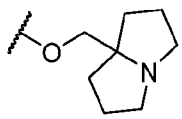


and $R^1$ is selected from  . In some cases, $R^3$ is -CN, and $R^1$ is selected from  . In some cases, $R^3$ is -CN, B is  , and $R^1$ is selected from  . In some cases, $R^3$ is -CN, B is  , and $R^1$ is selected from  . In some cases, $R^3$ is -CN, B is  , and $R^1$ is selected from  . In some cases, $R^3$ is -CN, and $R^1$ is selected from  ,  , and  ; B is an optionally substituted 8- to 9-membered fused heterocycle, wherein the 8- to 9-membered fused heterocycle has at least one sulfur atom; and Y-$R^2$ is selected from -O-L-heterocycle, wherein the heterocycle portion of -O-L-heterocycle is optionally substituted with one or more $R^6$.

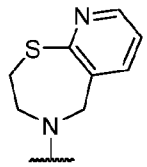
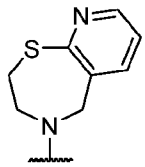
**[00272]** In some embodiments, for a compound or salt of Formula (I), B is an optionally substituted 8- to 10-membered fused carbocycle. In some cases, B is a substituted 8- to 10-membered fused carbocycle. In some cases, B is an optionally substituted 9-membered fused carbocycle. In some cases, B is a substituted 9-membered fused carbocycle. In some cases, B is  , which is optionally substituted with one or more substituents. In some cases, B is

 , which is substituted with one or more substituents. In some cases, for B, the one or more substituents are independently selected from halogen, oxo, -$NH_2$, $C_1$-$C_3$ alkyl, -$B(OH)_2$, -OH, -$C(O)NH_2$, -$NH_2$, =O, -CN, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{2-6}$ alkynyl. In some cases, B is substituted with at least one halogen. In some cases, B is substituted with at least one chlorine. In some cases, B is substituted with at least one fluorine. In some cases, B is selected from  ,  , and  . In some cases, B is  , which is substituted with one or more substituents selected from halogen and $C_{1-6}$ haloalkyl. In some cases, B is  , which is substituted with one or more substituents selected from halogen. In some cases, B is selected from  ,  , and . In some cases, B is  , which is substituted with one or more substituents selected from fluorine. In some cases, B is selected from , and . In some cases, B is , which is

substituted with one or more substituents selected from chlorine. In some cases, B is selected from  and  .

**[00273]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted unsaturated 10-membered fused heterocycle. In some cases, $R^1$ is  , which is optionally substituted. In some cases, the optional one or more substituents of $R^1$ are independently selected from halogen, =O, -OH, -CN, -NHCN, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl. In some cases, B is an optionally substituted 8- to 10-membered fused heterocycle, wherein the heterocycle contains one sulfur atom. In some cases, B is selected from  ,  ,  ,  ,  ,  and  , each of which is optionally substituted. In some cases, In some cases, for B, the one or more optional substituents of the heterocycle and carbocycle are independently selected at each occurrence from halogen, oxo, $-NH_2$, $C_1$-$C_3$ alkyl, -OH, -O-$C_1$-$C_3$ haloalkyl, $-C(O)NH_2$, $-NH_2$, =O, -CN, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{2-6}$ alkynyl. In some cases, Y-$R^2$ is selected from  , wherein the heterocycle portion is optionally substituted. In some cases, n is 0. In some cases, $R^3$ is selected from hydrogen, halogen, -CN, $-N(R^{20})_2$, -OH, $-S(O)_2(R^{20})$, $-C(O)R^{20}$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl. In some cases, $R^3$ is selected from hydrogen, halogen, and -CN.

**[00274]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from an optionally substituted 11-membered fused heterocycle. In some cases, $R^1$ is selected from an optionally substituted unsaturated 11-membered fused heterocycle. In some cases, the heterocycle contains at least one sulfur atom. In some cases, the heterocycle contains at least one

nitrogen atom. In some cases, the heterocycle contains 3 heteroatoms. In some cases, the heterocycle is  , which is optionally substituted. In some cases, $R^1$ is  .

**[00275]** In some embodiments, for a compound or salt of Formula (I), the one or more optional substituents of $R^1$ are each independently selected from halogen, -CN, $-NO_2$, =O, $-N(R^{20})_2$, $-B(OR^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-NR^{20}S(O)_2R^{20}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl. In some cases, the one or more optional substituents are independently selected from halogen, -OH, $-N(R^{20})_2$, $-NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl. In some cases, the optional substituents for $R^1$ are each independently selected from halogen, -OH, $-N(R^{20})_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl. In some cases, the optional substituents for $R^1$ are each independently selected from halogen, -CN, -OH, $-NH_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ haloalkyl. . In some cases, the optional substituents for $R^1$ are each independently selected from -OH, and $-NH_2$. In some cases, $R^{20}$ is selected from hydrogen and $C_{1-3}$ alkyl.

**[00276]** In some embodiments, for a compound or salt for Formula (I), n is selected from 0 to 4. In some cases, n is selected from 0 to 3. In some cases, n is selected from 0 to 2. In some cases, n is selected from 0 and 1. In some cases, n is 0. In some cases, n is 1. In some cases, n is 2.

**[00277]** In some embodiments, for a compound or salt for Formula (I), each $R^4$ is independently selected from halogen, $-NO_2$, =O, =S, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ haloalkyl. In some cases, $R^4$ is independently selected from halogen, =O, -CN, $C_{1-6}$ cyanoalkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl. In some cases, $R^4$ is independently selected from halogen, =O, -CN, $C_{1-6}$ cyanoalkyl, $C_{2-6}$ alkynyl, and $C_{1-6}$ haloalkyl. In some cases, $R^4$ is independently selected from -CN, $C_{1-6}$ cyanoalkyl, and $C_{2-6}$ alkynyl. In some cases, each $R^4$ is independently selected from halogen, $-NO_2$, =O, =S, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl.

**[00278]** In some embodiments, for a compound or salt for Formula (I), Q is a bond. In some cases, Q is a S. In some cases, Q is a O.

**[00279]** In some embodiments, for a compound or salt for Formula (I), each $R^7$ is independently selected from halogen, hydroxy, HC(=O)-, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$

haloalkyl, $C_1$-$C_4$ hydroxyalkyl, and -$N(R^5)_2$. In some cases, each $R^7$ is independently selected from halogen, hydroxy, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, and $C_1$-$C_4$ hydroxyalkyl.

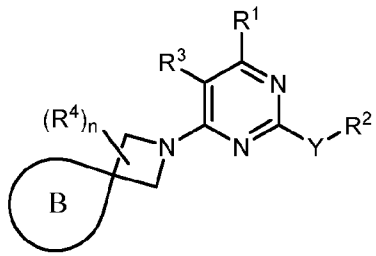
**[00280]** In some embodiments, for a compound or salt for Formula (I), each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle. In some cases, each $R^{20}$ is independently selected from hydrogen and $C_{1-6}$ alkyl. In some cases, each $R^{20}$ is independently selected from $C_{1-6}$ alkyl.

**[00281]** In some embodiments, for a compound or salt for Formula (I), each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle. In some cases, each $R^{21}$ is independently selected from hydrogen and $C_{1-6}$ alkyl. In some cases, each $R^{21}$ is independently selected from $C_{1-6}$ alkyl.

**[00282]** In some embodiments, for a compound or salt for Formula (I), each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle. In some cases, each $R^{20}$ is independently selected from hydrogen and $C_{1-6}$ alkyl. In some cases, each $R^{20}$ is independently selected from $C_{1-6}$ alkyl.

**[00283]** In some embodiments, for a compound or salt for Formula (I), each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle. In some cases, each $R^{23}$ is independently selected from hydrogen and $C_{1-6}$ alkyl. In some cases, each $R^{23}$ is independently selected from $C_{1-6}$ alkyl.

**[00284]** In an aspect, the present disclosure provides a compound of Formula (I-A)



Formula (I-A),

or a pharmaceutically acceptable salt thereof wherein:

$R^1$ is selected from 8- to 10-membered heterocycle, wherein the 8- to 10-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl(=$NOR^{20}$), $-C(O)R^{20}$ =O, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl-$SO_2R^{20}$, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, $-B(OR^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}$(=$NR^{20}$), $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, =$N(R^{20})$, =$NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, and $C_3$-$C_{12}$ carbocycle;

B is selected from a 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle, wherein the 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle are each optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, =O, $-N(R^{21})_2$, $-B(OR^{21})_2$, $-OR^{21}$, $-SR^{21}$, $-S(O)_2(R^{21})$, $-S(O)_2N(R^{21})_2$, $-NR^{21}S(O)_2R^{21}$, $-C(O)N(R^{21})_2$, $-C(O)NR^{21}OR^{21}$, $-N(R^{21})C(O)R^{21}$, $-N(R^{21})C(O)N(R^{21})_2$, $-N(R^{21})C(O)OR^{21}$, $-C(O)R^{21}$, $C(O)OR^{21}$, $-OC(O)R^{21}$, $-OC(O)N(R^{21})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

Y is selected from a bond, -O-, -S-, and $-N(R^5)$-;

$R^2$ is selected from heterocycle, aryl, $C_1$-$C_6$ alkyl, -L-heterocycle, -L-$N(R^{23})_2$, -L-$OR^{23}$, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-$NHC(=NH)NH_2$, -L-$C(O)N(R^{23})_2$, -L-$C_1$-$C_6$ haloalkyl, -L-$OR^{23}$, -L-$NR^{23}C(O)$-aryl, -L-COOH, -L-$NR^{23}S(O)_2(R^{23})$, -L-$S(O)_2N(R^{23})_2$, -L-$N(R^{23})C(O)(OR^{23})$, -L-$OC(O)N(R^{23})_2$, and -L-$C(=O)OC_1$-$C_6$ alkyl, wherein the heterocycle, the heterocycle portion of -L-heterocycle, and the cycloalkyl portion of the -L-cycloalkyl are each optionally substituted with one or more $R^6$, and wherein the aryl, aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl portion of -L-

$NR^{23}C(O)$-aryl, the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$;

$R^3$ is selected from hydrogen, halogen, -CN, $-NO_2$, $-N(R^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

each $R^4$ is independently selected from halogen, $-NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

n is selected from 0, 1, 2, 3, and 4;

each $R^5$ is independently selected from hydrogen and $C_1$-$C_6$ alkyl;

each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, $=CH_2$, =NO-$C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, $-N(R^5)S(O)_2(R^5)$, -Q-phenyl, -Q-phenyl$SO_2F$, -NHC(O)phenyl, -NHC(O)phenyl$SO_2F$, $C_1$-$C_3$ alkyl substituted pyrazolyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, $-C(O)N(R^5)_2$, tert-butyldimethylsilyloxy$CH_2$-, $-N(R^5)_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$ alkyl)C(=O), oxo, ($C_1$-$C_3$ haloalkyl)C(=O)-, $-SO_2F$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, $-CH_2OC(O)N(R^5)_2$, $-CH_2NHC(O)OC_1$-$C_6$ alkyl, $-CH_2NHC(O)N(R^5)_2$, $-CH_2NHC(O)C_1$-$C_6$ alkyl, $-CH_2$(pyrazolyl), $-CH_2NHSO_2C_1$-$C_6$ alkyl, $-CH_2OC(O)$heterocycle, $-OC(O)N(R^5)_2$, $-OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl), $-OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl$(C_1$-$C_3$ alkyl)$N(CH_3)_2$, $-OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl, -OC(O)heterocycle, -O-$C_1$-$C_3$ alkyl, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, and $-CH_2$heterocycle, wherein the phenyl of -NHC(O)phenyl and $-OC(O)NH(C_1$-$C_3$ alkyl)$(C_1$-$C_3$ alkyl)phenyl are optionally substituted with one or more substituents selected from -C(O)H and OH, and wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo and hydroxy; and wherein the heterocycle of -$CH_2$heterocyclyl is optionally substituted with oxo;

each Q is selected from a bond, S, and O;

each $R^7$ is independently selected from halogen, hydroxy, HC(=O)-, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, $-C(O)N(R^5)_2$, and $-N(R^5)_2$;

each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, hydroxy, $C_{1-6}$ alkoxy, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle, and 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents

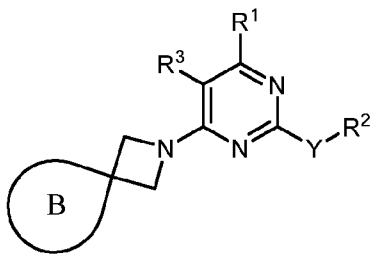
independently selected from halogen, -OH, $-NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, $-NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

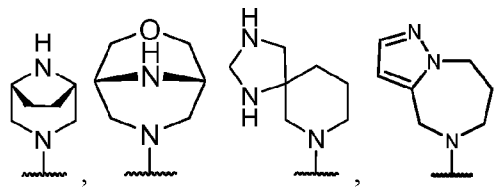
each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle.

**[00285]** In some embodiments, Formula (I) or Formula (I-A) is represented by Formula (I-B),




Formula (I-B),

or a pharmaceutically acceptable salt thereof wherein:

wherein $R^1$ is selected from  each of which is optionally substituted with one or more substituents independently selected from halogen, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)R^{20}$, =O, and 5- to 12-membered

heterocycle, wherein the 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, $-OR^{20}$, $-N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl;

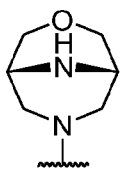
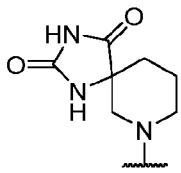
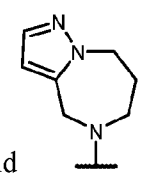
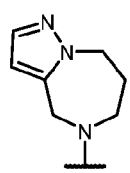
Y is -O-;

$R^2$ is selected from -L-heterocycle, -L-$N(R^{23})_2$, wherein the heterocycle portion of -L-heterocycle is optionally substituted with one or more $R^6$.

B is selected from a 7- to 15-membered heterocycle, wherein the 7- to 15-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, =O, $-N(R^{21})_2$, $-OR^{21}$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl;

$R^3$ is selected from hydrogen, halogen, -CN, $-N(R^{20})_2$, $-OR^{20}$, $-C(O)R^{20}$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl; and

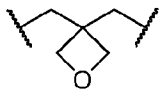
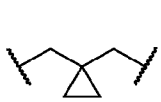
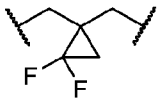
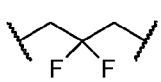
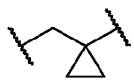
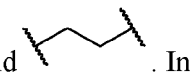
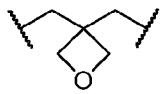
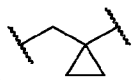
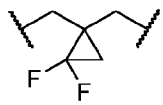
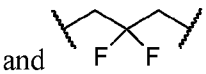
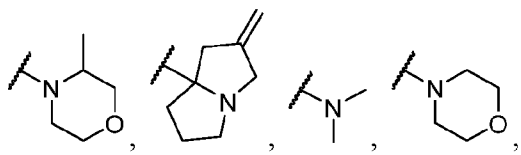
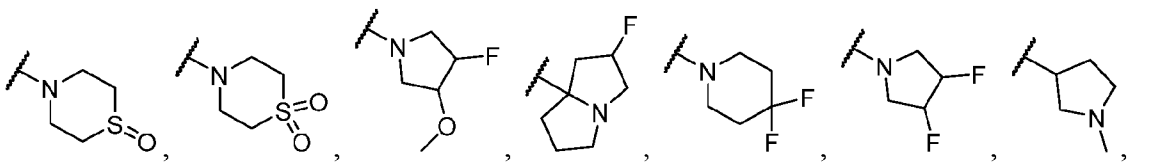
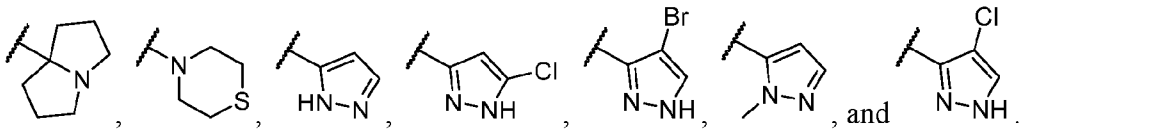
each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and $C_{3-12}$ carbocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, and oxo.

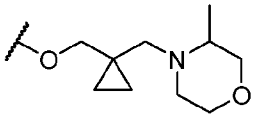
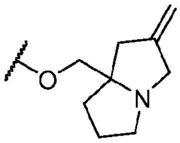
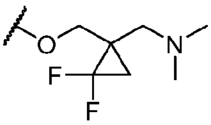
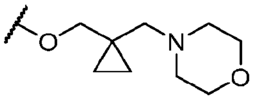
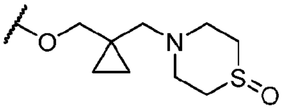
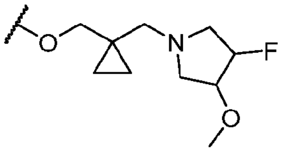
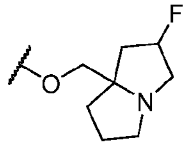
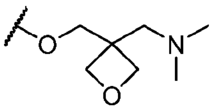
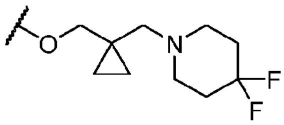
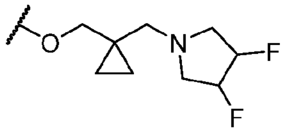
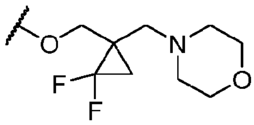
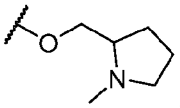
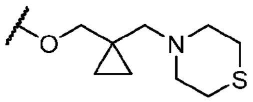
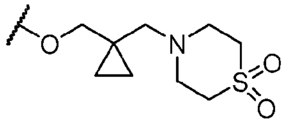
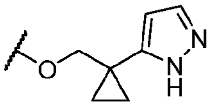
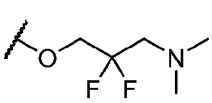
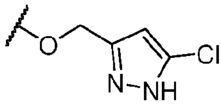
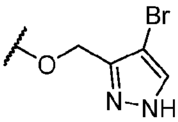
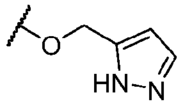
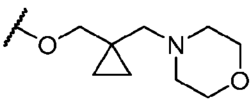
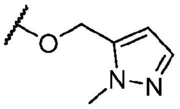
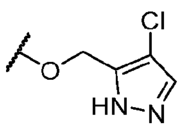
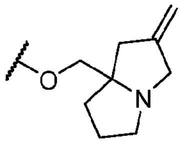
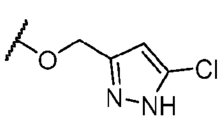
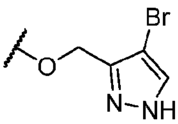
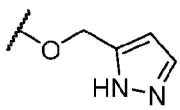
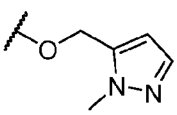
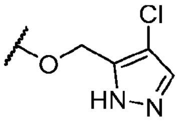
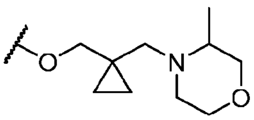
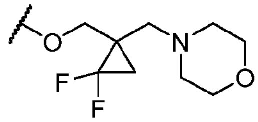
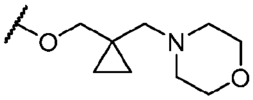
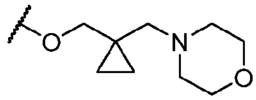
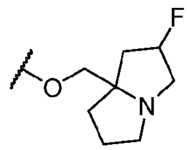
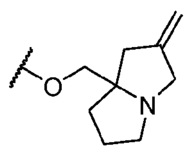
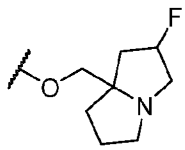
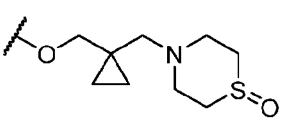
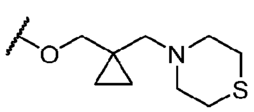
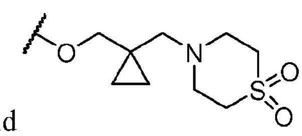
**[00286]** In some embodiments, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), $R^1$ is selected from  ,  ,  , and  , wherein  , is optionally substituted with one or more substituents independently selected from halogen, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)R^{20}$, =O, and 5- to 9-membered heterocycle, wherein the 5- to -membered heterocycle are each optionally substituted independently with one or more $R^{1*}$; and

each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

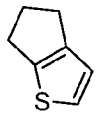
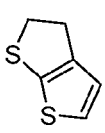
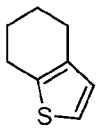
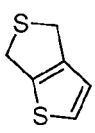
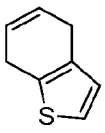
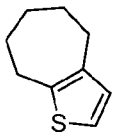
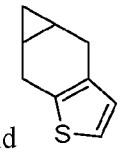
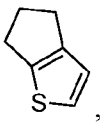
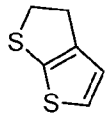
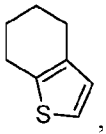
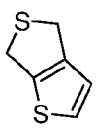
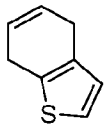
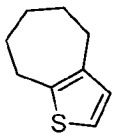
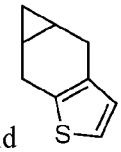
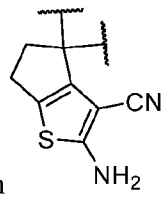
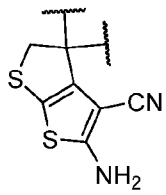
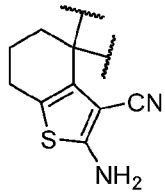
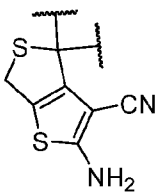
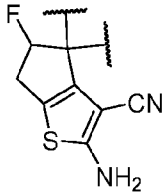
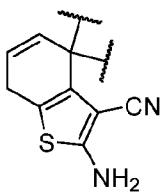
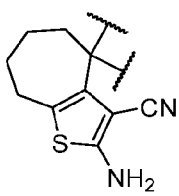
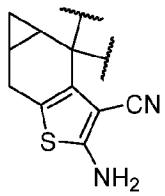
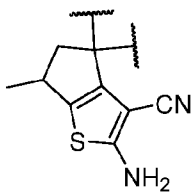
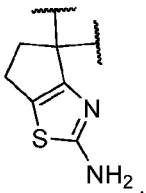
**[00287]** In some embodiments, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), Y is -O-.

**[00288]** In some embodiments, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), $R^2$ is selected from optionally substituted -L-heterocycle, and -L-$N(R^{23})_2$. In some cases, $R^2$ is selected from optionally substituted -L- 5-to 8-membered heterocycle, and -L-$N(R^{23})_2$. In some cases, $R^2$ is selected from optionally substituted -L-heterocycle. In some cases, $R^2$ is selected from -L-$N(R^{23})_2$. In some cases, the heterocycle contains at least one nitrogen atom. In

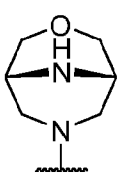
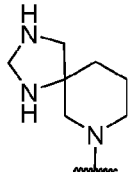
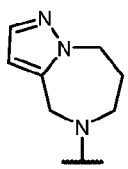
some cases, the heterocycle contains at least one sulfur atom. In some cases, the heterocycle contains at least one oxygen atom. In some cases, the heterocycle is a heteroaryl. In some cases, the heterocycle is a saturated heterocycle. In some cases, each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, $=CH_2$, $=NO$-$C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, $C_1$-$C_3$ alkyl substituted pyrazolyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, -$C(O)N(R^5)_2$, -$N(R^5)_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$ alkyl)C(=O), oxo, -O-$C_1$-$C_3$ alkyl. In some cases, each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $=CH_2$, and -O-$C_1$-$C_3$ alkyl. In some cases, when $R^2$ is a heteroaryl, $R^6$ is selected from halogen and $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkyl. In some cases, when $R^2$ is a heteroaryl, $R^6$ is selected from a halogen. In some cases, $R^{23}$ is selected from hydrogen and $C_1$-$C_3$ alkyl. In some cases, each $R^{23}$ is selected from $C_1$-$C_3$ alkyl. In some cases, each $R^{23}$ is selected from methyl. In some cases, each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, and $C_1$-$C_4$ alkyl; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 4- to 6-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 6-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen. In some cases, each L is selected from  ,  ,  ,  ,  ,  ,  , and  . In some cases, L is selected from  ,  ,  ,  ,  ,  , and . In some cases, $R^2$ is selected from  ,  ,  , and .

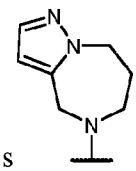
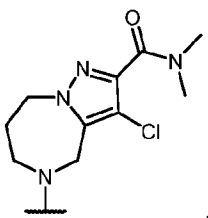
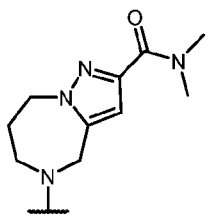
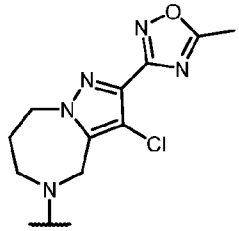
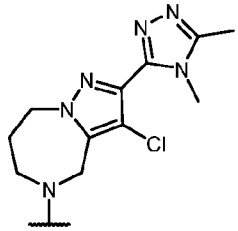
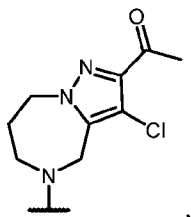
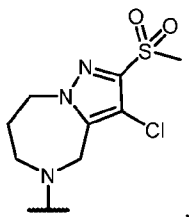
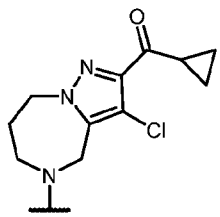
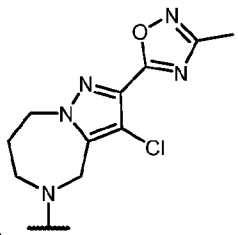
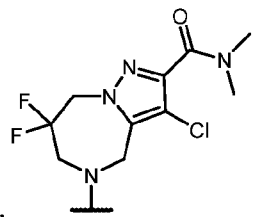
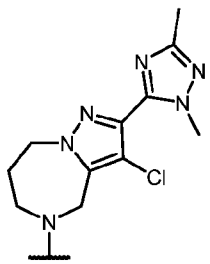
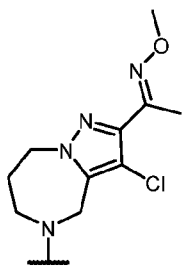
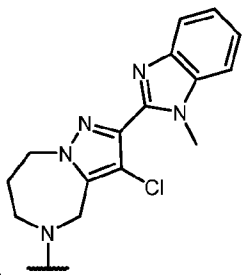
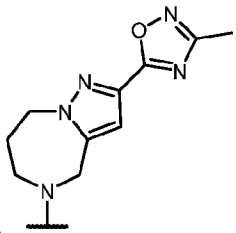
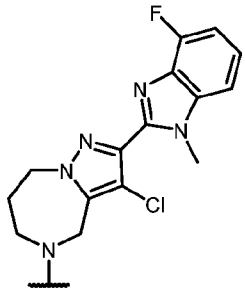
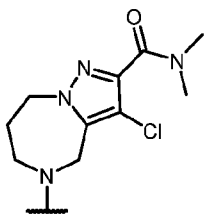
**[00289]** In some embodiments, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), Y-$R^2$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, Y-$R^2$ is selected  . In some cases, Y-$R^2$ is selected  ,  ,  ,  , and  . In some cases, Y-$R^2$ is selected  ,  , and  . In some cases, Y-$R^2$ is selected  . In some cases, Y-$R^2$ is selected from  , and  . In some cases, Y-$R^2$ is  . In some cases, Y-$R^2$ is  ,  , and  .

**[00290]** In some embodiments, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), B is selected from an 8- to 10-membered heterocycle, wherein the 8- to 10-membered

heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -$NH_2$, and $C_{1-6}$ alkyl. In some cases, the heterocycle of B is selected from  ,  ,  ,  ,  ,  , and  . In some cases, B is selected from  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -$NH_2$, and $C_{1-6}$ alkyl. In some cases, B is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

**[00291]** In some embodiments, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), $R^3$ is -CN. In some cases, $R^3$ is hydrogen. In some cases, $R^3$ is halogen. In some cases, $R^3$ is fluorine.

**[00292]** In some embodiments, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), $R^1$ is  . In some cases, $R^1$ is  . In some cases, $R^1$ is  . In some cases, $R^1$ is  , which is optionally substituted with one or more substituents. In some cases, the

one or more optional substituents are independently selected from halogen, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)R^{20}$ $=O$, and 5- to 9-membered heterocycle, wherein the 5- to -membered heterocycle are each optionally substituted independently with one or more $R^{1*}$. In some cases, the one or more optional substituents are independently selected from halogen, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)R^{20}$, $=O$, and 5- to 9-membered heterocycle, wherein the 5- to -membered heterocycle are each optionally substituted independently with one or more $R^{1*}$. In some cases, the one or more optional substituents are independently selected from halogen, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)R^{20}$, and 5- to 9-membered heterocycle, wherein the 5- to -membered heterocycle are each optionally substituted independently with one or more $R^{1*}$. In some cases, $R^1$ is  , which is subtituted with at least one substituent. In some cases, $R^1$ is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some cases, $R^1$ is  . In some cases, each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

**[00293]** In some embodiments, for a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), does not contain an electrophile moiety.

**[00294]** In some embodiments, for a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), the one or more optional substituents of $R^1$ are not electrophiles.

**[00295]** In some embodiments, for a compound or salt of Formula (I), $R^1$ is selected from a compound in the Examples. In some cases, B is selected from a compound in the Examples. In some cases, Y is selected from a compound in the Examples. In some cases, $R^2$ is selected from a compound in the Examples. In some cases, $R^3$ is selected from a compound in the Examples.

**[00296]** In some embodiments, for a compound or salt of Formula (I), each $R^{20}$ is selected from hydrogen and $C_{1-3}$ alkyl. In some cases, each $R^{20}$ is selected from hydrogen and $C_1$ alkyl.

**[00297]** In some embodiments, the compounds of Formula (I), Formula (I-A), or Formula (I-B), used in the methods include trifluoroacetic acid salts of the above compounds.

**[00298]** In some embodiments, the compound or salt of Formula (I) is selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111. In some cases, the compound or salt of Formula (I) is selected from compounds 2, 3, 4, 14, 25, and 74. In some cases, the compound or salt of Formula (I) is compound 2. In some cases, the compound or salt of Formula (I) is compound 3. In some cases, the compound or salt of Formula (I) is compound 4. In some cases, the compound or salt of Formula (I) is compound 14. In some cases, the compound or salt of Formula (I) is compound 25. In some cases, the compound or salt of Formula (I) is compound 74.

**[00299]** In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 5 mg to about 500 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 10 mg to about 150 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 10 mg to about 125 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 10 mg to about 100 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 25 mg to about 100 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 50 mg to about 100 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A),

or Formula (I-B), is administered to a subject at about 5 mg to about 75 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg. In some embodiments, the compound or salt of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, or 111, is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg. In some embodiments, the compound or salt of 2, 3, 4, 14, 25, or 74, is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg.

**[00300]** In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 15 mg, about 30 mg, about 45 mg, or about 60 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 15 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 30 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 45 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 60 mg. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00301]** In some embodiments, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered once daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), administered twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered 3 times daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered once weekly. In some embodiments the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered every other day. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered every 3 days.

**[00302]** In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at 10 mg to 150 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 10 mg to 125 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 10 mg to 100 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 25 mg to 100 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 50 mg to 100 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 5 mg to 75 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, or 150 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 15 mg, 30 mg, 45 mg, or 60 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 15 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 30 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 45 mg. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at 60 mg. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00303]** In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 10 mg to about 150 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is

administered to a subject at about 10 mg to about 125 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 10 mg to about 100 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 25 mg to about 100 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 50 mg to about 100 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 5 mg to about 75 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 15 mg, about 30 mg, about 45 mg, or about 60 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 15 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 30 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 45 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 60 mg, daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered once daily. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00304]** In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B), is administered to a subject at about 10 mg to about 150 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 10 mg to about 125 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 10 mg to about 100 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 25 mg to about 100 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 50 mg to about 100 mg, twice daily. In

some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 5 mg to about 75 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, or about 150 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 15 mg, about 30 mg, about 45 mg, or about 60 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 15 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 30 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 45 mg, twice daily. In some embodiments, the compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is administered to a subject at about 60 mg, twice daily. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00305]** In some embodiments, a compound of Formula (I), Formula (I-A), or Formula (I-B), is administered as a capsule during the period of time. In some cases, a tablet or capsule formulation of a compound of Formula (I), Formula (I-A), or Formula (I-B), or a pharmaceutically acceptable salt of any one thereof comprises about 10 mg to about 100 mg (e.g., about 10 mg to about 95 mg, about 10 mg to about 90 mg, about 10 mg to about 85 mg, about 10 mg to about 80 mg, about 10 mg to about 75 mg, about 10 mg to about 70 mg, about 10 mg to about 65 mg, about 10 mg to about 60 mg, about 10 mg to about 55 mg, about 10 mg to about 50 mg, about 10 mg to about 45 mg, about 10 mg to about 40 mg, about 10 mg to about 35 mg, about 10 mg to about 30 mg, about 10 mg to about 25 mg, about 10 mg to about 20 mg, about 10 mg to about 15 mg, about 15 mg to about 100 mg, about 15 mg to about 95 mg, about 15 mg to about 90 mg, about 15 mg to about 85 mg, about 15 mg to about 80 mg, about 15 mg to about 75 mg, about 15 mg to about 70 mg, about 15 mg to about 65 mg, about 15 mg to about 60 mg, about 15 mg to about 55 mg, about 15 mg to about 50 mg, about 15 mg to about 45 mg, about 15 mg to about 40 mg, about 15 mg to about 35 mg, about 15 mg to about 30 mg, about 15 mg to about 25 mg, about 15 mg to about 20 mg, about 20 mg to about 100 mg, about 20 mg to about 95 mg, about 20 mg to about 90 mg, about 20 mg to about 85 mg, about 20 mg to about 80

mg, about 20 mg to about 75 mg, about 20 mg to about 70 mg, about 20 mg to about 65 mg, about 20 mg to about 60 mg, about 20 mg to about 55 mg, about 20 mg to about 50 mg, about 20 mg to about 45 mg, about 20 mg to about 40 mg, about 20 mg to about 35 mg, about 20 mg to about 30 mg, about 20 mg to about 25 mg, about 25 mg to about 100 mg, about 25 mg to about 95 mg, about 25 mg to about 90 mg, about 25 mg to about 85 mg, about 25 mg to about 80 mg, about 25 mg to about 75 mg, about 25 mg to about 70 mg, about 25 mg to about 65 mg, about 25 mg to about 60 mg, about 25 mg to about 55 mg, about 25 mg to about 50 mg, about 25 mg to about 45 mg, about 25 mg to about 40 mg, about 25 mg to about 35 mg, about 25 mg to about 30 mg, about 30 mg to about 100 mg, about 30 mg to about 95 mg, about 30 mg to about 90 mg, about 30 mg to about 85 mg, about 30 mg to about 80 mg, about 30 mg to about 75 mg, about 30 mg to about 70 mg, about 30 mg to about 65 mg, about 30 mg to about 60 mg, about 30 mg to about 55 mg, about 30 mg to about 50 mg, about 30 mg to about 45 mg, about 30 mg to about 40 mg, about 30 mg to about 35 mg, about 35 mg to about 100 mg, about 35 mg to about 95 mg, about 35 mg to about 90 mg, about 35 mg to about 85 mg, about 35 mg to about 80 mg, about 35 mg to about 75 mg, about 35 mg to about 70 mg, about 35 mg to about 65 mg, about 35 mg to about 60 mg, about 35 mg to about 55 mg, about 35 mg to about 50 mg, about 35 mg to about 45 mg, about 35 mg to about 40 mg, about 40 mg to about 100 mg, about 40 mg to about 95 mg, about 40 mg to about 90 mg, about 40 mg to about 85 mg, about 40 mg to about 80 mg, about 40 mg to about 75 mg, about 40 mg to about 70 mg, about 40 mg to about 65 mg, about 40 mg to about 60 mg, about 40 mg to about 55 mg, about 40 mg to about 50 mg, about 40 mg to about 45 mg, about 45 mg to about 100 mg, about 45 mg to about 95 mg, about 45 mg to about 90 mg, about 45 mg to about 85 mg, about 45 mg to about 80 mg, about 45 mg to about 75 mg, about 45 mg to about 70 mg, about 45 mg to about 65 mg, about 45 mg to about 60 mg, about 45 mg to about 55 mg, about 45 mg to about 50 mg, about 50 mg to about 100 mg, about 50 mg to about 95 mg, about 50 mg to about 90 mg, about 50 mg to about 85 mg, about 50 mg to about 80 mg, about 50 mg to about 75 mg, about 50 mg to about 70 mg, about 50 mg to about 65 mg, about 50 mg to about 60 mg, about 50 mg to about 55 mg, about 55 mg to about 100 mg, about 55 mg to about 95 mg, about 55 mg to about 90 mg, about 55 mg to about 85 mg, about 55 mg to about 80 mg, about 55 mg to about 75 mg, about 55 mg to about 70 mg, about 55 mg to about 65 mg, about 55 mg to about 60 mg, about 60 mg to about 100 mg, about 60 mg to about 95 mg, about 60 mg to about 90 mg, about 60 mg to about 85 mg, about 60 mg to about 80 mg, about 60 mg to about 75 mg, about 60 mg to about 70 mg, about 60 mg to about 65 mg, about 65 mg to about 100 mg, about 65 mg to about 95 mg, about 65 mg to about 90 mg, about 65 mg to about 85 mg, about 65 mg to about 80 mg, about 65 mg to about 75 mg, about 65 mg to about 70 mg, about 70 mg to about 100 mg, about 70 mg to about 95 mg, about 70 mg to about 90 mg, about 70 mg to

about 85 mg, about 70 mg to about 80 mg, about 70 mg to about 75 mg, about 75 mg to about 100 mg, about 75 mg to about 95 mg, about 75 mg to about 90 mg, about 75 mg to about 85 mg, about 75 mg to about 80 mg, about 80 mg to about 100 mg, about 80 mg to about 95 mg, about 80 mg to about 90 mg, about 80 mg to about 85 mg, about 85 mg to about 100 mg, about 85 mg to about 95 mg, about 85 mg to about 90 mg, about 90 mg to about 100 mg, about 90 mg to about 95 mg, about 95 mg to about 100 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, or about 100 mg). In some cases, the compound or salt of Formula (I) is selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111. In some cases, the compound or salt of Formula (I) is selected from compounds 2, 3, 4, 14, 25, and 74. In some cases, the compound or salt of Formula (I) is compound 2. In some cases, the compound or salt of Formula (I) is compound 3. In some cases, the compound or salt of Formula (I) is compound 4. In some cases, the compound or salt of Formula (I) is compound 14. In some cases, the compound or salt of Formula (I) is compound 25. In some cases, the compound or salt of Formula (I) is compound 74.

**[00306]** In some embodiments, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is orally administered once a day (QD) on a daily basis during a period of time. In one embodiment, a compound or salt of Formula (I), Formula (I-A), or Formula (I-B) is orally administered twice a day (BID) on a daily basis during a period of time. In one embodiment, a compound of Formula (I), Formula (I-A), or Formula (I-B), is orally administered in the amount of about 20 mg to about 500 mg (e.g., about 20 mg to about 480 mg, about 20 mg to about 460 mg, about 20 mg to about 440 mg, about 20 mg to about 420 mg, about 20 mg to about 400 mg, about 20 mg to about 380 mg, about 20 mg to about 360 mg, about 20 mg to about 340 mg, about 20 mg to about 320 mg, about 20 mg to about 300 mg, about 20 mg to about 280 mg, about 20 mg to about 260 mg, about 20 mg to about 240 mg, about 20 mg to about 220 mg, about 20 mg to about 200 mg, about 20 mg to about 180 mg, about 20 mg to about 160 mg, about 20 mg to about 140 mg, about 20 mg to about 120 mg, about 20 mg to about 100 mg, about 20 mg to about 80 mg, about 20 mg to about 60 mg, about 20 mg to about 40 mg, about 40 mg to about 500 mg, about 40 mg to about 480 mg, about 40 mg to about 460 mg, about 40 mg to about 440 mg, about 40 mg to about 420 mg, about 40 mg to about 400 mg, about 40 mg to

about 380 mg, about 40 mg to about 360 mg, about 40 mg to about 340 mg, about 40 mg to about 320 mg, about 40 mg to about 300 mg, about 40 mg to about 280 mg, about 40 mg to about 260 mg, about 40 mg to about 240 mg, about 40 mg to about 220 mg, about 40 mg to about 200 mg, about 40 mg to about 180 mg, about 40 mg to about 160 mg, about 40 mg to about 140 mg, about 40 mg to about 120 mg, about 40 mg to about 100 mg, about 40 mg to about 80 mg, about 40 mg to about 60 mg, about 60 mg to about 500 mg, about 60 mg to about 480 mg, about 60 mg to about 460 mg, about 60 mg to about 440 mg, about 60 mg to about 420 mg, about 60 mg to about 400 mg, about 60 mg to about 380 mg, about 60 mg to about 360 mg, about 60 mg to about 340 mg, about 60 mg to about 320 mg, about 60 mg to about 300 mg, about 60 mg to about 280 mg, about 60 mg to about 260 mg, about 60 mg to about 240 mg, about 60 mg to about 220 mg, about 60 mg to about 200 mg, about 60 mg to about 180 mg, about 60 mg to about 160 mg, about 60 mg to about 140 mg, about 60 mg to about 120 mg, about 60 mg to about 100 mg, about 60 mg to about 80 mg, about 80 mg to about 500 mg, about 80 mg to about 480 mg, about 80 mg to about 460 mg, about 80 mg to about 440 mg, about 80 mg to about 420 mg, about 80 mg to about 400 mg, about 80 mg to about 380 mg, about 80 mg to about 360 mg, about 80 mg to about 340 mg, about 80 mg to about 320 mg, about 80 mg to about 300 mg, about 80 mg to about 280 mg, about 80 mg to about 260 mg, about 80 mg to about 240 mg, about 80 mg to about 220 mg, about 80 mg to about 200 mg, about 80 mg to about 180 mg, about 80 mg to about 160 mg, about 80 mg to about 140 mg, about 80 mg to about 120 mg, about 80 mg to about 100 mg, about 100 mg to about 500 mg, about 100 mg to about 480 mg, about 100 mg to about 460 mg, about 100 mg to about 440 mg, about 100 mg to about 420 mg, about 100 mg to about 400 mg, about 100 mg to about 380 mg, about 100 mg to about 360 mg, about 100 mg to about 340 mg, about 100 mg to about 320 mg, about 100 mg to about 300 mg, about 100 mg to about 280 mg, about 100 mg to about 260 mg, about 100 mg to about 240 mg, about 100 mg to about 220 mg, about 100 mg to about 200 mg, about 100 mg to about 180 mg, about 100 mg to about 160 mg, about 100 mg to about 140 mg, about 100 mg to about 120 mg, about 120 mg to about 500 mg, about 120 mg to about 480 mg, about 120 mg to about 460 mg, about 120 mg to about 440 mg, about 120 mg to about 420 mg, about 120 mg to about 400 mg, about 120 mg to about 380 mg, about 120 mg to about 360 mg, about 120 mg to about 340 mg, about 120 mg to about 320 mg, about 120 mg to about 300 mg, about 120 mg to about 280 mg, about 120 mg to about 260 mg, about 120 mg to about 240 mg, about 120 mg to about 220 mg, about 120 mg to about 200 mg, about 120 mg to about 180 mg, about 120 mg to about 160 mg, about 120 mg to about 140 mg, about 140 mg to about 500 mg, about 140 mg to about 480 mg, about 140 mg to about 460 mg, about 140 mg to about 440 mg, about 140 mg to about 420 mg, about 140 mg to about 400 mg, about 140 mg to about 380 mg, about 140 mg to

about 360 mg, about 140 mg to about 340 mg, about 140 mg to about 320 mg, about 140 mg to about 300 mg, about 140 mg to about 280 mg, about 140 mg to about 260 mg, about 140 mg to about 240 mg, about 140 mg to about 220 mg, about 140 mg to about 200 mg, about 140 mg to about 180 mg, about 140 mg to about 160 mg, about 160 mg to about 500 mg, about 160 mg to about 480 mg, about 160 mg to about 460 mg, about 160 mg to about 440 mg, about 160 mg to about 420 mg, about 160 mg to about 400 mg, about 160 mg to about 380 mg, about 160 mg to about 360 mg, about 160 mg to about 340 mg, about 160 mg to about 320 mg, about 160 mg to about 300 mg, about 160 mg to about 280 mg, about 160 mg to about 260 mg, about 160 mg to about 240 mg, about 160 mg to about 220 mg, about 160 mg to about 200 mg, about 160 mg to about 180 mg, about 180 mg to about 500 mg, about 180 mg to about 480 mg, about 180 mg to about 460 mg, about 180 mg to about 440 mg, about 180 mg to about 420 mg, about 180 mg to about 400 mg, about 180 mg to about 380 mg, about 180 mg to about 360 mg, about 180 mg to about 340 mg, about 180 mg to about 320 mg, about 180 mg to about 300 mg, about 180 mg to about 280 mg, about 180 mg to about 260 mg, about 180 mg to about 240 mg, about 180 mg to about 220 mg, about 180 mg to about 200 mg, about 200 mg to about 500 mg, about 200 mg to about 480 mg, about 200 mg to about 460 mg, about 200 mg to about 440 mg, about 200 mg to about 420 mg, about 200 mg to about 400 mg, about 200 mg to about 380 mg, about 200 mg to about 360 mg, about 200 mg to about 340 mg, about 200 mg to about 320 mg, about 200 mg to about 300 mg, about 200 mg to about 280 mg, about 200 mg to about 260 mg, about 200 mg to about 240 mg, about 200 mg to about 220 mg, about 220 mg to about 500 mg, about 220 mg to about 480 mg, about 220 mg to about 460 mg, about 220 mg to about 440 mg, about 220 mg to about 420 mg, about 220 mg to about 400 mg, about 220 mg to about 380 mg, about 220 mg to about 360 mg, about 220 mg to about 340 mg, about 220 mg to about 320 mg, about 220 mg to about 300 mg, about 220 mg to about 280 mg, about 220 mg to about 260 mg, about 220 mg to about 240 mg, about 240 mg to about 500 mg, about 240 mg to about 480 mg, about 240 mg to about 460 mg, about 240 mg to about 440 mg, about 240 mg to about 420 mg, about 240 mg to about 400 mg, about 240 mg to about 380 mg, about 240 mg to about 360 mg, about 240 mg to about 340 mg, about 240 mg to about 320 mg, about 240 mg to about 300 mg, about 240 mg to about 280 mg, about 240 mg to about 260 mg, about 260 mg to about 500 mg, about 260 mg to about 480 mg, about 260 mg to about 460 mg, about 260 mg to about 440 mg, about 260 mg to about 420 mg, about 260 mg to about 400 mg, about 260 mg to about 380 mg, about 260 mg to about 360 mg, about 260 mg to about 340 mg, about 260 mg to about 320 mg, about 260 mg to about 300 mg, about 260 mg to about 280 mg, about 280 mg to about 500 mg, about 280 mg to about 480 mg, about 280 mg to about 460 mg, about 280 mg to about 440 mg, about 280 mg to about 420 mg, about 280 mg to about 400 mg, about 280 mg to about 380 mg, about 280 mg to

about 360 mg, about 280 mg to about 340 mg, about 280 mg to about 320 mg, about 280 mg to about 300 mg, about 300 mg to about 500 mg, about 300 mg to about 480 mg, about 300 mg to about 460 mg, about 300 mg to about 440 mg, about 300 mg to about 420 mg, about 300 mg to about 400 mg, about 300 mg to about 380 mg, about 300 mg to about 360 mg, about 300 mg to about 340 mg, about 300 mg to about 320 mg, about 320 mg to about 500 mg, about 320 mg to about 480 mg, about 320 mg to about 460 mg, about 320 mg to about 440 mg, about 320 mg to about 420 mg, about 320 mg to about 400 mg, about 320 mg to about 380 mg, about 320 mg to about 360 mg, about 320 mg to about 340 mg, about 340 mg to about 500 mg, about 340 mg to about 480 mg, about 340 mg to about 460 mg, about 340 mg to about 440 mg, about 340 mg to about 420 mg, about 340 mg to about 400 mg, about 340 mg to about 380 mg, about 340 mg to about 360 mg, about 360 mg to about 500 mg, about 360 mg to about 480 mg, about 360 mg to about 460 mg, about 360 mg to about 440 mg, about 360 mg to about 420 mg, about 360 mg to about 400 mg, about 360 mg to about 380 mg, about 380 mg to about 500 mg, about 380 mg to about 480 mg, about 380 mg to about 460 mg, about 380 mg to about 440 mg, about 380 mg to about 420 mg, about 380 mg to about 400 mg, about 400 mg to about 500 mg, about 400 mg to about 480 mg, about 400 mg to about 460 mg, about 400 mg to about 440 mg, about 400 mg to about 420 mg, about 420 mg to about 500 mg, about 420 mg to about 480 mg, about 420 mg to about 460 mg, about 420 mg to about 440 mg, about 440 mg to about 500 mg, about 440 mg to about 480 mg, about 440 mg to about 460 mg, about 460 mg to about 500 mg, about 460 mg to about 480 mg, about 480 mg to about 500 mg, about 25, about 50, about 75, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, or about 500 mg), during a period of time. In some cases, the compound or salt of Formula (I) is selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111. In some cases, the compound or salt of Formula (I) is selected from compounds 2, 3, 4, 14, 25, and 74. In some cases, the compound or salt of Formula (I) is compound 2. In some cases, the compound or salt of Formula (I) is compound 3. In some cases, the compound or salt of Formula (I) is compound 4. In some cases, the compound or salt of Formula (I) is compound 14. In some cases, the compound or salt of Formula (I) is compound 25. In some cases, the compound or salt of Formula (I) is compound 74.

**[00307]** In some embodiments, the combination therapy comprises oral administration of a compound of Formula (I), Formula (I-A), or Formula (I-B), once or twice a day on a daily basis (during a period of time), e.g., in an amount of about 10 mg to about 400 mg (e.g., about 10 mg

to about 380 mg, about 10 mg to about 360 mg, about 10 mg to about 340 mg, about 10 mg to about 320 mg, about 10 mg to about 300 mg, about 10 mg to about 280 mg, about 10 mg to about 260 mg, about 10 mg to about 240 mg, about 10 mg to about 220 mg, about 10 mg to about 200 mg, about 10 mg to about 180 mg, about 10 mg to about 160 mg, about 10 mg to about 140 mg, about 10 mg to about 120 mg, about 10 mg to about 100 mg, about 10 mg to about 80 mg, about 10 mg to about 60 mg, about 10 mg to about 40 mg, about 10 mg to about 20 mg, about 20 mg to about 400 mg, about 20 mg to about 380 mg, about 20 mg to about 360 mg, about 20 mg to about 340 mg, about 20 mg to about 320 mg, about 20 mg to about 300 mg, about 20 mg to about 280 mg, about 20 mg to about 260 mg, about 20 mg to about 240 mg, about 20 mg to about 220 mg, about 20 mg to about 200 mg, about 20 mg to about 180 mg, about 20 mg to about 160 mg, about 20 mg to about 140 mg, about 20 mg to about 120 mg, about 20 mg to about 100 mg, about 20 mg to about 80 mg, about 20 mg to about 60 mg, about 20 mg to about 40 mg, about 40 mg to about 400 mg, about 40 mg to about 380 mg, about 40 mg to about 360 mg, about 40 mg to about 340 mg, about 40 mg to about 320 mg, about 40 mg to about 300 mg, about 40 mg to about 280 mg, about 40 mg to about 260 mg, about 40 mg to about 240 mg, about 40 mg to about 220 mg, about 40 mg to about 200 mg, about 40 mg to about 180 mg, about 40 mg to about 160 mg, about 40 mg to about 140 mg, about 40 mg to about 120 mg, about 40 mg to about 100 mg, about 40 mg to about 80 mg, about 40 mg to about 60 mg, about 60 mg to about 400 mg, about 60 mg to about 380 mg, about 60 mg to about 360 mg, about 60 mg to about 340 mg, about 60 mg to about 320 mg, about 60 mg to about 300 mg, about 60 mg to about 280 mg, about 60 mg to about 260 mg, about 60 mg to about 240 mg, about 60 mg to about 220 mg, about 60 mg to about 200 mg, about 60 mg to about 180 mg, about 60 mg to about 160 mg, about 60 mg to about 140 mg, about 60 mg to about 120 mg, about 60 mg to about 100 mg, about 60 mg to about 80 mg, about 80 mg to about 400 mg, about 80 mg to about 380 mg, about 80 mg to about 360 mg, about 80 mg to about 340 mg, about 80 mg to about 320 mg, about 80 mg to about 300 mg, about 80 mg to about 280 mg, about 80 mg to about 260 mg, about 80 mg to about 240 mg, about 80 mg to about 220 mg, about 80 mg to about 200 mg, about 80 mg to about 180 mg, about 80 mg to about 160 mg, about 80 mg to about 140 mg, about 80 mg to about 120 mg, about 80 mg to about 100 mg, about 100 mg to about 400 mg, about 100 mg to about 380 mg, about 100 mg to about 360 mg, about 100 mg to about 340 mg, about 100 mg to about 320 mg, about 100 mg to about 300 mg, about 100 mg to about 280 mg, about 100 mg to about 260 mg, about 100 mg to about 240 mg, about 100 mg to about 220 mg, about 100 mg to about 200 mg, about 100 mg to about 180 mg, about 100 mg to about 160 mg, about 100 mg to about 140 mg, about 100 mg to about 120 mg, about 120 mg to about 400 mg, about 120 mg to about 380 mg, about 120 mg to about 360 mg, about 120 mg to

about 340 mg, about 120 mg to about 320 mg, about 120 mg to about 300 mg, about 120 mg to about 280 mg, about 120 mg to about 260 mg, about 120 mg to about 240 mg, about 120 mg to about 220 mg, about 120 mg to about 200 mg, about 120 mg to about 180 mg, about 120 mg to about 160 mg, about 120 mg to about 140 mg, about 140 mg to about 400 mg, about 140 mg to about 380 mg, about 140 mg to about 360 mg, about 140 mg to about 340 mg, about 140 mg to about 320 mg, about 140 mg to about 300 mg, about 140 mg to about 280 mg, about 140 mg to about 260 mg, about 140 mg to about 240 mg, about 140 mg to about 220 mg, about 140 mg to about 200 mg, about 140 mg to about 180 mg, about 140 mg to about 160 mg, about 160 mg to about 400 mg, about 160 mg to about 380 mg, about 160 mg to about 360 mg, about 160 mg to about 360 mg, about 160 mg to about 340 mg, about 160 mg to about 320 mg, about 160 mg to about 300 mg, about 160 mg to about 280 mg, about 160 mg to about 260 mg, about 160 mg to about 240 mg, about 160 mg to about 220 mg, about 160 mg to about 200 mg, about 160 mg to about 180 mg, about 180 mg to about 400 mg, about 180 mg to about 380 mg, about 180 mg to about 360 mg, about 180 mg to about 340 mg, about 180 mg to about 320 mg, about 180 mg to about 300 mg, about 180 mg to about 280 mg, about 180 mg to about 260 mg, about 180 mg to about 240 mg, about 180 mg to about 220 mg, about 180 mg to about 200 mg, about 200 mg to about 400 mg, about 200 mg to about 380 mg, about 200 mg to about 360 mg, about 200 mg to about 340 mg, about 200 mg to about 320 mg, about 200 mg to about 300 mg, about 200 mg to about 280 mg, about 200 mg to about 260 mg, about 200 mg to about 240 mg, about 200 mg to about 220 mg, about 220 mg to about 400 mg, about 220 mg to about 380 mg, about 220 mg to about 360 mg, about 220 mg to about 340 mg, about 220 mg to about 320 mg, about 220 mg to about 300 mg, about 220 mg to about 280 mg, about 220 mg to about 260 mg, about 220 mg to about 240 mg, about 240 mg to about 400 mg, about 240 mg to about 380 mg, about 240 mg to about 360 mg, about 240 mg to about 340 mg, about 240 mg to about 320 mg, about 240 mg to about 300 mg, about 240 mg to about 280 mg, about 240 mg to about 260 mg, about 260 mg to about 400 mg, about 260 mg to about 380 mg, about 260 mg to about 360 mg, about 260 mg to about 340 mg, about 260 mg to about 320 mg, about 260 mg to about 300 mg, about 260 mg to about 280 mg, about 280 mg to about 400 mg, about 280 mg to about 380 mg, about 280 mg to about 360 mg, about 280 mg to about 340 mg, about 280 mg to about 320 mg, about 280 mg to about 300 mg, about 300 mg to about 400 mg, about 300 mg to about 380 mg, about 300 mg to about 360 mg, about 300 mg to about 340 mg, about 300 mg to about 320 mg, about 320 mg to about 400 mg, about 320 mg to about 380 mg, about 320 mg to about 360 mg, about 340 mg to about 360 mg, about 340 mg to about 400 mg, about 340 mg to about 380 mg, about 340 mg to about 360 mg, about 360 mg to about 400 mg, about 360 mg to about 380 mg, about 380 mg to

about 400 mg, about 100 mg, about 200 mg, about 300 mg, or about 400 mg), and oral administration of an inhibitor selected from:

1) RTK-MAPK pathway inhibitor;

2) RAF-MEK-ERK pathway inhibitor;

3) ERBB family inhibitor;

4) EGFR inhibitor;

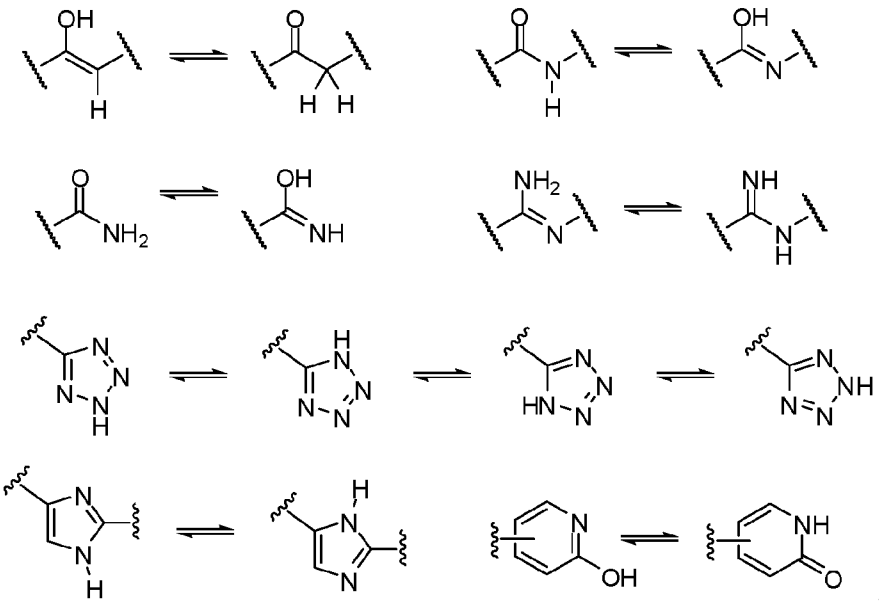
5) SHP-2 inhibitor; and

6) SOS1 inhibitor; or a pharmaceutically acceptable salt or a pharmaceutical composition thereof which is administered, for example once a day on a daily basis (during a period of time). In some cases, the inhibitor is an RTK-MAPK pathway inhibitor. In some cases, the inhibitor is an ERBB family inhibitor. In some cases, the inhibitor is an RAF-MEK-ERK pathway inhibitor. In some cases, the inhibitor is an EGFR inhibitor. In some cases, the inhibitor is an SHP-2 inhibitor. In some cases, the compound or salt of Formula (I) is selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111. In some cases, the compound or salt of Formula (I) is selected from compounds 2, 3, 4, 14, 25, and 74. In some cases, the compound or salt of Formula (I) is compound 2. In some cases, the compound or salt of Formula (I) is compound 3. In some cases, the compound or salt of Formula (I) is compound 4. In some cases, the compound or salt of Formula (I) is compound 14. In some cases, the compound or salt of Formula (I) is compound 25. In some cases, the compound or salt of Formula (I) is compound 74. In some cases, the compound and inhibitor are administered on separate days. In some cases, the compound and inhibitor are administered on the same day.

**[00308]** Included in the present disclosure are salts, particularly pharmaceutically acceptable salts, of the compounds described herein. The compounds of the present invention that possess a sufficiently acidic, a sufficiently basic, or both functional groups, can react with any of a number of inorganic bases, and inorganic and organic acids, to form a salt. Alternatively, compounds that are inherently charged, such as those with a quaternary nitrogen, can form a salt with an appropriate counterion, e.g., a halide such as bromide, chloride, or fluoride, particularly bromide.

**[00309]** Chemical entities having carbon-carbon double bonds or carbon-nitrogen double bonds may exist in *Z*- or *E*- form (or *cis*- or *trans*- form). Furthermore, some chemical entities may exist in various tautomeric forms. Unless otherwise specified, compounds described herein are intended to include all *Z*-, *E*- and tautomeric forms as well.

**[00310]** A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



**[00311]** The compounds disclosed herein, in some embodiments, are used in different enriched isotopic forms, e.g., enriched in the content of $^{2}H$, $^{3}H$, $^{11}C$, $^{13}C$ and/or $^{14}C$. In one particular embodiment, the compound is deuterated in at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the metabolic stability and or efficacy, thus increasing the duration of action of drugs.

**[00312]** Unless otherwise stated, compounds described herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by $^{13}C$- or $^{14}C$-enriched carbon are within the scope of the present disclosure.

**[00313]** The compounds of the present disclosure optionally contain unnatural proportions of atomic isotopes at one or more atoms that constitute such compounds. For example, the compounds may be labeled with isotopes, such as for example, deuterium ($^{2}H$), tritium ($^{3}H$), iodine-125 ($^{125}I$) or carbon-14 ($^{14}C$). Isotopic substitution with $^{2}H$, $^{11}C$, $^{13}C$, $^{14}C$, $^{15}C$, $^{12}N$, $^{13}N$, $^{15}N$, $^{16}N$, $^{16}O$, $^{17}O$, $^{14}F$, $^{15}F$, $^{16}F$, $^{17}F$, $^{18}F$, $^{33}S$, $^{34}S$, $^{35}S$, $^{36}S$, $^{35}Cl$, $^{37}Cl$, $^{79}Br$, $^{81}Br$, and $^{125}I$ are all

contemplated. All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

**[00314]** In certain embodiments, the compounds disclosed herein have some or all of the $^{1}H$ atoms replaced with $^{2}H$ atoms. The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the following synthetic methods.

**[00315]** Deuterium substituted compounds are synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

**[00316]** Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

**[00317]** Compounds of the present invention also include crystalline and amorphous forms of those compounds, pharmaceutically acceptable salts, and active metabolites of these compounds having the same type of activity, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

**[00318]** The compounds described herein may in some cases exist as diastereomers, enantiomers, or other stereoisomeric forms. Where absolute stereochemistry is not specified, the compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Separation of stereoisomers may be performed by chromatography or by forming diastereomers and separating by recrystallization, or chromatography, or any combination thereof. (Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981, herein incorporated by reference for this disclosure). Stereoisomers may also be obtained by stereoselective synthesis.

**[00319]** The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). The compounds described herein may be in the form of pharmaceutically acceptable salts. As well, in some embodiments, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well

as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

**[00320]** In certain embodiments, compounds or salts of the compounds may be prodrugs, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate, or carboxylic acid present in the parent compound is presented as an ester. The term "prodrug" is intended to encompass compounds which, under physiologic conditions, are converted into pharmaceutical agents of the present disclosure. One method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal such as specific target cells in the host animal. For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids and esters of phosphonic acids) are preferred prodrugs of the present disclosure.

**[00321]** Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound as set forth herein are included within the scope of the claims. In some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

**[00322]** Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. Prodrugs may help enhance the cell permeability of a compound relative to the parent drug. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues or to increase drug residence inside of a cell.

**[00323]** In some embodiments, the design of a prodrug increases the lipophilicity of the pharmaceutical agent. In some embodiments, the design of a prodrug increases the effective water solubility. See, e.g., Fedorak *et al.*, *Am. J. Physiol.*, 269:G210-218 (1995); McLoed *et al.*, *Gastroenterol*, 106:405-413 (1994); Hochhaus *et al.*, *Biomed. Chrom.*, 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics,* 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula *et al.*, *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, all incorporated herein for such disclosure). According to another embodiment, the present disclosure provides methods of producing the above-defined compounds. The compounds may be synthesized using conventional techniques.

Advantageously, these compounds are conveniently synthesized from readily available starting materials.

**[00324]** Synthetic chemistry transformations and methodologies useful in synthesizing the compounds described herein are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations* (1989); T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis,* 2d. Ed. (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis* (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis* (1995).

**Pharmaceutical Formulations**

**[00325]** Provided herein, in certain embodiments, are compositions comprising a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B); and a RTK-MAPK pathway inhibitor, an ERBB family inhibitor, a RAF-MEK-ERK pathway inhibitor, an EGFR inhibitor, a SHP-2 inhibitor, or a SOS1 inhibitor; or a pharmaceutically acceptable salt of any one thereof (also referred to herein as "a pharmaceutical agent").

**[00326]** Pharmaceutical compositions may be formulated using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the pharmaceutical agent into preparations which are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa., Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins, 1999).

**[00327]** The compositions and methods of the present disclosure may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the pharmaceutical agent, is preferably administered as a pharmaceutical composition comprising, for example, a pharmaceutical agent and a pharmaceutically acceptable carrier or excipient. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration, e.g., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier, the aqueous solution is

pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule, granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

**[00328]** A pharmaceutically acceptable excipient can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a pharmaceutical agent. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable excipient, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self emulsifying drug delivery system or a self microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

**[00329]** A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally, for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules, including sprinkle capsules and gelatin capsules, boluses, powders, granules, pastes for application to the tongue; absorption through the oral mucosa, e.g., sublingually; anally, rectally or vaginally, for example, as a pessary, cream or foam; parenterally, including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension; nasally; intraperitoneally; subcutaneously; transdermally, for example, as a patch applied to the skin; and topically, for example, as a cream, ointment or spray applied to the skin, or as an eye drop. The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water.

**[00330]** A pharmaceutical composition may be a sterile aqueous or non-aqueous solution, suspension or emulsion, *e.g.,* a microemulsion. The excipients described herein are examples and are in no way limiting. An effective amount or therapeutically effective amount refers to an amount of the one or more pharmaceutical agents administered to a subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

**[00331]** Subjects may generally be monitored for therapeutic effectiveness using assays and methods suitable for the condition being treated, which assays will be familiar to those having ordinary skill in the art and are described herein. Pharmacokinetics of a pharmaceutical agent, or one or more metabolites thereof, that is administered to a subject may be monitored by determining the level of the pharmaceutical agent or metabolite in a biological fluid, for example, in the blood, blood fraction, *e.g.*, serum, and/or in the urine, and/or other biological sample or biological tissue from the subject. Any method practiced in the art and described herein to detect the agent may be used to measure the level of the pharmaceutical agent or metabolite during a treatment course.

**[00332]** The dose of a pharmaceutical agent described herein for treating a disease or disorder may depend upon the subject's condition, that is, stage of the disease, severity of symptoms caused by the disease, general health status, as well as age, gender, and weight, and other factors apparent to a person skilled in the medical art. Pharmaceutical compositions may be administered in a manner appropriate to the disease to be treated as determined by persons skilled in the medical arts. In addition to the factors described herein and above related to use of pharmaceutical agent for treating a disease or disorder, suitable duration and frequency of administration of the pharmaceutical agent may also be determined or adjusted by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. Optimal doses of an agent may generally be determined using experimental models and/or clinical trials. The optimal dose may depend upon the body mass, weight, or blood volume of the subject. The use of the minimum dose that is sufficient to provide effective therapy is usually preferred. Design and execution of pre-clinical and clinical studies for a pharmaceutical agent, including when administered for prophylactic benefit, described herein are well within the skill of a person skilled in the relevant art. When two or more pharmaceutical agents are administered to treat a disease or disorder, the optimal dose of each pharmaceutical agent may be different, such as less than when either agent is administered alone as a single agent therapy. In certain particular embodiments, two pharmaceutical agents in combination may act synergistically or additively, and either agent may be used in a lesser amount than if administered alone. An amount of a pharmaceutical agent that may be administered per day may be, for example, between about 0.01 mg/kg and 100 mg/kg, *e.g.*, between about 0.1 to 1 mg/kg, between about 1 to 10 mg/kg, between about 10-50 mg/kg, between about 50-100 mg/kg body weight. In other embodiments, the amount of a pharmaceutical agent that may be administered per day is between about 0.01 mg/kg and 1000 mg/kg, between about 100-500 mg/kg, or between about 500-1000 mg/kg body weight. The

optimal dose, per day or per course of treatment, may be different for the disease or disorder to be treated and may also vary with the administrative route and therapeutic regimen.

**[00333]** Pharmaceutical compositions comprising a pharmaceutical agent can be formulated in a manner appropriate for the delivery method by using techniques routinely practiced in the art. The composition may be in the form of a solid, *e.g.,* tablet, capsule, semi-solid, *e.g.,* gel, liquid, or gas, e.g., aerosol. In other embodiments, the pharmaceutical composition is administered as a bolus infusion.

**[00334]** Pharmaceutical acceptable excipients are well known in the pharmaceutical art and described, for example, in Rowe et al., Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety, 5th Ed., 2006, and in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)). Exemplary pharmaceutically acceptable excipients include sterile saline and phosphate buffered saline at physiological pH. Preservatives, stabilizers, dyes, buffers, and the like may be provided in the pharmaceutical composition. In addition, antioxidants and suspending agents may also be used. In general, the type of excipient is selected based on the mode of administration, as well as the chemical composition of the active ingredient(s). Alternatively, compositions described herein may be formulated as a lyophilizate. A composition described herein may be lyophilized or otherwise formulated as a lyophilized product using one or more appropriate excipient solutions for solubilizing and/or diluting the pharmaceutical agent(s) of the composition upon administration. In other embodiments, the pharmaceutical agent may be encapsulated within liposomes using technology known and practiced in the art. In certain particular embodiments, a pharmaceutical agent is not formulated within liposomes for application to a stent that is used for treating highly, though not totally, occluded arteries. Pharmaceutical compositions may be formulated for any appropriate manner of administration described herein and in the art.

**[00335]** A pharmaceutical composition, *e.g.,* for oral administration or for injection, infusion, subcutaneous delivery, intramuscular delivery, intraperitoneal delivery or other method, may be in the form of a liquid. A liquid pharmaceutical composition may include, for example, one or more of the following: a sterile diluent such as water, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils that may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents; antioxidants; chelating agents; buffers and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral composition can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. The use of physiological saline is preferred, and an injectable pharmaceutical composition is preferably sterile. In another embodiment, for treatment of an ophthalmological condition or disease, a

liquid pharmaceutical composition may be applied to the eye in the form of eye drops. A liquid pharmaceutical composition may be delivered orally.

**[00336]** For oral formulations, at least one of the pharmaceutical agents described herein can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, and if desired, with diluents, buffering agents, moistening agents, preservatives, coloring agents, and flavoring agents. The pharmaceutical agents may be formulated with a buffering agent to provide for protection of the compound from low pH of the gastric environment and/or an enteric coating. A pharmaceutical agent included in a pharmaceutical composition may be formulated for oral delivery with a flavoring agent, *e.g.*, in a liquid, solid or semi-solid formulation and/or with an enteric coating.

**[00337]** A pharmaceutical composition comprising any one of the pharmaceutical agents described herein may be formulated for sustained or slow release, also called timed release or controlled release. Such compositions may generally be prepared using well known technology and administered by, for example, oral, rectal, intradermal, or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain the compound dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Excipients for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of pharmaceutical agent contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release, and the nature of the condition, disease or disorder to be treated or prevented.

**[00338]** In certain embodiments, the pharmaceutical compositions comprising a pharmaceutical agent are formulated for transdermal, intradermal, or topical administration. The compositions can be administered using a syringe, bandage, transdermal patch, insert, or syringe-like applicator, as a powder/talc or other solid, liquid, spray, aerosol, ointment, foam, cream, gel, paste. This preferably is in the form of a controlled release formulation or sustained release formulation administered topically or injected directly into the skin adjacent to or within the area to be treated, e.g., intradermally or subcutaneously. The active compositions can also be delivered via iontophoresis. Preservatives can be used to prevent the growth of fungi and other microorganisms. Suitable preservatives include, but are not limited to, benzoic acid, butylparaben, ethyl paraben, methyl paraben, propylparaben, sodium benzoate, sodium propionate, benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetypyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, thimerosal, and combinations thereof.

**[00339]** Pharmaceutical compositions comprising a pharmaceutical agent can be formulated as emulsions for topical application. An emulsion contains one liquid distributed in the body of a

second liquid. The emulsion may be an oil-in-water emulsion or a water-in-oil emulsion. Either or both of the oil phase and the aqueous phase may contain one or more surfactants, emulsifiers, emulsion stabilizers, buffers, and other excipients. The oil phase may contain other oily pharmaceutically approved excipients. Suitable surfactants include, but are not limited to, anionic surfactants, non-ionic surfactants, cationic surfactants, and amphoteric surfactants. Compositions for topical application may also include at least one suitable suspending agent, antioxidant, chelating agent, emollient, or humectant.

**[00340]** Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Liquid sprays may be delivered from pressurized packs, for example, via a specially shaped closure. Oil-in-water emulsions can also be used in the compositions, patches, bandages and articles. These systems are semisolid emulsions, micro-emulsions, or foam emulsion systems.

**[00341]** In some embodiments, the pharmaceutical agent described herein can be formulated as in inhalant. Inhaled methods can deliver medication directly to the airway. The pharmaceutical agent can be formulated as aerosols, microspheres, liposomes, or nanoparticles. The pharmaceutical agent can be formulated with solvents, gases, nitrates, or any combinations thereof. Compositions described herein are optionally formulated for delivery as a liquid aerosol or inhalable dry powder. Liquid aerosol formulations are optionally nebulized predominantly into particle sizes that can be delivered to the terminal and respiratory bronchioles. Liquid aerosol and inhalable dry powder formulations are preferably delivered throughout the endobronchial tree to the terminal bronchioles and eventually to the parenchymal tissue.

**[00342]** Aerosolized formulations described herein are optionally delivered using an aerosol forming device, such as a jet, vibrating porous plate or ultrasonic nebulizer, preferably selected to allow the formation of aerosol particles having with a mass medium average diameter predominantly between 1 to 5 μ. Further, the formulation preferably has balanced osmolarity ionic strength and chloride concentration, and the smallest aerosolizable volume able to deliver effective dose of the pharmaceutical agent. Additionally, the aerosolized formulation preferably does not impair negatively the functionality of the airways and does not cause undesirable side effects.

**[00343]** Aerosolization devices suitable for administration of aerosol formulations described herein include, for example, jet, vibrating porous plate, ultrasonic nebulizers and energized dry powder inhalers, that are able to nebulize the formulation into aerosol particle size predominantly in the size range from 1-5 μ. Predominantly in this application means that at least

70% but preferably more than 90% of all generated aerosol particles are within 1-5 μ range. A jet nebulizer works by air pressure to break a liquid solution into aerosol droplets. Vibrating porous plate nebulizers work by using a sonic vacuum produced by a rapidly vibrating porous plate to extrude a solvent droplet through a porous plate. An ultrasonic nebulizer works by a piezoelectric crystal that shears a liquid into small aerosol droplets. A variety of suitable devices are available, including, for example, AeroNebTM and AeroDoseTM vibrating porous plate nebulizers (AeroGen, Inc., Sunnyvale, California), Sidestream® nebulizers (Medic-Aid Ltd., West Sussex, England), Pari LC® and Pari LC Star® jet nebulizers (Pari Respiratory Equipment, Inc., Richmond, Virginia), and AerosonicTM (DeVilbiss Medizinische Produkte (Deutschland) GmbH, Heiden, Germany) and UltraAire® (Omron Healthcare, Inc., Vernon Hills, Illinois) ultrasonic nebulizers.

**[00344]** In some embodiments, the pharmaceutical agent(s) can be formulated with oleaginous bases or ointments to form a semisolid composition with a desired shape. In addition to the pharmaceutical agent, these semisolid compositions can contain dissolved and/or suspended bactericidal agents, preservatives and/or a buffer system. A petrolatum component that may be included may be any paraffin ranging in viscosity from mineral oil that incorporates isobutylene, colloidal silica, or stearate salts to paraffin waxes. Absorption bases can be used with an oleaginous system. Additives may include cholesterol, lanolin (lanolin derivatives, beeswax, fatty alcohols, wool wax alcohols, low HLB (hydrophobellipophobe balance) emulsifiers, and assorted ionic and nonionic surfactants, singularly or in combination.

**[00345]** Controlled or sustained release transdermal or topical formulations can be achieved by the addition of time-release additives, such as polymeric structures, matrices, that are available in the art. For example, the compositions may be administered through use of hot-melt extrusion articles, such as bioadhesive hot-melt extruded film. The formulation can comprise a cross-linked polycarboxylic acid polymer formulation. A cross-linking agent may be present in an amount that provides adequate adhesion to allow the system to remain attached to target epithelial or endothelial cell surfaces for a sufficient time to allow the desired release of the compound.

**[00346]** An insert, transdermal patch, bandage or article can comprise a mixture or coating of polymers that provide release of the pharmaceutical agents at a constant rate over a prolonged period of time. In some embodiments, the article, transdermal patch or insert comprises water-soluble pore forming agents, such as polyethylene glycol (PEG) that can be mixed with water insoluble polymers to increase the durability of the insert and to prolong the release of the active ingredients.

**[00347]** Transdermal devices (inserts, patches, bandages) may also comprise a water insoluble polymer. Rate controlling polymers may be useful for administration to sites where pH change can be used to effect release. These rate controlling polymers can be applied using a continuous coating film during the process of spraying and drying with the active compound. In one embodiment, the coating formulation is used to coat pellets comprising the active ingredients that are compressed to form a solid, biodegradable insert.

**[00348]** A polymer formulation can also be utilized to provide controlled or sustained release. Bioadhesive polymers described in the art may be used. By way of example, a sustained-release gel and the compound may be incorporated in a polymeric matrix, such as a hydrophobic polymer matrix. Examples of a polymeric matrix include a microparticle. The microparticles can be microspheres, and the core may be of a different material than the polymeric shell. Alternatively, the polymer may be cast as a thin slab or film, a powder produced by grinding or other standard techniques, or a gel such as a hydrogel. The polymer can also be in the form of a coating or part of a bandage, stent, catheter, vascular graft, or other device to facilitate delivery of the pharmaceutical agent. The matrices can be formed by solvent evaporation, spray drying, solvent extraction and other methods known to those skilled in the art.

**[00349]** Kits with unit doses of one or more of the agents described herein, usually in oral or injectable doses, are provided. Such kits may include a container containing the unit dose, an informational package insert describing the use and attendant benefits of the drugs in treating disease, and optionally an appliance or device for delivery of the composition.

## KITS AND PRODUCTS

### RTK-MAPK combination Kit

**[00350]** Some embodiments relate to kits and products that include the compound or salt of Formulas (I), (I-A), or (I-B); and at least one RTK-MAPK pathway inhibitor. For example, the kit or product can include a package or container with a compound or salt of Formulas (I), (I-A), or (I-B). Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound or salt of Formulas (I), (I-A), or (I-B), in combination with an RTK-MAPK pathway inhibitor that is separately provided. The kits can be used in the methods of treating cancer as described herein.

**[00351]** In some embodiments, the kits or products can include both a compound or salt of Formulas (I), (I-A), or (I-B), and at least one RTK-MAPK pathway inhibitor.

**[00352]** Such kits can include one or more containers or packages, which include one or both combination drugs together in a single container and/or package, or in separate packages/containers. In some instances, the two drugs are separately wrapped, but included in a

single package, container or box. Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound of Formulas (I), (I-A), or (I-B), in combination with an RTK-MAPK pathway inhibitor. The kits can be used in the methods of treating cancer as described herein.

**RAF-MEK-ERK pathway inhibitor combination Kit**

**[00353]** Some embodiments relate to kits and products that include the compound or salt of Formulas (I), (I-A), or (I-B), and at least on RAF-MEK-ERK pathway inhibitor. For example, the kit or product can include a package or container with a compound or salt of Formulas (I), (I-A), or (I-B). Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound or salt of Formulas (I), (I-A), or (I-B), in combination with an RTK-MAPK pathway inhibitor that is separately provided. The kits can be used in the methods of treating cancer as described herein.

**[00354]** In some embodiments, the kits or products can include both a compound or salt of Formulas (I), (I-A), or (I-B), and at least one RTK-MAPK pathway inhibitor.

**[00355]** Such kits can include one or more containers or packages, which include one or both combination drugs together in a single container and/or package, or in separate packages/containers. In some instances, the two drugs are separately wrapped, but included in a single package, container or box. Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound or salt of Formulas (I), (I-A), or (I-B), in combination with an RTK-MAPK pathway inhibitor. The kits can be used in the methods of treating cancer as described herein.

**ERBB family inhibitor combination Kit**

**[00356]** Some embodiments relate to kits and products that include the compound of Formulas (I), (I-A), or (I-B), and/or at least one ERBB inhibitor. For example, the kit or product can include a package or container with a compound or salt of Formulas (I), (I-A), or (I-B). Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound of Formulas (I), (I-A), or (I-B), in combination with an ERBB inhibitor that is separately provided. The kits can be used in the methods of treating cancer as described herein.

**[00357]** In some embodiments, the kits or products can include both a compound of Formulas (I), (I-A), or (I-B), and at least one ERBB inhibitor.

**[00358]** Such kits can include one or more containers or packages, which include one or both combination drugs together in a single container and/or package, or in separate packages/containers. In some instances, the two drugs are separately wrapped, but included in a single package, container or box. Such kits and products can further include a product insert or

label with approved drug administration and indication information, including how to use the compound of Formulas (I), (I-A), or (I-B), in combination with an ERBB inhibitor. The kits can be used in the methods of treating cancer as described herein.

**Epidermal growth factor receptor (EGFR) inhibitor combination Kit**

**[00359]** Some embodiments relate to kits and products that include the compound or salt of Formulas (I), (I-A), or (I-B), and/or at least one EGFR inhibitor. For example, the kit or product can include a package or container with a compound or salt of Formulas (I), (I-A), or (I-B). Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound or salt of Formulas (I), (I-A), or (I-B) in combination with an EGFR inhibitor that is separately provided. The kits can be used in the methods of treating cancer as described herein.

**[00360]** In some embodiments, the kits or products can include both a compound or salt of Formulas (I), (I-A), or (I-B), and at least one EGFR inhibitor.

**[00361]** Such kits can include one or more containers or packages, which include one or both combination drugs together in a single container and/or package, or in separate packages/containers. In some instances, the two drugs are separately wrapped, but included in a single package, container or box. Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound or salt of Formulas (I), (I-A), or (I-B), in combination with an EGFR inhibitor. The kits can be used in the methods of treating cancer as described herein.

**SHP-2 inhibitor combination Kit**

**[00362]** Some embodiments relate to kits and products that include the compound of Formulas (I), (I-A), or (I-B), and/or at least one SHP-2 inhibitor. For example, the kit or product can include a package or container with a compound or salt of Formulas (I), (I-A), or (I-B). Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound or salt of Formulas (I), (I-A), or (I-B), in combination with a SHP-2 inhibitor that is separately provided. The kits can be used in the methods of treating cancer as described herein.

**[00363]** In some embodiments, the kits or products can include both a compound or salt of Formulas (I), (I-A), or (I-B) and at least one SHP-2 inhibitor.

**[00364]** Such kits can include one or more containers or packages, which include one or both combination drugs together in a single container and/or package, or in separate packages/containers. In some instances, the two drugs are separately wrapped, but included in a single package, container or box. Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the

compound or salt of Formulas (I), (I-A), or (I-B), in combination with a SHP-2 inhibitor. The kits can be used in the methods of treating cancer as described herein.

**SOS1 inhibitor combination Kit**

**[00365]** Some embodiments relate to kits and products that include the compound or salt of Formulas (I), (I-A), or (I-B), and/or at least one SOS1 inhibitor. For example, the kit or product can include a package or container with a compound or salt of Formulas (I), (I-A), or (I-B). Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound or salt of Formulas (I), (I-A), or (I-B), in combination with a SOS1 inhibitor that is separately provided. The kits can be used in the methods of treating cancer as described herein.

**[00366]** In some embodiments, the kits or products can include both a compound or salt of Formulas (I), (I-A), or (I-B) and at least one SOS1 inhibitor.

**[00367]** Such kits can include one or more containers or packages, which include one or both combination drugs together in a single container and/or package, or in separate packages/containers. In some instances, the two drugs are separately wrapped, but included in a single package, container or box. Such kits and products can further include a product insert or label with approved drug administration and indication information, including how to use the compound or salt of Formulas (I), (I-A), or (I-B), in combination with a SOS1 inhibitor. The kits can be used in the methods of treating cancer as described herein.

**DOSINGS**

**[00368]** In some embodiments, the dosage regimen for the compounds herein (e.g, an RTK-MAPK pathway inhibitor; an ERBB family inhibitor; an RAF-MEK-ERK pathway inhibitor; an EGFR inhibitor; a SHP-2 inhibitor; an SOS1 inhibitor; or a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition of any one thereof) will vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. In some embodiments, a clinical practitioner can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the disease or disorder. In some cases, depending on the patient's condition and the intended therapeutic effect, the dosing frequency for the therapeutic agent may vary, for example, from once per day to six times per day. That is, the dosing frequency may be QD, i.e., once per day, BID, i.e., twice per day; TID, i.e., three times per day; QID, i.e., four times per day; five times per day, or six times

per day. In another embodiment, dosing frequency may be BIW, i.e., twice weekly, TIW, i.e., three times a week, or QIW, i.e. four times a week. In some cases, depending on the patient's condition and the intended therapeutic effect, the treatment cycle may have a period of time where no therapeutic agent is administered. As used herein, "interval administration" refers to administration of the therapeutic agent (e.g, an RTK-MAPK pathway inhibitor; an ERBB family inhibitor; an RAF-MEK-ERK pathway inhibitor; an EGFR inhibitor; a SHP-2 inhibitor; an SOS1 inhibitor; or a compound or salt of Formulas (I), (I-A), or (I-B), followed by void days or void weeks. For example, the treatment cycle may be 3 weeks long which includes 2 weeks of dosing of the therapeutic agent(s) followed by 1 week where no therapeutic agent is administered. In some embodiments, the treatment cycle is 4 weeks long which includes 3 weeks of dosing followed by 1 week where no therapeutic agent is administered.

**[00369]** In some embodiments, the daily oral dosage of each active ingredient (e.g, an RTK-MAPK pathway inhibitor; an ERBB family inhibitor; an RAF-MEK-ERK pathway inhibitor; an EGFR inhibitor; a SHP-2 inhibitor; an SOS1 inhibitor; or a compound or salt of Formulas (I), (I-A), or (I-B), when used for the indicated effects, will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, an active ingredient (e.g, an RTK-MAPK pathway inhibitor; an ERBB family inhibitor; an RAF-MEK-ERK pathway inhibitor; an EGFR inhibitor; a SHP-2 inhibitor; an SOS1 inhibitor; or a compound or salt of Formulas (I), (I-A), or (I-B), may be administered at a dose of between about 10 mg/day and about 200 mg/day. In some embodiments, an active ingredient (e.g, an RTK-MAPK pathway inhibitor; an ERBB family inhibitor; an RAF-MEK-ERK pathway inhibitor; an EGFR inhibitor; a SHP-2 inhibitor; an SOS1 inhibitor; or a compound or salt of Formulas (I), (I-A), or (I-B), may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The dose may be any value or subrange within the recited ranges.

**[00370]** In some embodiments, the daily oral dosage of each active ingredient (e.g, an RTK-MAPK pathway inhibitor; an ERBB family inhibitor; an RAF-MEK-ERK pathway inhibitor; an EGFR inhibitor; a SHP-2 inhibitor; an SOS1 inhibitor; or a compound or salt of Formula (I)), when used for the indicated effects, will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, an active ingredient (e.g, an RTK-MAPK pathway inhibitor; an ERBB family inhibitor; an RAF-MEK-ERK pathway

inhibitor; an EGFR inhibitor; a SHP-2 inhibitor; an SOS1 inhibitor; or a compound or salt of Formula (I)), may be administered at a dose of between about 10 mg/day and about 200 mg/day. In some embodiments, an active ingredient (e.g, an RTK-MAPK pathway inhibitor; an ERBB family inhibitor; an RAF-MEK-ERK pathway inhibitor; an EGFR inhibitor; a SHP-2 inhibitor; an SOS1 inhibitor; or a compound or salt of Formula (I)), may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The dose may be any value or subrange within the recited ranges.

**[00371]** The term "treatment cycle" as used herein, means a pre-determined period of time for administering the therapeutic agent (e.g, an RTK-MAPK pathway inhibitor; an ERBB family inhibitor; an RAF-MEK-ERK pathway inhibitor; an EGFR inhibitor; a SHP-2 inhibitor; an SOS1 inhibitor; or a compound or salt of Formulas (I), (I-A), or (I-B). In some embodiments, the patient is examined at the end of each treatment cycle to evaluate the effect of the therapy. In some cases, each of the treatment cycle has about 3 or more days. In some cases, each of the treatment cycle has from about 3 days to about 60 days. In some cases, each of the treatment cycle has from about 5 days to about 50 days. In some cases, each of the treatment cycle has from about 7 days to about 28 days. In some cases, each of the treatment cycle has 28 days. In some cases, the treatment cycle has about 29 days. In some cases, the treatment cycle has about 30 days. In some cases, the treatment cycle has about 31 days. In some cases, the treatment cycle has about a month-long treatment cycle. In some cases, the treatment cycle is any length of time from 3 weeks to 8 weeks. In some cases, the treatment cycle is any length of time from 3 weeks to 6 weeks. In some cases, the treatment cycle is 3 weeks. In some cases, the treatment cycle is one month. In some cases, the treatment cycle is 4 weeks. In some cases, the treatment cycle is 5 weeks. In some cases, the treatment cycle is 6 weeks. In some cases, the treatment cycle is 7 weeks. In some cases, the treatment cycle is 8 weeks. In some cases, the duration of the treatment cycle may include any value or subrange within the recited ranges, including endpoints.

**[00372]** In some embodiments, drugs are administered at the maximum tolerated dose ("MTD"), which is the highest dose of drug that does not cause unacceptable side effects.

**RTK-MAPK pathway inhibitor Dosing**

**[00373]** In some embodiments, the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof is administered prior to administration of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

**[00374]** In some embodiments, the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, is administered after administration of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof.

**[00375]** In some embodiments, the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, is administered at about the same time as administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof or pharmaceutical composition thereof. In some embodiments, separate administration of each inhibitor/compound, at different times and by different routes, may be advantageous. In some cases, the components in the combination i.e. compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, and the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt thereof, or pharmaceutical composition thereof, need not be necessarily administered at essentially the same time or in any order.

**[00376]** In some embodiments, a pharmaceutical composition comprises a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, a pharmaceutical composition comprises a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, the pharmaceutical compositions may be used in the methods simultaneously, separately, or sequentially. In some cases, a pharmaceutical composition comprises a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt thereof, and/or a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, for use in the methods for simultaneous, separate or sequential use.

**[00377]** In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are each dosed at their respective MTDs. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at its MTD and the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed in an amount less than its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at an amount less than its MTD and the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical

composition thereof and the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each dosed at less than their respective MTDs. In some cases, the administration can be so timed that the peak pharmacokinetic effect of one compound coincides with the peak pharmacokinetic effect of the other.

**[00378]** In some embodiments, the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered QD. In some cases, the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered BID. In some cases, the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, of the invention are administered TID. In some cases, the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered twice weekly. In some cases, the RTK-MAPK pathway inhibitor is administered intraperitoneally.

**[00379]** In some embodiments, a single dose of compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each administered once daily.

**[00380]** In some embodiments, the therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination may be any value or subrange within the recited ranges.

**[00381]** In some embodiments, the therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination will range between about 0.1 to about 50 mg/kg of body weight. In some embodiments the therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination will range between about 10

mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination may be any value or subrange within the recited ranges.

**[00382]** In some embodiments, the RTK-MAPK pathway inhibitor is administered to a subject at about 200 mg to about 500 mg. In some embodiments, the RTK-MAPK pathway inhibitor, or pharmaceutically salt thereof is administered to a subject at about 440 mg to about 520 mg. In some embodiments the RTK-MAPK pathway inhibitor is administered to a subject at about 10 mg to about 100 mg. In some embodiments, the RTK-MAPK pathway inhibitor is administered to a subject at about 240 mg to about 480 mg. In some embodiments, the RTK-MAPK pathway inhibitor, or pharmaceutically salt thereof is administered to a subject at about 50 mg to about 100 mg. In some embodiments, the RTK-MAPK pathway inhibitor, or pharmaceutically salt thereof of is administered to a subject at about 5 mg to about 75 mg. In some embodiments, the RTK-MAPK pathway inhibitor, or pharmaceutically salt thereof is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 170 mg, about 190 mg, about 210 mg, about 240 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, about 440 mg, about 460 mg, about 480 mg, about 500 mg, about 540 mg, about 580 mg, or about 650 mg. In some embodiments, the RTK-MAPK pathway inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg , about 30 mg, about 45 mg, or about 60 mg. In some embodiments, the RTK-MAPK pathway inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg. In some embodiments, the RTK-MAPK pathway inhibitor, or pharmaceutically salt thereof is administered to a subject at about 30 mg. In some embodiments, the RTK-MAPK pathway inhibitor, or pharmaceutically salt thereof is administered to a subject at about 240 mg. In some embodiments, the RTK-MAPK pathway inhibitor, or pharmaceutically salt thereof is administered to a subject at about 480 mg. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some

embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00383]** In some embodiments, the RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt thereof, and the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, can be formulated into separate or individual dosage forms which can be co-administered one after the other. In some embodiments, if the route of administration is the same (e.g. oral) two active compounds can be formulated into a single form for co-administration, both methods of co-administration, however, being part of the same therapeutic treatment or regimen. In some embodiments, the combination therapy comprises oral administration of a compound of Formulas (I), (I-A), or (I-B), once or twice a day on a daily basis (during a period of time), e.g., in an amount of about 10 mg to about 400 mg and oral administration of an RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof which is administered, for example once a day on a daily basis (during a period of time).

**RAF-MEK-ERK pathway inhibitor Dosing**

**[00384]** In some embodiments, a pharmaceutical composition comprises a RAF-MEK-ERK inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, a pharmaceutical composition comprises a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, the pharmaceutical compositions may be used in the methods simultaneously, separately, or sequentially.

**[00385]** In some embodiments, a pharmaceutical composition comprises a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt thereof, and/or a compound or salt of Formulas (I), (I-A), or (I-B), for use in the methods which may be for simultaneous, separate or sequential use.

**[00386]** In some cases, the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered prior to administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In another embodiment, the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered after administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In another embodiment, the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered at about the same time as administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some embodiments, separate

administration of each inhibitor, at different times and by different routes, may be advantageous. In some cases, the components in the combination i.e. compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, and the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, may need not to be administered at essentially the same time or in any order.

**[00387]** In some embodiments, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof and the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are each dosed at their respective MTDs. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, is dosed at its MTD and the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed in an amount less than its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, is dosed at an amount less than its MTD and the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof and the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each dosed at less than their respective MTDs. In some cases, the administration can be so timed that the peak pharmacokinetic effect of one compound coincides with the peak pharmacokinetic effect of the other.

**[00388]** In some embodiments, the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered QD. In some cases, the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered BID. In some cases, the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, of the invention are administered TID. In some cases, the RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered twice weekly. In some cases, the RAF-MEK-ERK pathway inhibitor is administered intraperitoneally.

**[00389]** In some embodiments, a single dose of compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each administered once daily.

**[00390]** In some embodiments, the therapeutically effective amount of the RAF-MEK-ERK pathway inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most

preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, a RAF-MEK-ERK pathway inhibitor the therapeutically effective amount of the RAF-MEK-ERK pathway inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the RAF-MEK-ERK pathway inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the RAF-MEK-ERK pathway inhibitor of the combination may be any value or subrange within the recited ranges.

**[00391]** In some embodiments, the therapeutically effective amount of the RAF-MEK-ERK pathway inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the RAF-MEK-ERK pathway inhibitor of the combination will range between about 0.1 to about 50 mg/kg of body weight. In some embodiments, the therapeutically effective amount of the RAF-MEK-ERK pathway inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the RAF-MEK-ERK pathway inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the RAF-MEK-ERK pathway inhibitor of the combination may be any value or subrange within the recited ranges.

**[00392]** In some embodiments, the RAF-MEK-ERK inhibitor is administered to a subject at about 200 mg to about 500 mg. In some embodiments, the RAF-MEK-ERK inhibitor, or pharmaceutically salt thereof is administered to a subject at about 440 mg to about 520 mg. In some embodiments the RAF-MEK-ERK inhibitor is administered to a subject at about 10 mg to about 100 mg. In some embodiments, the RAF-MEK-ERK inhibitor is administered to a subject at about 240 mg to about 480 mg. In some embodiments, the RAF-MEK-ERK inhibitor, or pharmaceutically salt thereof is administered to a subject at about 50 mg to about 100 mg. In some embodiments, the RAF-MEK-ERK inhibitor, or pharmaceutically salt thereof of is administered to a subject at about 5 mg to about 75 mg. In some embodiments, the RAF-MEK-ERK inhibitor, or pharmaceutically salt thereof is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about

85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 170 mg, about 190 mg, about 210 mg, about 240 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, about 440 mg, about 460 mg, about 480 mg, about 500 mg, about 540 mg, about 580 mg, or about 650 mg. In some embodiments, the RAF-MEK-ERK inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg , about 30 mg, about 45 mg, or about 60 mg. In some embodiments, the RAF-MEK-ERK inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg. In some embodiments, the RAF-MEK-ERK inhibitor, or pharmaceutically salt thereof is administered to a subject at about 30 mg. In some embodiments, the RAF-MEK-ERK inhibitor, or pharmaceutically salt thereof is administered to a subject at about 240 mg. In some embodiments, the RAF-MEK-ERK inhibitor, or pharmaceutically salt thereof is administered to a subject at about 480 mg. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00393]** In some embodiments, the RAF-MEK-ERK inhibitor, or a pharmaceutically acceptable salt thereof, and the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, can be formulated into separate or individual dosage forms which can be co-administered one after the other. In some cases, if the route of administration is the same (e.g. oral) two active compounds can be formulated into a single form for co-administration, both methods of co-administration, however, being part of the same therapeutic treatment or regimen. In some embodiments, the combination therapy comprises oral administration of a compound of Formulas (I), (I-A), or (I-B), once or twice a day on a daily basis (during a period of time), e.g., in an amount of about 10 mg to about 400 mg and oral administration of a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof which is administered, for example once a day on a daily basis (during a period of time).

**ERBB family inhibitor Dosing**

**[00394]** In some embodiments, a pharmaceutical composition comprises a ERBB family inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, a pharmaceutical composition comprises a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, the pharmaceutical compositions may be used in the methods simultaneously, separately, or sequentially.

**[00395]** In some embodiments, the pharmaceutical compositions comprises a ERBB family inhibitor, or a pharmaceutically acceptable salt thereof, and/or a compound or salt of Formulas (I), (I-A), or (I-B), for use in the methods may be for simultaneous, separate or sequential use. In some cases, the ERBB family inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered prior to administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In another embodiment, the ERBB family inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered after administration of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In another embodiment, the ERBB family inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered at about the same time as administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In some embodiments, separate administration of each inhibitor, at different times and by different routes, may be advantageous. Thus, the components in the combination i.e. compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and the ERBB family inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, may need not be necessarily administered at essentially the same time or in any order. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof and the ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are each dosed at their respective MTDs. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at its MTD and the ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed in an amount less than its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at an amount less than its MTD and the ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof and the ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each dosed at less than their respective MTDs. In some cases, the administration can be so timed that the peak pharmacokinetic effect of one compound coincides with the peak pharmacokinetic effect of the other.

**[00396]** In some embodiments, the ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered QD. In some cases, the ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered BID. In some cases, the ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, of the invention are administered TID. In some cases, the ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered twice weekly. In some cases, the ERBB family pathway inhibitor is administered intraperitoneally.

**[00397]** In some embodiments, a single dose of compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, and ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each administered once daily.

**[00398]** In some embodiments, the therapeutically effective amount of the ERBB family inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, an ERBB family inhibitor the therapeutically effective amount of the ERBB family inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the ERBB family inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the ERBB family inhibitor of the combination may be any value or subrange within the recited ranges.

**[00399]** In some embodiments, the therapeutically effective amount of the ERBB family inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the ERBB family inhibitor of the combination will range between about 0.1 to about 50 mg/kg of body weight. In some embodiments, the therapeutically effective amount of the ERBB family inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the ERBB family inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200

mg/day. The therapeutically effective amount of the ERBB family inhibitor of the combination may be any value or subrange within the recited ranges.

**[00400]** In some embodiments, the ERBB family inhibitor is administered to a subject at about 200 mg to about 500 mg. In some embodiments, the ERBB family inhibitor, or pharmaceutically salt thereof is administered to a subject at about 440 mg to about 520 mg. In some embodiments the ERBB family inhibitor is administered to a subject at about 10 mg to about 100 mg. In some embodiments, the ERBB family inhibitor is administered to a subject at about 240 mg to about 480 mg. In some embodiments, the ERBB family inhibitor, or pharmaceutically salt thereof is administered to a subject at about 50 mg to about 100 mg. In some embodiments, the ERBB family inhibitor, or pharmaceutically salt thereof of is administered to a subject at about 5 mg to about 75 mg. In some embodiments, the ERBB family inhibitor, or pharmaceutically salt thereof is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 170 mg, about 190 mg, about 210 mg, about 240 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, about 440 mg, about 460 mg, about 480 mg, about 500 mg, about 540 mg, about 580 mg, or about 650 mg. In some embodiments, the ERBB family inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg , about 30 mg, about 45 mg, or about 60 mg. In some embodiments, the ERBB family inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg. In some embodiments, the ERBB family inhibitor, or pharmaceutically salt thereof is administered to a subject at about 30 mg. In some embodiments, the ERBB family inhibitor, or pharmaceutically salt thereof is administered to a subject at about 240 mg. In some embodiments, the ERBB family inhibitor, or pharmaceutically salt thereof is administered to a subject at about 480 mg. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00401]** In some embodiments, the ERBB family inhibitor, or a pharmaceutically acceptable salt thereof, and the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, can be formulated into separate or individual dosage forms which can be co-administered one after the other. Another option is that if the route of administration is the same (e.g. oral) two active compounds can be formulated into a single form for co-administration, both methods of co-administration, however, being part of the same therapeutic treatment or regimen.

In some embodiments, the combination therapy comprises oral administration of a compound of Formulas (I), (I-A), or (I-B), once or twice a day on a daily basis (during a period of time), e.g., in an amount of about 10 mg to about 400 mg and oral administration of an ERBB inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof which is administered, for example once a day on a daily basis (during a period of time). In some cases, the compound and inhibitor are administered on separate days. In some cases, the compound and inhibitor are administered on the same day.

**Epidermal growth factor receptor (EGFR) inhibitor Dosing**

**[00402]** In some embodiments, a pharmaceutical composition comprises a EGFR inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, a pharmaceutical composition comprises a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, the pharmaceutical compositions may be used in the methods simultaneously, separately, or sequentially.

**[00403]** In some embodiments, the pharmaceutical compositions comprising an EGFR inhibitor, or a pharmaceutically acceptable salt thereof, and/or a compound or salt of Formulas (I), (I-A), or (I-B), for use in the methods may be for simultaneous, separate or sequential use.

**[00404]** In some embodiments, the EGFR inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered prior to administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In another embodiment, the EGFR inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered after administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In another embodiment, the EGFR inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered at about the same time as administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some embodiments, separate administration of each inhibitor, at different times and by different routes, may be advantageous. In some cases, the components in the combination i.e. compound or salt of Formulas (I), (I-A), or (I-B), and the EGFR inhibitor, or a pharmaceutically acceptable salt thereof, need not be necessarily administered at essentially the same time or in any order. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof and the EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are each dosed at their respective MTDs. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, is dosed at its MTD and the EGFR inhibitor, or a pharmaceutically acceptable salt or a

pharmaceutical composition thereof, is dosed in an amount less than its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, is dosed at an amount less than its MTD and the EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof and the EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each dosed at less than their respective MTDs. In some cases, the administration can be so timed that the peak pharmacokinetic effect of one compound coincides with the peak pharmacokinetic effect of the other.

**[00405]** In some embodiments, the EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered QD. In some cases, the EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered BID. In some cases, the EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, of the invention are administered TID. In some cases, the EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered twice weekly (BIW). In some cases, the EGFR inhibitor is administered intraperitoneally.

**[00406]** In some embodiments, a single dose of compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, and EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each administered once daily.

**[00407]** In some embodiments, the therapeutically effective amount of the EGFR inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the EGFR inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some cases, the therapeutically effective amount of the EGFR inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the EGFR inhibitor of the combination may be any value or subrange within the recited ranges.

**[00408]** In some embodiments, the therapeutically effective amount of the EGFR inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the EGFR inhibitor of the combination will range between about 0.1 to about 50 mg/kg of body

weight. In some embodiments, the therapeutically effective amount of the EGFR inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the EGFR inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the EGFR inhibitor of the combination may be any value or subrange within the recited ranges.

**[00409]** In some embodiments, the EGFR inhibitor is administered to a subject at about 200 mg to about 500 mg. In some embodiments, the EGFR inhibitor, or pharmaceutically salt thereof is administered to a subject at about 440 mg to about 520 mg. In some embodiments the EGFR inhibitor is administered to a subject at about 10 mg to about 100 mg. In some embodiments, the EGFR inhibitor is administered to a subject at about 240 mg to about 480 mg. In some embodiments, the EGFR inhibitor, or pharmaceutically salt thereof is administered to a subject at about 50 mg to about 100 mg. In some embodiments, the EGFR inhibitor, or pharmaceutically salt thereof of is administered to a subject at about 5 mg to about 75 mg. In some embodiments, the EGFR inhibitor, or pharmaceutically salt thereof is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 170 mg, about 190 mg, about 210 mg, about 240 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, about 440 mg, about 460 mg, about 480 mg, about 500 mg, about 540 mg, about 580 mg, or about 650 mg. In some embodiments, the EGFR inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg , about 30 mg, about 45 mg, or about 60 mg. In some embodiments, the EGFR inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg. In some embodiments, the EGFR inhibitor, or pharmaceutically salt thereof is administered to a subject at about 30 mg. In some embodiments, the EGFR inhibitor, or pharmaceutically salt thereof is administered to a subject at about 240 mg. In some embodiments, the EGFR inhibitor, or pharmaceutically salt thereof is administered to a subject at about 480 mg. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00410]** In some embodiments, the EGFR inhibitor, or a pharmaceutically acceptable salt thereof, and the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, can be formulated into separate or individual dosage forms which can be co-administered one after the other. In some cases, if the route of administration is the same (e.g. oral) two active compounds can be formulated into a single form for co-administration, both methods of co-administration, however, being part of the same therapeutic treatment or regimen. In some embodiments, the combination therapy comprises oral administration of a compound of Formulas (I), (I-A), or (I-B), once or twice a day on a daily basis (during a period of time), e.g., in an amount of about 10 mg to about 400 mg and oral administration of an EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof which is administered, for example once a day on a daily basis (during a period of time).

**[00411]** In some cases, the compound and inhibitor are administered on separate days. In some cases, the compound and inhibitor are administered on the same day.

**SHP-2 inhibitor Dosing**

**[00412]** In some embodiments, a pharmaceutical composition comprises a SHP-2 inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, a pharmaceutical composition comprises a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, the pharmaceutical compositions may be used in the methods simultaneously, separately, or sequentially.

**[00413]** In some embodiments, the pharmaceutical compositions comprise a SHP-2 inhibitor, or a pharmaceutically acceptable salt thereof, and/or a compound or salt of Formulas (I), (I-A), or (I-B), for use in the methods may be for simultaneous, separate or sequential use.

**[00414]** In some embodiments, the SHP-2 inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof is administered prior to administration of the compound or salt of Formulas (I), (I-A), or (I-B). In another embodiment, the SHP-2 inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, is administered after administration of the compound or salt of Formulas (I), (I-A), or (I-B). In another embodiment, the SHP-2 inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof is administered at about the same time as administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some embodiments, separate administration of each inhibitor, at different times and by different routes, may be advantageous. In some cases, the components in the combination i.e. compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, and the SHP-2 inhibitor, or a pharmaceutically acceptable salt thereof, need not be necessarily administered at

essentially the same time or in any order. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof and the SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are each dosed at their respective MTDs. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, is dosed at its MTD and the SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed in an amount less than its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, is dosed at an amount less than its MTD and the SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof and the SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each dosed at less than their respective MTDs. In some cases, the administration can be so timed that the peak pharmacokinetic effect of one compound coincides with the peak pharmacokinetic effect of the other.

**[00415]** In some embodiments, the SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered QD. In some cases, the SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered BID. In some cases, the SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, of the invention are administered TID. In some cases, the SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered twice weekly. In some cases, the SHP-2 is administered intraperitoneally.

**[00416]** In some embodiments, a single dose of compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, and SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each administered once daily.

**[00417]** In some embodiments, the therapeutically effective amount of the SHP-2 inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the SHP-2 inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the SHP-2 inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the SHP-2 inhibitor of the combination may be any value or subrange within the recited ranges.

**[00418]** In some embodiments, the therapeutically effective amount of the SHP-2 inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the SHP-2 inhibitor of the combination will range between about 0.1 to about 50 mg/kg of body weight. In some embodiments, the therapeutically effective amount of the SHP-2 inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the SHP-2 inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the SHP-2 inhibitor of the combination may be any value or subrange within the recited ranges.

**[00419]** In some embodiments, the SHP-2 inhibitor is administered to a subject at about 200 mg to about 500 mg. In some embodiments, the SHP-2 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 440 mg to about 520 mg. In some embodiments the SHP-2 inhibitor is administered to a subject at about 10 mg to about 100 mg. In some embodiments, the SHP-2 inhibitor is administered to a subject at about 240 mg to about 480 mg. In some embodiments, the SHP-2 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 50 mg to about 100 mg. In some embodiments, the SHP-2 inhibitor, or pharmaceutically salt thereof of is administered to a subject at about 5 mg to about 75 mg. In some embodiments, the SHP-2 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 170 mg, about 190 mg, about 210 mg, about 240 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, about 440 mg, about 460 mg, about 480 mg, about 500 mg, about 540 mg, about 580 mg, or about 650 mg. In some embodiments, the SHP-2 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg , about 30 mg, about 45 mg, or about 60 mg. In some embodiments, the SHP-2 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg. In some embodiments, the SHP-2 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 30 mg. In some embodiments, the SHP-2 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 240 mg. In some embodiments, the SHP-2 inhibitor, or pharmaceutically salt thereof is administered

to a subject at about 480 mg. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00420]** The SHP-2 inhibitor, or a pharmaceutically acceptable salt thereof, and the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, can be formulated into separate or individual dosage forms which can be co-administered one after the other. Another option is that if the route of administration is the same (e.g. oral) two active compounds can be formulated into a single form for co-administration, both methods of co-administration, however, being part of the same therapeutic treatment or regimen. In some embodiments, the combination therapy comprises oral administration of a compound or salt of Formulas (I), (I-A), or (I-B), once or twice a day on a daily basis (during a period of time), e.g., in an amount of about 10 mg to about 400 mg and oral administration of a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof which is administered, for example once a day on a daily basis (during a period of time).

**SOS1 inhibitor Dosing**

**[00421]** In some embodiments, a pharmaceutical composition comprises a SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, a pharmaceutical composition comprises a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some cases, the pharmaceutical compositions may be used in the methods simultaneously, separately, or sequentially.

**[00422]** In some embodiments, the pharmaceutical compositions comprise a SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, and/or a compound or salt of Formulas (I), (I-A), or (I-B), for use in the methods may be for simultaneous, separate or sequential use.

**[00423]** In some cases, the SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, is administered prior to administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In another embodiment, the SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof is administered after administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In another embodiment, the SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, is administered at about the same time as administration of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some embodiments, separate administration of each inhibitor, at different times and by different routes, may be advantageous. Thus, the components in the combination

i.e. compound or salt of Formulas (I), (I-A), or (I-B), and the SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, need not be necessarily administered at essentially the same time or in any order. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof and the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are each dosed at their respective MTDs. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), a pharmaceutical composition thereof, is dosed at its MTD and the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed in an amount less than its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, is dosed at an amount less than its MTD and the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is dosed at its MTD. In some cases, the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof and the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each dosed at less than their respective MTDs. In some cases, the administration can be so timed that the peak pharmacokinetic effect of one compound coincides with the peak pharmacokinetic effect of the other.

**[00424]** In some embodiments, the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered QD. In some cases, the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, are administered BID. In some cases, the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, of the invention are administered TID. In some cases, the SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, is administered twice weekly. In some cases, the SOS1 inhibitor is administered intraperitoneally.

**[00425]** In some embodiments, a single dose of compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, and SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof are each administered once daily.

**[00426]** In some embodiments, the therapeutically effective amount of the SOS1 inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the SOS1 inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the SOS1 inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200

mg/day. The therapeutically effective amount of the SOS1 inhibitor of the combination may be any value or subrange within the recited ranges.

**[00427]** In some embodiments, the therapeutically effective amount of the SOS1 inhibitor of the combination will range between about 0.001 to about 1000 mg/kg of body weight, preferably between about 0.01 to about 100 mg/kg of body weight per day, and most preferably between about 0.1 to about 20 mg/kg/day. In some embodiments, the therapeutically effective amount of the SOS1 inhibitor of the combination will range between about 0.1 to about 50 mg/kg of body weight. In some embodiments, the therapeutically effective amount of the SOS1 inhibitor of the combination will range between about 10 mg/day and about 200 mg/day. In some embodiments, the therapeutically effective amount of the SOS1 inhibitor of the combination may be administered at a dose of about 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day, 80 mg/day, 90 mg/day, 100 mg/day, 110 mg/day, 120 mg/day, 130 mg/day, 140 mg/day, 150 mg/day, 160 mg/day, 170 mg/day, 180 mg/day, 190 mg/day, or 200 mg/day. The therapeutically effective amount of the SOS1 inhibitor of the combination may be any value or subrange within the recited ranges.

**[00428]** In some embodiments, the SOS1 inhibitor is administered to a subject at about 200 mg to about 500 mg. In some embodiments, the SOS1 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 440 mg to about 520 mg. In some embodiments the SOS1 inhibitor is administered to a subject at about 10 mg to about 100 mg. In some embodiments, the SOS1 inhibitor is administered to a subject at about 240 mg to about 480 mg. In some embodiments, the SOS1 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 50 mg to about 100 mg. In some embodiments, the SOS1 inhibitor, or pharmaceutically salt thereof of is administered to a subject at about 5 mg to about 75 mg. In some embodiments, the SOS1 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 170 mg, about 190 mg, about 210 mg, about 240 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, about 440 mg, about 460 mg, about 480 mg, about 500 mg, about 540 mg, about 580 mg, or about 650 mg. In some embodiments, the SOS1 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg, about 30 mg, about 45 mg, or about 60 mg. In some embodiments, the SOS1 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 15 mg. In some embodiments, the SOS1 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 30 mg. In some embodiments,

the SOS1 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 240 mg. In some embodiments, the SOS1 inhibitor, or pharmaceutically salt thereof is administered to a subject at about 480 mg. In some embodiments, the subject is between 12 years old to 18 years old. In some embodiments, the subject is between greater than or equal 12 years old to less than or equal to 18 years. In some embodiments, the subject is an adult. In some embodiments, the subject is greater than or equal to 18 years old.

**[00429]** The SOS1 inhibitor, or a pharmaceutically acceptable salt thereof, and the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt thereof, can be formulated into separate or individual dosage forms which can be co-administered one after the other. In some cases, if the route of administration is the same (e.g. oral) two active compounds can be formulated into a single form for co-administration, both methods of co-administration, however, being part of the same therapeutic treatment or regimen. In some embodiments, the combination therapy comprises oral administration of a compound of Formulas (I), (I-A), or (I-B), once or twice a day on a daily basis (during a period of time), e.g., in an amount of about 10 mg to about 400 mg and oral administration of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof which is administered, for example once a day on a daily basis (during a period of time).

**KRAS Inhibitor Dosing**

**[00430]** In some embodiments, a single dose of compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, is administered per day (i.e., in about 24 hour intervals) (i.e., QD). In some cases, two doses of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, are administered per day (i.e., BID). In some cases, three doses of the compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, are administered per day (i.e., TID).

## COMBINATION THERAPIES

### RTK-MAPK pathway inhibitor combination therapy

**[00431]** In an aspect the present disclosure provides methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a combination of an RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00432]** In an aspect the present disclosure provides methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a

pharmaceutical composition thereof, and a compound of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00433]** In an aspect the present disclosure provides methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of an RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof.

**[00434]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of an RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In one embodiment, the cancer is a KRas G12D-associated cancer. In one embodiment, the cancer is a KRas G12V-associated cancer. In one embodiment, the cancer is a KRas wildtype-associated cancer. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a solid tumor cancer with KRAS wildtype. In some cases, the cancer is a solid tumor cancer with a G12D mutation. In some cases, the cancer is a solid tumor cancer with a G12V mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In some cases, the KRas G12D-associated cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer.

**[00435]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B).In some cases, the compound of Formulas (I), (I-A), or (I-B), is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00436]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B).In some cases, the

compound of Formulas (I), (I-A), or (I-B), is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00437]** In an aspect the present disclosure provides methods for increasing the sensitivity of a cancer cell to a compound or salt of Formulas (I), (I-A), or (I-B),comprising contacting the cancer cell with an effective amount of a combination of a compound of Formulas (I), (I-A), or (I-B),or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the RTK-MAPK pathway inhibitor synergistically increases the sensitivity of the cancer cell to the compound or salt of Formulas (I), (I-A), or (I-B),In some cases, the contacting is in vitro. In one embodiment, the contacting is in vivo.

**[00438]** In an aspect the present disclosure provides methods of inhibiting KRas G12 mutants or wildtype in a subject comprising administering to the subject a therapeutically effective amount of a combination of a RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the method may inhibit KRas G12 mutants or wildtype activity in a cell. In some cases, inhibiting KRas G12 mutants or wildtype activity in a cell may include contacting the cell in which inhibition of KRas G12 mutants or wildtype activity is desired with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt thereof and a RTK-MAPK pathway inhibitor or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00439]** In some cases, a cell in which inhibition of KRas G12 mutants or wildtype activity is desired is contacted with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutically acceptable salt of any one thereof and a RTK-MAPK pathway inhibitor to negatively modulate the activity of KRas G12 mutants or wildtype. In some cases, by negatively modulating the activity of KRas G12 mutants or wildtype, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12 mutants or wildtype activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to effect the desired negative modulation of KRas G12 mutants or wildtype. The ability of compounds to bind KRas G12 mutants or wildtype may be monitored in vitro using well known methods.

**[00440]** In some embodiments, the inhibitory activity of compounds of Formulas (I), (I-A), or (I-B), and a RTK-MAPK pathway inhibitor in cells may be monitored, for example, by measuring the inhibition of KRas G12 mutants or wildtype activity of the amount of phosphorylated ERK.

**[00441]** In another aspect, methods of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof are provided and a RTK-MAPK pathway inhibitor.

**[00442]** The compositions and methods provided herein may be used for the treatment of a KRas G12 mutants or wildtype-associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and a RTK-MAPK pathway inhibitor are provided. In some cases, the KRas G12 mutants or wildtype associated cancer is lung cancer. In some cases, the KRas G12 mutants or wildtype associated cancer is solid tumor cancer. In some cases, the KRAS G12 mutants are selected from G12D and G12V. In some cases, the KRAS G12 mutants is G12D. In some cases, the KRAS G12 mutants is G12V.

**[00443]** In some embodiments, the method of treating a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a RTK-MAPK pathway inhibitor and a compound or salt of Formulas (I), (I-A), or (I-B), synergistically increases the potency of the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the synergistic increase in potency of the compound or salt of Formulas (I), (I-A), or (I-B), results in an improved efficacy of the compound or salt of Formulas (I), (I-A), or (I-B).

**[00444]** In some embodiments, the compound and inhibitor are administered on separate days. In some cases, the compound and inhibitor are administered on the same day.

**RAF-MEK-ERK pathway inhibitor combination therapy**

**[00445]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a combination of a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formula (II), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00446]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a

RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formula (II), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In some cases, the compound of Formulas (I), (I-A), or (I-B), is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00447]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In one embodiment, the cancer is a KRas G12D-associated cancer. In one embodiment, the cancer is a KRas G12V-associated cancer. In one embodiment, the cancer is a KRas wildtype-associated cancer. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a solid tumor cancer with KRAS wildtype. In some cases, the cancer is a solid tumor cancer with a G12D mutation. In some cases, the cancer is a solid tumor cancer with a G12V mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In some cases, the KRas G12D-associated cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the compound of Formulas (I), (I-A), or (I-B), is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00448]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a

pharmaceutical composition thereof, and a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00449]** In an aspect the present disclosure provides methods for increasing the sensitivity of a cancer cell to a compound or salt of Formulas (I), (I-A), or (I-B), comprising contacting the cancer cell with an effective amount of a combination of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, and a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the RAF-MEK-ERK pathway inhibitor synergistically increases the sensitivity of the cancer cell to the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the contacting is in vitro. In one embodiment, the contacting is in vivo.

**[00450]** In an aspect the present disclosure provides methods of inhibiting KRas G12 mutants in a subject comprising administering to the subject a therapeutically effective amount of a combination of a RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the method may inhibit KRas G12 mutants or wildtype activity in a cell. In some cases, inhibiting KRas G12 mutants or wildtype activity in a cell may include contacting the cell in which inhibition of KRas G12 mutants or wildtype activity is desired with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt of any one thereof and a RAF-MEK-ERK pathway inhibitor. In some cases, the contacting is in vitro. In some cases, the contacting is in vivo. In some cases, a cell in which inhibition of KRas G12 mutants or wildtype activity is desired is contacted with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutically acceptable salt of any one thereof and a RAF-MEK-ERK pathway inhibitor to negatively modulate the activity of KRas G12 mutants or wildtype. In some cases, by negatively modulating the activity of KRas G12 mutants or wildtype, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12 mutants or wildtype activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to effect the desired negative modulation of KRas G12 mutants or wildtype. The ability of compounds to bind KRas G12 mutants or wildtype may be monitored in vitro using well known methods.

**[00451]** In some embodiments, the inhibitory activity of exemplary compounds and a RAF-MEK-ERK pathway inhibitor in cells may be monitored, for example, by measuring the inhibition of KRas G12 mutants or wildtype activity of the amount of phosphorylated ERK.

**[00452]** In another aspect, methods of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof are provided and a RAF-MEK-ERK pathway inhibitor.

**[00453]** The compositions and methods provided herein may be used for the treatment of a KRas G12 mutants or wildtype -associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and a RAF-MEK-ERK pathway inhibitor are provided. In some cases, the KRas G12 mutants or wildtype associated cancer is lung cancer.

**[00454]** The compositions and methods provided herein may be used for the treatment of a KRas G12D-associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and a RAF-MEK-ERK pathway inhibitor are provided.

**[00455]** In some embodiments, the method of treating a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a RAF-MEK-ERK pathway inhibitor and a compound or salt of Formulas (I), (I-A), or (I-B), synergistically increases the potency of the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the synergistic increase in potency of the compound or salt of Formulas (I), (I-A), or (I-B), results in an improved efficacy of the compound or salt of Formulas (I), (I-A), or (I-B).

**[00456]** In some embodiments, the compound and inhibitor are administered on separate days. In some cases, the compound and inhibitor are administered on the same day.

**ERBB family inhibitor combination therapy**

**[00457]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a combination of an ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00458]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition

thereof, and a compound or salt of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In some cases, the compound of Formulas (I) is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00459]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of an ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In one embodiment, the cancer is a KRas G12D-associated cancer. In one embodiment, the cancer is a KRas G12V-associated cancer. In one embodiment, the cancer is a KRas wildtype-associated cancer. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a solid tumor cancer with KRAS wildtype. In some cases, the cancer is a solid tumor cancer with a G12D mutation. In some cases, the cancer is a solid tumor cancer with a G12V mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In some cases, the KRas G12D-associated cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the compound of Formulas (I), (I-A), or (I-B), is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00460]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of an ERBB family inhibitor, or a pharmaceutically acceptable salt or a

pharmaceutical composition thereof, and a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00461]** In an aspect the present disclosure provides methods for increasing the sensitivity of a cancer cell to a compound or salt of Formulas (I), (I-A), or (I-B), comprising contacting the cancer cell with an effective amount of a combination of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, and a ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the ERBB inhibitor synergistically increases the sensitivity of the cancer cell to the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the contacting is in vitro. In one embodiment, the contacting is in vivo.

**[00462]** In an aspect the present disclosure provides methods of inhibiting KRas G12 mutants or wildtype in a subject comprising administering to the subject a therapeutically effective amount of a combination of a ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the method may inhibit KRas G12 mutants or wildtype activity in a cell. In some cases, inhibiting KRas G12 mutants or wildtype activity in a cell may include contacting the cell in which inhibition of KRas G12 mutants or wildtype activity is desired with an effective amount of a compound or salt of Formulas (I), (I-A), or (I-B), or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt of any one thereof and a ERBB family inhibitor. In some cases, the contacting is in vitro. In some cases, the contacting is in vivo. In some cases, a cell in which inhibition of KRas G12 mutants or wildtype activity is desired is contacted with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutically acceptable salt of any one thereof and an ERBB family inhibitor to negatively modulate the activity of KRas G12 mutants or wildtype.. In some cases, by negatively modulating the activity of KRas G12 mutants or wildtype, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12 mutants or wildtype activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to effect the desired negative modulation of KRas G12 mutants or wildtype. The ability of compounds to bind KRas G12 mutants or wildtype may be monitored in vitro using well known methods.

**[00463]** In some embodiments, the inhibitory activity of exemplary compounds and an ERBB family inhibitor in cells may be monitored, for example, by measuring the inhibition of KRAS G12 mutants and wildtype activity of the amount of phosphorylated ERK.

**[00464]** In another aspect, methods of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound or salt of

Formulas (I), (I-A), or (I-B), or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof are provided and an ERBB family inhibitor.

**[00465]** The compositions and methods provided herein may be used for the treatment of a KRas G12 mutants or wildtype-associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and a ERBB family inhibitor are provided. In some cases, the KRas G12 mutants or wildtype associated cancer is lung cancer.

In some embodiments, the method of treating a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a ERBB family inhibitor and a compound or salt of Formulas (I), (I-A), or (I-B), synergistically increases the potency of the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the synergistic increase in potency of the compound or salt of Formulas (I), (I-A), or (I-B), results in an improved efficacy of the compound or salt of Formulas (I), (I-A), or (I-B).

**[00466]** In some embodiments, the compound and inhibitor are administered on separate days. In some cases, the compound and inhibitor are administered on the same day.

**Epidermal growth factor receptor (EGFR) inhibitor combination therapy**

**[00467]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a combination of a EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00468]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In some cases, the compound of Formula (I) is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof. In some cases, the EGFR inhibitor is selected from cetuximab, afatinib and erlotinib. In

some cases, the EGFR inhibitor is cetuximab. In some cases, the compound or salt of Formula (I) is selected from compounds 2, 3, 4, 14, 25, and 74. In some cases, the compound or salt of Formula (I) is compound 2. In some cases, the compound or salt of Formula (I) is compound 3. In some cases, the compound or salt of Formula (I) is compound 4. In some cases, the compound or salt of Formula (I) is compound 14. In some cases, the compound or salt of Formula (I) is compound 25. In some cases, the compound or salt of Formula (I) is compound 74.

**[00469]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In some cases, the compound of Formulas (I) is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00470]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In one embodiment, the cancer is a KRas G12D-associated cancer. In one embodiment, the cancer is a KRas G12V-associated cancer. In one embodiment, the cancer is a KRas wildtype-associated cancer. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a solid tumor cancer with KRAS wildtype. In some cases, the cancer is a solid tumor cancer with a G12D mutation. In some cases, the cancer is a solid tumor cancer with a G12V mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In some cases, the KRas G12D-associated cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer.

**[00471]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a

combination of an EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound of Formulas (I), (I-A), or (I-B). In some cases, the compound of Formulas (I), (I-A), or (I-B), is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00472]** In an aspect the present disclosure provides methods for increasing the sensitivity of a cancer cell to a compound or salt of Formulas (I), (I-A), or (I-B),comprising contacting the cancer cell with an effective amount of a combination of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and an EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the EGFR inhibitor synergistically increases the sensitivity of the cancer cell to the compound or salt of Formulas (I), (I-A), or (I-B),. In some cases, the contacting is in vitro. In one embodiment, the contacting is in vivo.

**[00473]** In an aspect the present disclosure provides methods of inhibiting KRas G12 mutants or wildtype in a subject comprising administering to the subject a therapeutically effective amount of a combination of an EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the method may inhibit KRas G12 mutants or wildtype activity in a cell. In some cases, inhibiting KRas G12 mutants or wildtype activity in a cell may include contacting the cell in which inhibition of KRas G12 mutants activity is desired with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt of any one thereof and an EGFR inhibitor. In some cases, the contacting is in vitro. In some cases, the contacting is in vivo. In some cases, a cell in which inhibition of KRas G12 mutants or wildtype activity is desired is contacted with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutically acceptable salt of any one thereof and an EGFR inhibitor to negatively modulate the activity of KRas G12 mutants or wildtype. In some cases, by negatively modulating the activity of KRas G12 mutants or wildtype, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12 mutants or wildtype activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to effect the desired negative

modulation of KRas G12 mutants or wildtype. The ability of compounds to bind KRas G12 mutants or wildtype may be monitored in vitro using well known methods.

**[00474]** In some embodiments, the inhibitory activity of exemplary compounds and an EGFR inhibitor in cells may be monitored, for example, by measuring the inhibition of KRas G12 mutants or wildtype activity of the amount of phosphorylated ERK.

**[00475]** In another aspect, methods of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof are provided and an EGFR inhibitor.

**[00476]** The compositions and methods provided herein may be used for the treatment of a KRas G12 mutants or wildtype-associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and an EGFR inhibitor are provided. In some cases, KRas G12 mutants or wildtype associated cancer is lung cancer.

**[00477]** The compositions and methods provided herein may be used for the treatment of a KRas G12D-associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and an EGFR inhibitor are provided.

**[00478]** In some embodiments, the method of treating a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of an EGFR inhibitor and a compound or salt of Formulas (I), (I-A), or (I-B), synergistically increases the potency of the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the synergistic increase in potency of the compound or salt of Formulas (I), (I-A), or (I-B), results in an improved efficacy of the compound or salt of Formulas (I), (I-A), or (I-B).

**[00479]** In some embodiments, the compound and inhibitor are administered on separate days. In some cases, the compound and inhibitor are administered on the same day.

**SHP-2 inhibitor combination therapy**

**[00480]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a combination of a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or

salt of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00481]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In some cases, the compound of Formula (I) is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00482]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In one embodiment, the cancer is a KRas G12D-associated cancer. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In one embodiment, the cancer is a KRas G12D-associated cancer. In one embodiment, the cancer is a KRas G12V-associated cancer. In one embodiment, the cancer is a KRas wildtype-associated cancer. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a solid tumor cancer with KRAS wildtype. In some cases, the cancer is a solid tumor cancer with a G12D mutation. In some cases, the cancer is a solid tumor cancer with a G12V mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In some cases, the KRas G12D-associated cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer.

**[00483]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically

acceptable salt or a pharmaceutical composition thereof. In some cases, the compound of Formulas (I), (I-A), or (I-B), is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00484]** In an aspect the present disclosure provides methods for increasing the sensitivity of a cancer cell to a compound or salt of Formulas (I), (I-A), or (I-B),comprising contacting the cancer cell with an effective amount of a combination of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof, and a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the SHP-2 inhibitor synergistically increases the sensitivity of the cancer cell to the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the contacting is in vitro. In one embodiment, the contacting is in vivo.

**[00485]** In an aspect the present disclosure provides methods of inhibiting KRas G12 mutants or wildtype in a subject comprising administering to the subject a therapeutically effective amount of a combination of a SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the method may inhibit KRas G12 mutants or wildtype activity in a cell. In some cases, inhibiting KRas G12 mutants or wildtype activity in a cell may include contacting the cell in which inhibition of KRas G12 mutants activity is desired with an effective amount of a compound of Formulas (I), (I-A), or (I-B),or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt of any one thereof and a SHP-2 inhibitor. In some cases, the contacting is in vitro. In some cases, the contacting is in vivo. In some cases, a cell in which inhibition of KRas G12 mutants or wildtype activity is desired is contacted with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutically acceptable salt of any one thereof and a SHP-2 inhibitor to negatively modulate the activity of KRas G12 mutants or wildtype. In some cases, by negatively modulating the activity of KRas G12 mutants or wildtype, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12 mutants or wildtype activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to affect the desired negative modulation of KRas G12 mutants or wildtype. The ability of compounds to bind KRas G12 mutants or wildtype may be monitored in vitro using well known methods.

**[00486]** In some embodiments, the inhibitory activity of exemplary compounds and a SHP-2 inhibitor in cells may be monitored, for example, by measuring the inhibition of KRas G12 mutants or wildtype activity of the amount of phosphorylated ERK.

**[00487]** In another aspect, methods of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof are provided and a SHP-2 inhibitor.

**[00488]** The compositions and methods provided herein may be used for the treatment of a KRas G12 mutants or wildtype -associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and a SHP-2 inhibitor are provided. In some cases, the KRas G12 mutants or wildtype associated cancer is lung cancer. The compositions and methods provided herein may be used for the treatment of a KRas G12D-associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and a SHP-2 inhibitor are provided.

**[00489]** In some embodiments, the method of treating a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SHP-2 inhibitor and a compound or salt of Formulas (I), (I-A), or (I-B), synergistically increases the potency of the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the synergistic increase in potency of the compound or salt of Formulas (I), (I-A), or (I-B), results in an improved efficacy of the compound or salt of Formulas (I), (I-A), or (I-B).

**SOS1 inhibitor combination therapy**

**[00490]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00491]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a

compound or salt of Formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In some cases, the compound of Formula (I) is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00492]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In one embodiment, the cancer is a KRas G12D-associated cancer. In one embodiment, the cancer is a KRas G12V-associated cancer. In one embodiment, the cancer is a KRas wildtype-associated cancer. In some cases, the cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer. In some cases, the cancer is a solid tumor cancer with a KRAS mutation. In some cases, the cancer is a solid tumor cancer with KRAS wildtype. In some cases, the cancer is a solid tumor cancer with a G12D mutation. In some cases, the cancer is a solid tumor cancer with a G12V mutation. In some cases, the cancer is a KRAS wildtype-associated cancer. In some cases, the KRas G12D-associated cancer is pancreatic, colorectal, endometrial, and non-small cell lung cancer. In some cases, the compound of Formulas (I), (I-A), or (I-B), is selected from compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

**[00493]** In an aspect the present disclosure provides methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

**[00494]** In an aspect the present disclosure provides methods for increasing the sensitivity of a cancer cell to a compound or salt of Formulas (I), (I-A), or (I-B),comprising contacting the cancer cell with an effective amount of a combination of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, wherein the SOS1 inhibitor synergistically increases the sensitivity of the cancer cell to the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the contacting is in vitro. In one embodiment, the contacting is in vivo.

**[00495]** In an aspect the present disclosure provides methods of inhibiting KRas G12 mutants or wildtype in a subject comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, and a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition thereof. In some cases, the method may inhibit KRas G12 mutants or wildtype activity in a cell. In some cases, inhibiting KRas G12 mutants or wildtype activity in a cell may include contacting the cell in which inhibition of KRas G12 mutants activity is desired with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt of any one thereof and a SOS1 inhibitor. In some cases, the contacting is in vitro. In some cases, the contacting is in vivo. In some cases, a cell in which inhibition of KRas G12 mutants or wildtype activity is desired is contacted with an effective amount of a compound of Formulas (I), (I-A), or (I-B), or pharmaceutically acceptable salt of any one thereof and a SOS1 inhibitor to negatively modulate the activity of KRas G12 mutants or wildtype. In some cases, by negatively modulating the activity of KRas G12 mutants or wildtype, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced KRas G12 mutants or wildtype activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to affect the desired negative modulation of KRas G12 mutants or wildtype. The ability of compounds to bind KRas G12 mutants or wildtype may be monitored in vitro using well known methods.

**[00496]** In some embodiments, the inhibitory activity of exemplary compounds and a SOS1 inhibitor in cells may be monitored, for example, by measuring the inhibition of KRas G12 mutants or wildtype activity of the amount of phosphorylated ERK.

**[00497]** In another aspect, methods of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound or salt of Formulas (I), (I-A), or (I-B), or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof are provided and a SOS1 inhibitor.

**[00498]** The compositions and methods provided herein may be used for the treatment of a KRas G12 mutants or wildtype-associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and a SOS1 inhibitor are provided. In some cases, the KRas G12D and/or other G12 mutants associated cancer is lung cancer.

**[00499]** The compositions and methods provided herein may be used for the treatment of a KRas G12D-associated cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formulas (I), (I-A), or (I-B), a pharmaceutically acceptable salt any one thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one thereof and a SOS1 inhibitor are provided. In some embodiments, the method of treating a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a SOS1 inhibitor and a compound or salt of Formulas (I), (I-A), or (I-B), synergistically increases the potency of the compound or salt of Formulas (I), (I-A), or (I-B). In some cases, the synergistic increase in potency of the compound or salt of Formulas (I), (I-A), or (I-B), results in an improved efficacy of the compound or salt of Formulas (I), (I-A), or (I-B).

**[00500]** As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" a KRas G12 mutants or wildtype with a compound provided herein and a RTK-MAPK pathway inhibitor includes the administration of the compound provided herein and a RTK-MAPK pathway inhibitor to an individual or patient, such as a human, having KRas G12D and/or other G12 mutants, as well as, for example, introducing a compound provided herein and a RTK-MAPK pathway inhibitor into a sample containing a cellular or purified preparation containing the KRas G12D and/or other G12 mutants.

**[00501]** The compositions and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as lung, prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the invention include, but are not limited to tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More specifically, these compounds can be used to treat: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell,

undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In some cases, the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer. In

some cases, the cancer is non-small cell lung cancer. In some cases, the cancer is a solid tumor cancer.

**[00502]** In some cases, the concentration and route of administration to the patient will vary depending on the cancer to be treated. The compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions comprising such compounds and salts also may be co-administered with other anti-neoplastic compounds, e.g., chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively.

**[00503]** The compounds described herein can be used in the preparation of medicaments for the prevention or treatment of diseases or conditions. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

**[00504]** The compositions containing the compound(s) described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. Amounts effective for this use will depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician.

**[00505]** In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

**[00506]** In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

**[00507]** Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder

or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

**[00508]** The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease or condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be determined in a manner recognized in the field according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of about 0.02 - about 5000 mg per day, in some embodiments, about 1 – about 1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

**[00509]** The pharmaceutical composition described herein may be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers can be used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection may be presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

**[00510]** Toxicity and therapeutic efficacy of such therapeutic regimens can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the $LD_{50}$ (the dose lethal to 50% of the population) and the $ED_{50}$ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between $LD_{50}$ and $ED_{50}$. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the $ED_{50}$ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

**[00511]** In certain embodiments, the invention provides a method of treating or preventing a disease, state or condition in a patient in need thereof comprising administering to the patient an

effective amount of a compound of any one of embodiments of the invention or a pharmaceutically acceptable salt thereof. The disease, state or condition may be selected from a group as described elsewhere herein.

**SYNERGY**

**[00512]** In some embodiments, the addition of an RTK-MAPK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, synergistically increases the activity of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof against cancer or cancer cell lines expressing a KRas mutation or KRas wildtype.

**[00513]** In some embodiments, the addition of an RAF-MEK-ERK pathway inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, synergistically increases the activity of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof against cancer or cancer cell lines expressing a KRas mutation or KRas wildtype.

**[00514]** In some embodiments, the addition of an ERBB family inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, synergistically increases the activity of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof against cancer or cancer cell lines expressing a KRas mutation or KRas wildtype.

**[00515]** In some embodiments, the addition of an EGFR inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, synergistically increases the activity of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof against cancer or cancer cell lines expressing a KRas mutation or KRas wildtype. In some cases, the KRas mutation is KRas G12D.

**[00516]** In some embodiments, the addition of cetuximab, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, synergistically increases the activity of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof against cancer or cancer cell lines expressing a KRas mutation or KRas wildtype. In some cases, the KRas mutation is KRas G12D.

**[00517]** In some embodiments, the addition of an SHP-2 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, synergistically increases the activity of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof against cancer or cancer cell lines expressing a KRas mutation or KRas wildtype.

**[00518]** In some embodiments, the addition of an SOS1 inhibitor, or a pharmaceutically acceptable salt or a pharmaceutical composition thereof, synergistically increases the activity of the compound of Formulas (I), (I-A), or (I-B), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof against cancer or cancer cell lines expressing a KRas mutation or KRas wildtype.

**[00519]** Any method for determining whether two compounds exhibit synergy may be used for determining the synergistic effect of the combination (e.g., example 14). In some cases, the Zip synergy score is at least 8. In some cases, the Zip synergy score is at least 9. In some cases, the Zip synergy score is at least 10. In some cases, the Zip synergy score is at least 11. In some cases, the Zip synergy score is at least 12. In some cases, the Zip synergy score is at least 13. In some cases, the Zip synergy score is at least 14. In some cases, the Zip synergy score is at least 15. In some cases, the Zip synergy score is at least 16. In some cases, Zip the synergy score is at least 17. In some cases, the Zip synergy score is at least 18. In some cases, the Zip synergy score is at least 19. In some cases, the Zip synergy score is at least 20. In some cases, the Zip synergy score is at least 21. In some cases, the Zip synergy score is at least 22. In some cases, the Zip synergy score is from 8 to 10. In some cases, the Zip synergy score is from 8 to 24. In some cases, the Zip synergy score is from 10 to 24. In some cases, the Zip synergy score is from 10 to 20. In some cases, the ZIP synergy score is from 10 to 15. In some cases, the Zip synergy score is from 9 to 15. In some cases, the Zip synergy score is from 8 to 15. In some cases, the Zip synergy score is from 9 to 24. In some cases, the Zip synergy score is from 9 to 12. In some cases, the Zip synergy score is from 9 to 15. In some cases, the Zip synergy score is from 9 to 16. In some cases, the Zip synergy score is from 10 to 14. In some cases, the Zip synergy score is from 17 to 23. In some cases, the Zip synergy score is from 13 to 18. In some cases, the Zip synergy score is from 9 to 19. In some cases, the Zip synergy score is from 9 to 20. In some cases, the Zip synergy score is from 11 to 18. In some cases, the Zip synergy score is from 8 to 14. In some cases, the Zip synergy score is from 9 to 18.

**Bifunctional Compounds**

**[00520]** In some embodiments, compounds herein can adopt to selectively eliminate an over activated KRas signaling which is induced by KRas mutations by directly binding with the mutated KRas protein, either by stabilizing its GDP bound form (the inactive form) or by blocking the interaction between GTP bound form and its downstream target protein. In some embodiments, another way is to hijack the protein degradation mechanism in a cell and leverage E3 ligases' (like VHL, CRBN or IAPs) substrate specificity through a bi-functional molecule called Proteolysis targeting chimera (PROTAC) (Winter GE, Buckley DL, Paulk J, Roberts JM, Souza A, Dhe-

Paganon S, Bradner JE. DRUG DEVELOPMENT. Phthalimide conjugation as a strategy for in vivo target protein degradation. Science. 2015 Jun 19; 348 (6241): 1376-81), which can bind with both mutated KRas protein and E3 ligase, create interactions between those two proteins and induce KRas degradation.

**[00521]** Disclosed herein is a bifunctional compound composed of a target protein (i.e., KRAS G12D)-binding moiety and an E3 ubiquitin ligase-binding moiety, which may induce proteasome-mediated degradation of selected proteins. In some embodiments, the bifunctional compound comprises a target protein (i.e., KRAS G12D)-binding moiety and an E3 ubiquitin ligase-binding moiety known in the art. In some embodiments, disclosed herein is the use of the compound disclosed herein in the preparation of degrading a target protein compound by using chemical modification of the compound disclosed herein. In some cases, the target protein-binding moiety is derived from a compound of Formulas (I), (I-A), or (I-B).

**Preparation of Cmpounds**

**[00522]** The compounds of the present disclosure can generally be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present disclosure can be synthesized using the methods described herein, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. The compounds of the present disclosure may be prepared as described in the schemes and examples described elsewhere herein.

**[00523]** The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

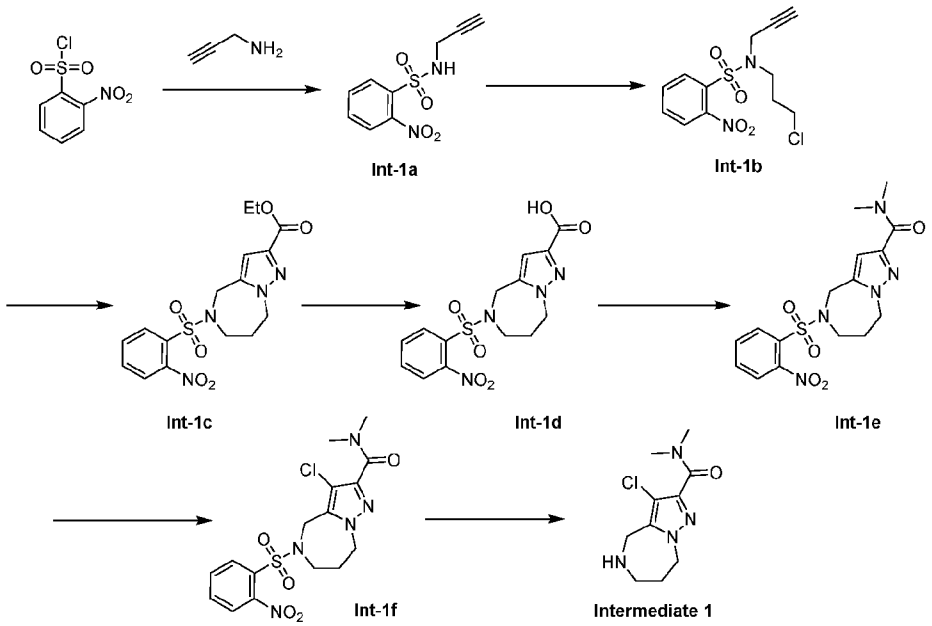
## EXAMPLES

**[00524]** The following synthetic schemes are provided for purposes of illustration, not limitation. The following examples illustrate the various methods of making compounds described herein. It is understood that one skilled in the art may be able to make these compounds by similar methods or by combining other methods known to one skilled in the art. It is also understood that one skilled in the art would be able to make, in a similar manner as described below by using the appropriate starting materials and modifying the synthetic route as needed. In general, starting materials and reagents can be obtained from commercial vendors or synthesized according to sources known to those skilled in the art or prepared as described herein.

**[00525]** The present disclosure provides processes for preparing the compounds described herein (described in greater detail below).

**Synthesis of Intermediates**

**Intermediate 1**. Synthesis of 3-chloro-*N*,*N*-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.




**[00526]** Step 1. Synthesis of 2-nitro-prop-2-ynyl-benzenesulfonamide (Int-1a). A solution of prop-2-yl-1-amine (1.87 mL, 29.1 mmol) and *N*,*N*-diisopropylethylamine (10.15 mL, 58.3 mmol) in DCM (100 mL) was cooled to 0 °C. 2-nitrobenzenesulfonyl chloride (6.46 g, 29.15 mmol) was added portion wise.The solution was then allowed to warm to rt and was further stirred for 1 hr. The mixture was washed with water and brine, dried over $Na_2SO_4$, concentrated. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 20% to 50%) to afford 2-nitro-prop-2-ynyl-benzenesulfonamide (**Int-1a**, 5.98 g, 24.9 mmol, 85.4% yield) as a yellow solid. LCMS calcld for $C_9H_9N_2O_4S$ $(M+H)^+$ m/z = 241.0, found: 241.0.

**[00527]** Step 2. Synthesis of (3-chloropropyl)-2-nitro-prop-2-ynyl-benzenesulfonamide (**Int-1b**). A solution of 2-nitro-prop-2-ynyl-benzenesulfonamide (**Int-1a**, 1.0 g, 4.16 mmol) and cesium carbonate (6.764 g, 20.81 mmol) in acetone (30 mL) was added neat 1-bromo-3-chloro-propane (6.05 mL, 61.19 mmol) dropwise. Upon complete addition, the reaction mixture was stirred at rt for 2 hrs. The mixture was concentrated, then washed with water and brine, dried over $Na_2SO_4$, concentrated. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 20% to 50%). (3-chloropropyl)-2-nitro-prop-2-ynyl-benzenesulfonamide (**Int-1b**, 2.43 g, 7.67 mmol, 92.1% yield) was obtained as a yellow oil. LCMS calcld for $C_{12}H_{14}ClN_2O_4S$ $(M+H)^+$ m/z = 317.0, found: 317.0.

**[00528]** Step 3. Synthesis of ethyl 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1c**). To solution of (3-chloropropyl)-2-nitro-prop-2-ynyl-

benzenesulfonamide (**Int-1b**, 10.0 g, 31.6 mmol) and ethyl 2-diazoacetate (5.4 g, 47.3 mmol) in chlorobenzene (80 mL) was added *N*,*N*-diisopropylethylamine (5.5 mL, 31.57 mmol). Then heated at 140 °C for 1.5 hours. Followed by the addition of cesium carbonate (12.3 g, 37.9 mmol), then heated at 140 °C for 30 minutes. The solvent was concentrated, and the mixture was extracted with EtOAc, washed with brine, dried over $Na_2SO_4$, concentrated. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 20% to 90%), then triturated in EtOAc to afford ethyl 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1c**, 5.80 g, 14.7 mmol, 46.6% yield) as a yellow solid. LCMS calcld for $C_{16}H_{19}N_4O_6S$ $(M+H)^+$ m/z = 395.1, found: 395.0.

**[00529]** Step 4. Synthesis of ethyl 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1d**). To a solution of ethyl 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1c**, 12.6 g, 31.95 mmol) in THF (100 mL) and methanol (25 mL) was added 1M LiOH (128 mL, 128 mmol) at 25 °C. The mixture was stirred at 55 °C for 2 h. The mixture was acidified with HCl (1mol/L in $H_2O$) to pH= 6 and the crude product was triturated in water and filtered. 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**Int-1d**, 11.5 g, 31.1 mmol, 97.3% yield) was obtained as yellow solid. LCMS calcld for $C_{14}H_{14}N_4O_6S$ $(M+H)^+$ m/z = 367.1, found: 367.0.

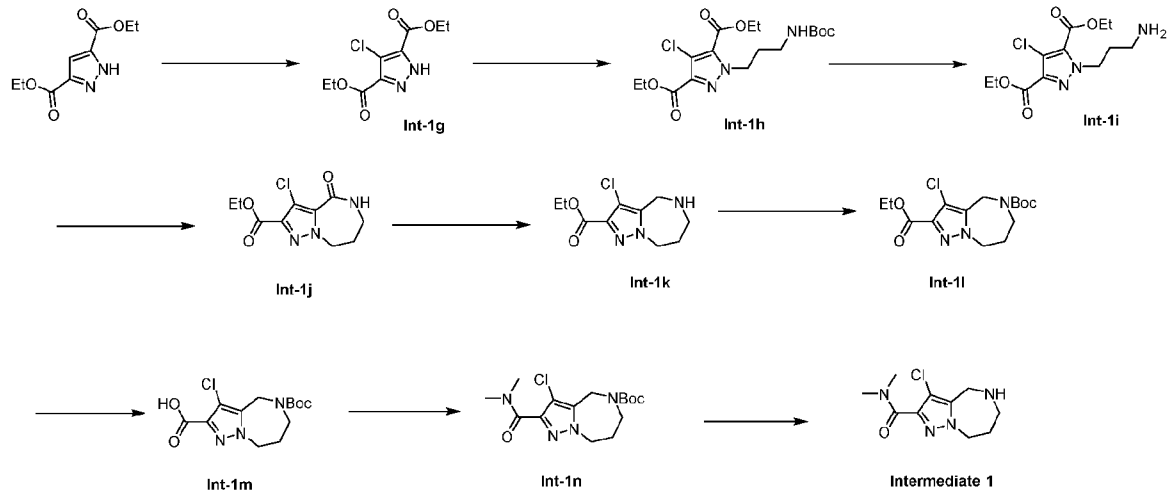
**[00530]** Step 5. Synthesis of *N*,*N*-dimethyl-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Int-1e**). To a solution of 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**Int-1d**, 9.6 mg, 26.2 mmol), DIEA (18.3 mL, 104.8 mmol) and HATU (14.95 g, 39.3 mmol) in DMF (90 mL) was added 2M methylmethanamine in THF (20 mL, 39.3 mmol) at 30 °C. The mixture was stirred at 30 °C for 2h. The mixture was diluted with DCM (300 x 2 mL), washed with water (400 mL) and brine (400 x 2 mL), dried over $Na_2SO_4$ and concentrated to afford a crude product *N*,*N*-dimethyl-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Int-1e**, 10.1 g, 24.4 mmol, 93.1% yield) as yellow oil. LCMS calcld for $C_{16}H_{20}N_4O_3S$ $(M+H)^+$ m/z =394.1 , found: 394.2.

**[00531]** Step 6. Synthesis of 3-chloro-*N*,*N*-dimethyl-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Int-1f**). To a solution of *N*,*N*-dimethyl-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Int-1e**, 10 g, 25.67 mmol) in DMF (100 mL) was added Chlorosuccinimide (3.428 g, 25.67mmol) at 0 °C under argon. The mixture was stirred at 45 °C for 1h. The mixture was concentrated to afford a crude product. The crude product was triturated in water and filtered to afford 3-chloro-*N*,*N*-dimethyl-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-

carboxamide (**Int-1f**, 10.2 g, 23.4 mmol, 91.0% yield) was obtained as crude yellow solid. LCMS calcld for $C_{16}H_{17}ClN_4O_6S$ $(M+H)^+$ m/z = 428.1, found: 428.0.

**[00532]** Step 7. Synthesis of 3-chloro-*N*,*N*-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Intermediate 1**). To a solution of 3-chloro-*N*,*N*-dimethyl-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Int-1f**, 10.2 g, 23.84 mmol), 4-methoxybenzenethiol (8.8 mL, 71.52 mmol) and $Cs_2CO_3$ (31067.73mg, 95.36 mmol) in acetonitrile (100 mL) . The mixture was stirred at 25 °C for 2 h. The mixture was concentrated, and the crude product was purified by silica gel chromatography (eluted with MeOH in DCM from 3% to 10%) to afford 3-chloro-*N*,*N*-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Intermediate 1**, 3.2 g, 13.2 mmol, 55.3% yield) as yellow solid. LCMS calcld for $C_{10}H_{15}ClN_4O$ $(M+H)^+$ m/z = 243.1, found: 243.0

**Alternative synthesis of Intermediate 1**. Synthesis of 3-chloro-*N*,*N*-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide.




**[00533]** Step 1. Synthesis of diethyl 4-chloro-1H-pyrazole-3,5-dicarboxylate (**Int-1g**). To a solution of diethyl 1H-pyrazole-3,5-dicarboxylate (20 g, 94.25 mmol) in Acetic acid (360mL) was added dropwise NaClO (264 mL, 1980 mmol). After stirring for 3 h at 25 °C, the remaining mixture was diluted with water, and the mixture was extracted with ethyl acetate. The combined organic layers were concentrated to afford yellowish solid, the solid was dissolved of Petroleum Ether (160 mL) and EtOAc (20 mL), then filtered and collected solids to afford diethyl 4-chloro-1H-pyrazole-3,5-dicarboxylate (**Int-1g,** 15.20 g, 61.6 mmol, 65.38% yield) as a white solid and mother liquid 7g. LCMS calculated for $C_9H_{12}ClN_2O_4$ $(M+H)^+$ m/z = 247.6; found: 247. $^1$H NMR (400 MHz, $CD_3OD$) δ 4.44 – 4.36 (m, 4H), 1.39 (t, *J* = 7.1 Hz, 6H).

**[00534]** Step 2. Synthesis of diethyl 1-[3-(tert-butoxycarbonylamino)propyl]-4-chloro-pyrazole-3,5-dicarboxylate (**Int-1h**). To a solution of diethyl 1-[3-(tert-

butoxycarbonylamino)propyl]-4-chloro-pyrazole-3,5-dicarboxylate (**Int-1g,** 24.7 g,24.46 mmol, 39.70% yield) in DMF (150mL) was added tert-butyl N-(3-bromopropyl)carbamate (16141.77 mg, 67.79 mmol), Potassium Iodide (204.6 mg, 1.2 3mmol), $Cs_2CO_3$ (40157.83 mg, 123.25 mmol), then the mixture was stirred at rt for 16h. The reaction was quenched with water, extracted it with EtOAc three times, combined the organic phase, washed it with water for 3 times, dry and filter it, collected the filtrate, and concentrated afford diethyl 1-[3-(tert-butoxycarbonylamino)propyl]-4-chloro-pyrazole-3,5-dicarboxylate (**Int-1h,** 24.70 g, 24.5 mmol, 39.70% yield as reddish brown oil oil. LCMS calculated for $C_{17}H_{27}ClN_3O_6$ $(M+H)^+$ m/z =404.8; found: 304.1(M+H-Boc).

**[00535]** Step 3. Synthesis of diethyl 1-(3-aminopropyl)-4-chloro-pyrazole-3,5-dicarboxylate;hydrochloride (**Int-1i**). To a solution of diethyl 1-(3-aminopropyl)-4-chloro-pyrazole-3,5-dicarboxylate;hydrochloride (**Int-1h,** 25.5 g, 23.99 mmol, 98.05% yield) in 1,4-Dioxane (50mL) was added HCl/Dioxane (150 mL, 600 mmol), then the mixture was stirred at 25 °C for 1h. The reaction was concentrated to afford diethyl 1-(3-aminopropyl)-4-chloro-pyrazole-3,5-dicarboxylate;hydrochloride (**Int-1i,** 25.50 g, 24.0 mmol, 98.05% yield) as yellow oil for next step. LCMS calculated for $C_{12}H_{19}ClN_3O_4$ $(M+H)^+$ m/z = 304.1; found: 304.3.

**[00536]** Step 4. Synthesis of ethyl 3-chloro-4-oxo-5,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1j**). To a solution of diethyl 1-(3-aminopropyl)-4-chloro-pyrazole-3,5-dicarboxylate;hydrochloride (**Int-1i,** 25.5 g, 23.99 mmol) in Methanol (500mL) was added $Et_3N$ (16.74 mL, 119.93 mmol), the mixture was stirred overnight at 80 °C. The reaction was concentrated to a volume of 20 mL, the resulting white solid was filtered, then diluted with MeOH, stirred for 10 min, filtered. Then the solid was washed with water for three times, and extracted by DCM for three times to give ethyl 3-chloro-4-oxo-5,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1j,** 4.80 g, 18.6 mmol, 77.66 %yield). LCMS calculated for $C_{10}H_{13}ClN_3O_3$ $(M+H)^+$ m/z = 258.67; found: 258.1.

**[00537]** Step 5. Synthesis of ethyl 3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1k**). To a solution of ethyl 3-chloro-4-oxo-5,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1j,** 4.8 g, 18.63 mmol) in THF (60mL) was added Borane-Methyl Sulfide Complex (27.94 mL, 55.89 mmol) under $N_2$. Thereaction was stirred at rt for 2h and then was stirred at 45 °C for 32h. MeOH to added to quench the reaction at 0°C, then the mixture was concentrated to afford ethyl 3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1k,** 4.50 g, 18.5 mmol). LCMS calculated for $C_{10}H_{15}ClN_3O_2$ $(M+H)^+$ m/z = 244.7; found: 244.3.

**[00538]** Step 6. Synthesis of O5-tert-butyl O2-ethyl 3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2,5-dicarboxylate (**Int-1l**). To a solution of ethyl 3-chloro-5,6,7,8-tetrahydro-

4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1k,** 4.5 g, 18.47 mmol) in DCM (60 mL) was added $Et_3N$ (7.73 mL, 55.4 mmol) and DMAP (225.6 mg, 1.85 mmol), then the mixture was stirred at rt for 10 min, $Boc_2O$ (8.87 g, 40.63 mmol) was added, the mixture was stirred at 25 °C for 4h. The mixture was concentrated and purified by flash column chromatography (silica gel, eluting with 0% to 6% EtOAc/DCM) to afford O5-tert-butyl O2-ethyl 3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2,5-dicarboxylate (**Int-1l,** 4.10 g, 9.54 mmol, 51.66 %yield). LCMS calculated for $C_{15}H_{23}ClN_3O_4$ $(M+H)^+$ m/z = 344.8; found: 344.1.

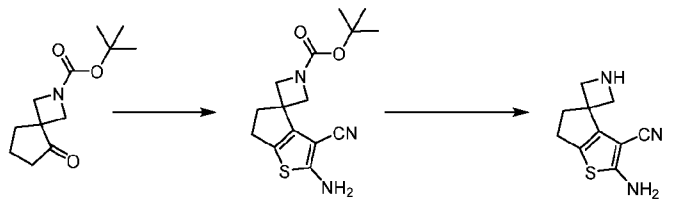
**[00539]** Step 7. Synthesis of 5-tert-butoxycarbonyl-3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**Int-1m**). To a solution of O5-tert-butyl O2-ethyl 3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2,5-dicarboxylate (**Int-1l,** 4.1 g, 9.54 mmol) in THF (36mL) and Methanol (9mL) a was added hydroxylithium (913.95 mg, 38.16 mmol) in Water (38.16mL) at 25 °C. The mixture was stirred at 55 °C for 2 h. The mixture was concentrated and acidified with HCl (1mol/L in $H_2O$) to pH= 1 and the crude product was triturated in water and filtered. 5-tert-butoxycarbonyl-3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**Int-1m,** 2.4 g,7.60 mmol, 79.67% yield) was obtained as white solid. LCMS calculated for $C_{13}H_{19}ClN_3O_4$ $(M+H)^+$ m/z = 316.7, found: 316.1.

**[00540]** Step 8. Synthesis of tert-butyl 3-chloro-2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-1n).** The mixture of 5-tert-butoxycarbonyl-3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**Int-1m,** 100 mg, 0.32 mmol) in DCM (1mL) was added Oxalyl Chloride (0.32 mL, 0.63 mmol) at 0 °C, the mixture was stirred at 0 °C for 0.5h and rt for 0.5h. Then the mixture was concentrated, diluted it with DCM (1mL), and drop it into Dimethylamine (0.63 mL, 1.27 mmol) (2M in THF), then the mixture was stirred at rt for 1h. The mixture was quenched with $NH_4Cl$ aqueous, extracted with EtOAc. washed with water and brine, dried over $Na_2SO_4$ and concentrated to afford a crude product tert-butyl 3-chloro-2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-1n,** 108 mg, 0.315 mmol) as yellow oil. LCMS calcld for $C_{15}H_{24}ClN_4O_3$ $(M+H)^+$ m/z =343.8 , found: 343.2. $^1H$ NMR (400 MHz, DMSO) δ 4.45 – 4.58 (m, 2H), 4.33 – 4.43 (m, 2H), 3.69 – 3.78 (m, 2H), 3.09 (s, 6H), 1.92 – 2.01 (m, 2H), 1.44 (s, 9H).

**[00541]** Step 9. Synthesis if 3-chloro-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Intermediate 1).** To a solution of tert-butyl 3-chloro-2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (108 mg, 0.32 mmol), tert-butyl 3-chloro-2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (199 mg, 0.58 mmol) and tert-butyl 3-chloro-2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (9.96 g,

27.6 mmol) in 1,4-Dioxane (50mL) was added HCl/Dioxane (150 mL, 600 mmol). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated and the crude product was purified by Prep-HPLC on a C18 column (5 uM, 50 x 150 mm) with mobile phase: H2O (0.1% $NH_4HCO_3$)/ MeCN at flow rate : 35 mL/min to afford 3-chloro-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (6.18 g, 25.46 mmol, 89.36% yield) as white solid. LCMS calcld for $C_{10}H_{15}ClN_4O$ $(M+H)^+$ m/z = 243.1, found: 243.1. $^1H$ NMR (400 MHz, DMSO) δ 4.24 – 4.38 (m, 2H), 3.26 – 3.37 (m, 2H), 3.00 – 3.05 (m, 2H), 2.98 (d, *J* = 15.2 Hz, 6H), 1.66 – 1.77 (m, 2H).

**Intermediate 2**

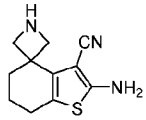



Int-2a Intermediate 2

**[00542]** Step 1. Synthesis of *tert*-butyl 2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-2a**). A solution of propanedinitrile (219.93 mg, 3.33 mmol) *tert*-butyl 5-oxo-2-azaspiro[3.4]octane-2-carboxylate (500 mg, 2.22 mmol) in DMF (5 mL) was added L-proline (255 mg, 2.22 mmol) and sulfur (113.5 mg, 3.33 mmol) at 25 °C under $N_2$. Then the mixture was stirred at 60 °C for 4 h. The mixture was filtered to afford a crude solution. The reaction mixture was purified by prep-HPLC (eluted with $CH_3CN$ in $H_2O$ from 5.0% to 95%) to afford *tert*-butyl 2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-2a,** 380 mg, 1.244 mmol, 56.1% yield) as yellow solid. LCMS calcld for $C_{15}H_{19}N_3O_2S$ $(M+H)^+$ m/z = 306.1, found: 306.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.19 (s, 2H), 3.95 (d, *J* = 8.1 Hz, 2H), 2.76 – 2.69 (m, 2H), 2.69 – 2.61 (m, 2H), 1.45 (s, 9H).

**[00543]** Step 2. Synthesis of 2-aminospiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Intermediate 2**). A solution of *tert*-butyl 2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-2a**, 380 mg, 1.24 mmol) in DCM (5 mL) was added TFA (1.91 mL, 24.89 mmol) at 25 °C under $N_2$. Then the mixture was stirred at 20 °C for 1 h. The mixture was concentrated and the crude product 2-aminospiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Intermediate 2**, 380 mg, 0.678 mmol, 54.5% yield) was used directly for the next step. LCMS calcld for $C_{10}H_{11}N_3S$ $(M+H)^+$ m/z = 206.2, found: 206.1.

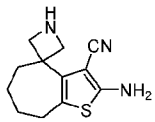
**Intermediate 3.**



Intermediate 3

**[00544]** Intermediate **3** was prepared similarly to that of **Intermediate 2** from 5-oxo-2-azaspiro[3.5]nonane (ref. *Angew. Chem. Int. Ed. 2021, 60, 7360–7365*). LCMS calcld for $C_{11}H_{13}N_3S$ $(M+H)^+$ m/z =220.1, found: 220.1.

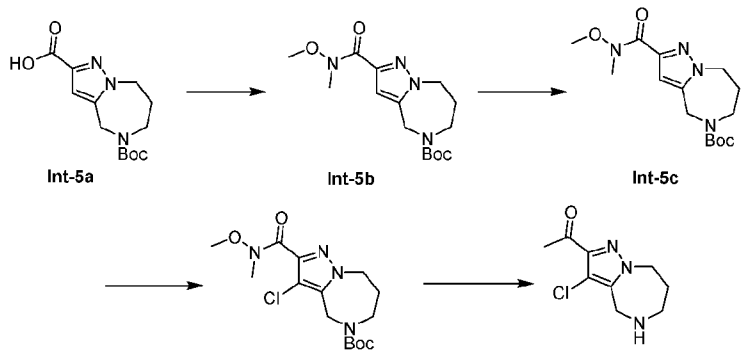
**[00545]** **Intermediate 4**. 2-aminospiro[5,6,7,8-tetrahydrocyclohepta[b]thiophene-4,3'-azetidine]-3-carbonitrile



Intermediate 4

**[00546]** Intermediate **4** was prepared similarly to that of **Intermediate 2**. LCMS calcld for $C_{12}H_{15}N_3S$ $(M+H)^+$ m/z = 234.1, found:234.1.

**Intermediate 5.** Synthesis of 1-(3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)ethanone



Int-5a Int-5b Int-5c Int-5d Intermediate 5

**[00547]** Step 1. Preparation of tert-butyl 2-[methoxy(methyl)carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-5b**). To a solution of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**Int 5a** prepared similarly to **Int-1m**, 500 mg, 1.78 mmol) , DIEA (1.24 mL, 7.11 mmol) and HATU (1013.76 mg, 2.67 mmol) in DMF (10 mL) was added N,O-Dimethylhydroxylamine Hydrochloride (260.05 mg, 2.67 mmol) at 25 °C. The mixture was stirred at 25 °C for 1h. The mixture was diluted with EtOAC (50x2 mL), washed with water (50 mL) and brine (50 ml), dried over $Na_2SO_4$, concentrated. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 10% to 90%). tert-butyl 2-

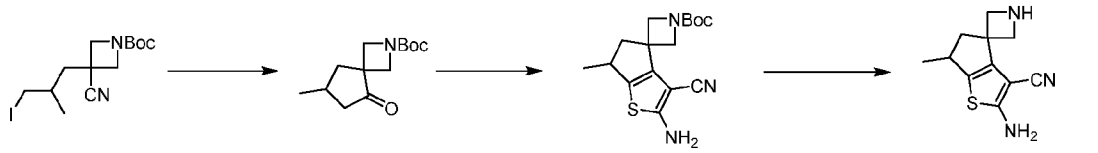
[methoxy(methyl)carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-5b**, 300 mg,0.925 mmol, 52.03% yield) was obtained as white solid. LCMS calcld for $C_{15}H_{24}N_4O_4$ $(M+H)^+$ m/z = 325.2, found: 325.1. $^1H$ NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1H), 4.47 (dd, *J* = 14.7, 9.4 Hz, 4H), 3.74 (s, 5H), 3.42 (s, 3H), 1.94 (s, 2H), 1.41 (s, 9H).

**[00548]** Step 2. Preparation of tert-butyl 3-chloro-2-[methoxy(methyl)carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-5c**). To a solution of tert-butyl 2-[methoxy(methyl)carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-5b,** 400 mg, 1.23 mmol) in Acetic acid (1 mL) was added NCS (246.99 mg, 1.85 mmol) at 60 °C. The mixture was stirred at 60 °C for 3h. The mixture was concentrated to afford a crude product and used without further purification. tert-butyl 3-chloro-2-[methoxy(methyl)carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-5c,** 300 mg, 67.80% yield). LCMS calcld for $C_{15}H_{24}ClN_4O_4$ $(M+H)^+$ m/z = 359.82, found: 359.2.

**[00549]** Step 3. Preparation of tert-butyl 2-acetyl-3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-5d**). To a solution of tert-butyl 3-chloro-2-[methoxy(methyl)carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-5c,** 240 mg, 0.67 mmol) in THF (1 mL) was added chloro(methyl)magnesium (0.67 mL, 2.01 mmol) at -20 °C. The resulting mixture was allowed to rt and stirred for 16 h. The reaction mixture was added sat. $NH_4Cl$ aq. (30 mL) and extracted with EtOAc (2 x 30 mL) and the combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuum to give the residue. The crude product was purified by flash chromatography (eluted with EtOAc in petroleum ether from 10% to 90%). tert-butyl 2-acetyl-3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-5d,** 140 mg,0.446 mmol, 66.71% yield) was obtained as white solid. LCMS calcld for $C_{14}H_{20}ClN_3O_3$ $(M+H)^+$ m/z = 314.1, found: 314.2.

**[00550]** Step 4. Preparation of 1-(3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)ethenone (**Intermediate 5**). tert-butyl 2-acetyl-3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-5d,** 140 mg, 0.45 mmol) in HCl in Dioxane (56 mL, 224 mmol). The mixture was stirred at 25°C. The mixture was concentrated to afford a crude product and used without further purification. 1-(3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)ethanone (**Intermediate 5**, 150 mg) was obtained as white solid. LCMS calcld for $C_9H_{13}ClN_3O$ $(M+H)^+$ m/z = 214.66, found: 214.2.

**Intermediate 6.** Synthesis of 2-amino-6-methyl-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile.



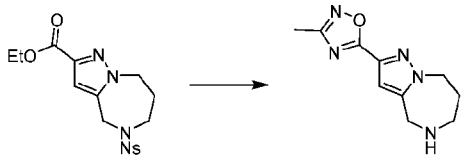

Int-6a Int-6b Int-6c Intermediate 6

**[00551]** Step 1. Preparation of tert-butyl 7-methyl-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (**Int-6b**) To a solution of THF (4 mL) was added 1.6M butyllithium in hexane (4.12 mL, 6.59 mmol) at -68 °C. The mixture was stirred at -68 °C for 10 min. Then, a solution of tert-butyl 3-cyano-3-(3-iodo-2-methyl-propyl)azetidine-1-carboxylate (**Int-6a**, CN 11257408, 800 mg, 2.2 mmol) in THF (4 mL) was added at -68 °C . The mixture was stirred at -68 °C for 3 h. The mixture was quenched with Acetic acid (5 mL) at -40 °C, extracted with tert-Butyl methyl ether (60 x 2 mL) and water (60 mL). The solution was washed with $NaHCO_3$ (60 mL), $Na_2S_2O_3$ (20% 60 mL) and brine (60 mL), dried over $Na_2SO_4$, concentrated. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 0% to 5%). tert-butyl 7-methyl-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (**Int-6b**, 110 mg,0.45 mmol, 20.93% yield) was obtained as yellow oil.

**[00552]** Step 2. Preparation of tert-butyl 2-amino-3-cyano-6-methyl-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-6c**). A solution of propanedinitrile (45.55 mg, 0.69 mmol) tert-butyl 7-methyl-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (**Int-6b**, 110 mg, 0.46 mmol) in DMF (1 mL) was added L-Proline (52.92 mg, 0.46 mmol) and Sulfur (23.5 mg, 0.69 mmol) at 25 °C under $N_2$. Then the mixture was stirred at 60 °C for 6 h. The mixture was filtered to afford a crude solution. The reaction mixture was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ from 40% to 60%). tert-butyl 2-amino-3-cyano-6-methyl-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-6c,** 30 mg, 0.094 mmol, 20.43% yield) was obtained as yellow solid. LCMS calcld for $C_{16}H_{21}N_3O_2S$ $(M+Na)^+$ m/z = 342.1, found: 342.1.

**[00553]** Step 3. Preparation of 2-amino-6-methyl-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Intermediate 6**). To a solution of tert-butyl 2-amino-3-cyano-6-methyl-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-6c,** 30 mg, 0.09 mmol) in DCM (1 mL) was added TFA (0.14 mL, 1.8 mmol) at rt. The reaction mixture was then stirred at 25 °C for 30 min. The mixture was concentrated to afford a crude product. The crude product 2-amino-6-methyl-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Intermediate 6**, 30 mg) was used without purification. LCMS calcld for $C_{11}H_{13}N_3S$ $(M+H)^+$ m/z =220.1, found: 220.1.

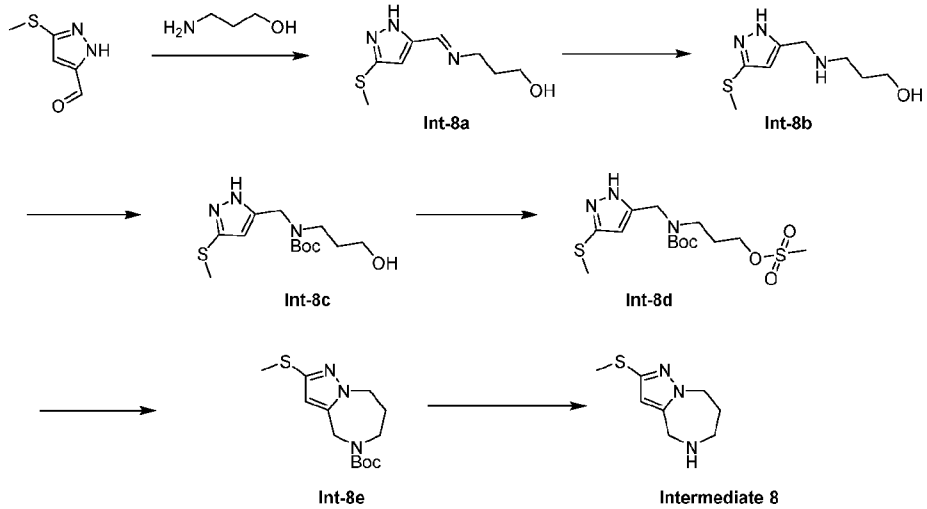
**Intermediate 7.** Synthesis of 3-methyl-5-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)-1,2,4-oxadiazole




Int-1c Intermediate 7

**[00554]** Preparation of 3-methyl-5-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)-1,2,4-oxadiazole. To a solution of N-hydroxyacetamidine (375.66 mg, 5.07 mmol) and 3Å molecular sieves in THF (5 mL) were added NaH (76.06 mg, 3.17 mmol), The mixture was stirred at RT for 15 min. ethyl 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1c,** 500 mg, 1.27 mmol) was added to the mixture. The mixture was stirred at 25 °C for 3 h. The mixture was filtered over celite and concentrated. The crude product was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ from 5.0% to 95%). The product 3-methyl-5-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)-1,2,4-oxadiazole (230 mg, 1.05 mmol, 82.75% yield) was obtained as a yellow solid. LCMS calcld for $C_{10}H_{13}N_5O$ (M+H) m/z =220.1, found: 220.1.

**Intermediate 8.** Synthesis of 2-methylsulfanyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine




**[00555]** Step 1. Preparation of 3-[(E)-(3-methylsulfanyl-1H-pyrazol-5-yl)methyleneamino]propan-1-ol (**Int-8a**). The solution of 3-methylsulfanyl-1H-pyrazole-5-carbaldehyde (*Bioorganic and Medicinal Chemistry, 2012, vol. 20, # 3, p. 1319 – 1336*, 1.1 g, 7.74 mmol) and 3-aminopropan-1-ol (639.21 mg, 8.51 mmol) in Ethanol (10 mL) was stirred at 80 °C for 16 h. The mixture was concentrated to afford a crude product which was used directly

in the next step. 3-[(E)-(3-methylsulfanyl-1H-pyrazol-5-yl)methyleneamino]propan-1-ol (**Int-8a,** 1.7 g, 3.23 mmol, 41.79% yield) was obtained as crude yellow oil. LCMS calcld for $C_8H_{13}N_3OS$ $(M-H)^-$ m/z = 199.1, found: 199.1.

**[00556]** Step 2. Preparation of 3-[(3-methylsulfanyl-1H-pyrazol-5-yl)methylamino]propan-1-ol (**Int-8b**) To a solution of 3-[(E)-(3-methylsulfanyl-1H-pyrazol-5-yl)methyleneamino]propan-1-ol (**Int-8a** crude, 1.7 g, 8.53 mmol) in Methanol (30mL) was added Sodium triacetoxyborohydride (3.62 g, 17.06 mmol) at 0 °C. The mixture was stirred at 25 °C for 6 h. The mixture was concentrated directly to 10mL. The crude product was purified by C18 flash chromatography (eluted with $CH_3CN$ in water from 0% to 7%) to afford 3-[(3-methylsulfanyl-1H-pyrazol-5-yl)methylamino]propan-1-ol (**Int-8b,** 1.5 g, 7.452 mmol, 87.35% yield). LCMS calcld for $C_8H_{15}N_3OS$ $(M+H)^+$ m/z = 202.2, found: 202.2.

**[00557]** Step 3. Preparation of tert-butyl N-(3-hydroxypropyl)-N-[(3-methylsulfanyl-1H-pyrazol-5-yl)methyl]carbamate (**Int-8c**). To a solution of 3-[(3-methylsulfanyl-1H-pyrazol-5-yl)methylamino]propan-1-ol (**Int-8b,** 100 mg, 0.5 mmol) and $Et_3N$ (0.14 mL, 0.99 mmol) in DCM (3 mL) was added $Boc_2O$ (0.14 mL, 0.6 mmol) at 0 °C. The mixture was stirred at 25 °C for 2 h. The mixture was diluted with DCM (10 mL) and filtered. The solution was washed with water (10 mL) and brine (10 mL), dried over $Na_2SO_4$, concentrated. The crude product was purified by Prep-TLC (eluted with EtOAc 100%). tert-butyl N-(3-hydroxypropyl)-N-[(3-methylsulfanyl-1H-pyrazol-5-yl)methyl]carbamate (**Int-8c,** 50 mg,0.149 mmol, 30.05% yield) was obtained as colorless viscous semi-solid. LCMS calcld for $C_{13}H_{24}N_3O_3S$ $(M+H)^+$ m/z = 302.1, found: 302.1.

**[00558]** Step 4. Preparation of 3-[tert-butoxycarbonyl-[(3-methylsulfanyl-1H-pyrazol-5-yl)methyl]amino]propyl methanesulfonate (**Int-8d**). To a solution of tert-butyl N-(3-hydroxypropyl)-N-[(3-methylsulfanyl-1H-pyrazol-5-yl)methyl]carbamate (**Int-8c,** 50 mg, 0.17 mmol) and in DCM (2 mL) was added MsCl (28.5 mg, 0.25 mmol) at 0 °C. The mixture was stirred at 25 °C for 2 h. The mixture was quenched with $H_2O$ (20 mL), extracted with DCM (10x2 mL), dried over $Na_2SO_4$, concentrated. The crude product was purified by Prep-TLC (eluted with EtOAc in petroleum ether 50%). 3-[tert-butoxycarbonyl-[(3-methylsulfanyl-1H-pyrazol-5-yl)methyl]amino]propyl methanesulfonate (**Int-8d,** 27 mg, 0.069 mmol, 41.60% yield) was obtained as colorless viscous semi-solid. LCMS calcld for $C_{14}H_{25}N_3O_5S_2$ $(M+Na)^+$ m/z = 402.1, found: 402.0

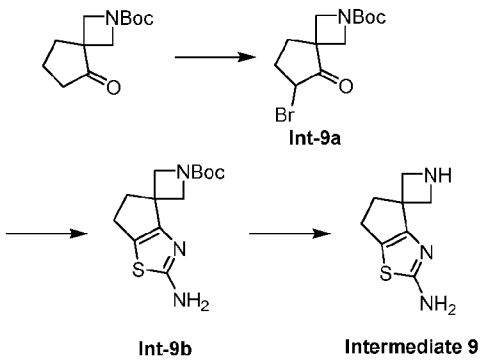
**[00559]** Step 5. Preparation of tert-butyl 2-methylsulfanyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-8e**). To a solution of 3-[tert-butoxycarbonyl-[(3-methylsulfanyl-1H-pyrazol-5-yl)methyl]amino]propyl methanesulfonate (**Int-8d** 200 mg, 0.53 mmol) in THF (20 mL) was added sodium hydride (63.24 mg, 1.58 mmol) at 0 °C under $N_2$. The

mixture was stirred at 25 °C for 3 h. The mixture was quenched with the mixture of $NH_4Cl$ (20 mL) and iced water (20 mL), extracted with EtOAC (20*3 mL), dried over $Na_2SO_4$, concentrated.

**[00560]** The crude product was purified by flash chromatography (eluted with EtOAc in petroleum ether from 0% to 35%). tert-butyl 2-methylsulfanyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-8e,** 50 mg,0.1764 mmol, 33.479% yield) was obtained as crude yellow oil.

**[00561]** Step 6. Preparation of 2-methylsulfanyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (**Intermediate 8**). To a solution of tert-butyl 2-methylsulfanyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-8e,** 120 mg, 0.42 mmol) in DCM (4 mL) was added TFA (0.4 mL, 5.23 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to afford a crude product and was used without purified. 2-methylsulfanyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (**Intermediate 8,** 70 mg) was obtained as crude yellow oil.

**Intermediate 9.** Synthesis of



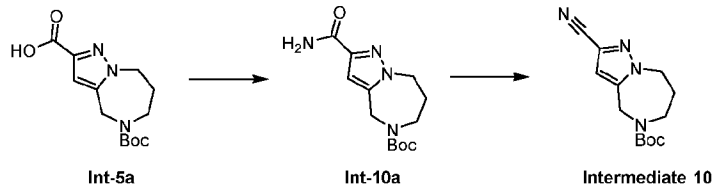

**[00562]** Step 1. Preparation of tert-butyl 6-bromo-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (**Int-9a**). To the solution of tert-butyl 5-oxo-2-azaspiro[3.4]octane-2-carboxylate (200 mg, 0.89 mmol) in Ether (5 mL) was added 5,5-dibromohexahydropyrimidine-2,4,6-trione (507.6 mg, 1.78 mmol), and the mixture was stirred at 35 °C for 48h. The mixture was extracted with Ether and water, dried with brine and $Na_2SO_4$, concentrated and purified by silica gel chromatography (PE:EtOAc = 15:1) to get tert-butyl 6-bromo-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (**Int-9a,** 140 mg, 0.460 mmol, 51.84%yield).

Step 2. Preparation of tert-butyl 2-aminospiro[5,6-dihydrocyclopenta[d]thiazole-4,3'-azetidine]-1'-carboxylate (**Int-9b**). To the solution of tert-butyl 6-bromo-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (**Int-9a** 140 mg, 0.46 mmol) in Ethanol (2 mL) was added Thiourea (35.03 mg, 0.46 mmol), and the mixture was stirred at 80 °C for 2h. The solvent was removed and purified by prep-TLC (DCM: MeOH=15: 1) to get tert-butyl 2-aminospiro[5,6-dihydrocyclopenta[d]thiazole-4,3'-

azetidine]-1'-carboxylate (**Int-9b,** 20 mg, 0.0711 mmol, 15.44 %yield). LCMS calcld for $C_{13}H_{19}N_3O_2S$ $(M+H)^+$ m/z =282.37, found: 282.2.

**[00563]** Step 3. Preparation of spiro[5,6-dihydrocyclopenta[d]thiazole-4,3'-azetidine]-2-amine (**Intermediate 9**). The solution of tert-butyl 2-aminospiro[5,6-dihydrocyclopenta[d]thiazole-4,3'-azetidine]-1'-carboxylate (**Int-9b,** 15 mg, 0.05 mmol) and Trifluoroacetic acid (0.04 mL, 0.53 mmol) in DCM (2 mL) was stirred at 25 °C for 1h. The solvent was removed to get spiro[5,6-dihydrocyclopenta[d]thiazole-4,3'-azetidine]-2-amine (**Intermediate 9,** 15 mg). LCMS calcld for $C_{13}H_{19}N_3O_2S$ $(M+H)^+$ m/z =182.26, found: 182.2.

**Intermediate 10.** Synthesis of tert-butyl 2-cyano-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate



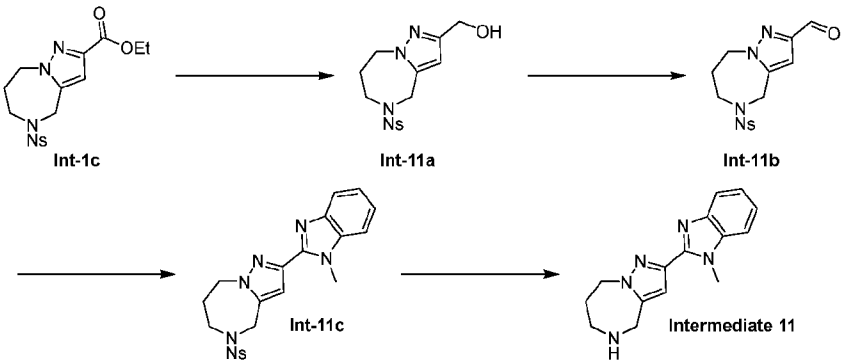

Int-5a Int-10a Intermediate 10

**[00564]** Step 1. Synthesis of tert-butyl 2-carbamoyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-10a**). To a solution of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**Int-5a,** 450 mg, 1.6 mmol) , DIEA (0.84 mL, 4.8 mmol) and HATU (0.91 g, 2.4 mmol) in DMF (45mL) was added $NH_4Cl$ (0.12 g, 1.92 mmol) at 30 °C. The mixture was stirred at 30 °C for 2h. The mixture was diluted with EtOAc (60 mL), washed with water (40 mL) and brine (40 mL), dried over $Na_2SO_4$, concentrated. The mixture was concentrated to afford a crude product. The crude product was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ (0.1 % TFA) from 5.0% to 95%); tert-butyl 2-carbamoyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-10a,** 350 mg, 1.25 mmol, 78.05% yield) was obtained as yellow solid. LCMS calcld for $C_{13}H_{20}N_4O_3$ $(M+H)+$ m/z =281.0 , found: 281.0.

**[00565]** Step 2. Synthesis of tert-butyl 2-cyano-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Intermediate 10**). To a solution of tert-butyl 2-carbamoyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (**Int-10a,** 300 mg, 1.07 mmol) and Pyridine (0.26 mL, 3.21 mmol) in THF (1mL) was added TFAA (674.36 mg, 3.21 mmol) slowly at 25 °C. The mixture was stirred at 25 °C for 48h. The mixture was quenched with $H_2O$ (8 mL) at 25 °C, extracted with EtOAC (10 mL), dried over $Na_2SO_4$, concentrated. The crude product was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ (0.1 % TFA) from 5.0% to 95%). tert-butyl 2-cyano-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate

(**Intermediate 10,** 145 mg,0.553 mmol, 51.65% yield) was obtained as yellow solid. LCMS calcld for $C_{13}H_{18}N_4O_2$ $(M+H)^+$ m/z = 263.3, found: 263.3.

**Intermediate 11.** Synthesis of 2-(1-methylbenzimidazol-2-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine




**[00566]** Step 1. Synthesis of [5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-2-yl]methanol (Int-11a). To a solution of ethyl 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (Int-1c 1500 mg, 3.8 mmol) in THF (15 mL) was added 1M DABAL-H in hexane (11.41 mL, 11.41 mmol) at -68 °C under argon. The mixture was stirred at 25 °C for 2 h. The reaction was added water and Isopropyl alcohol (1:1,12mL) and extracted with EtOAc (50 ml x 3), and concentrated. The crude product [5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-2-yl]methanol (Int-11a, 850 mg, 2.39 mmol, 62.79% yield) was used without purification. LCMS calcld for $C_{14}H_{16}N_4O_5S(M+H)^+$ m/z =353.1, found:353.1.

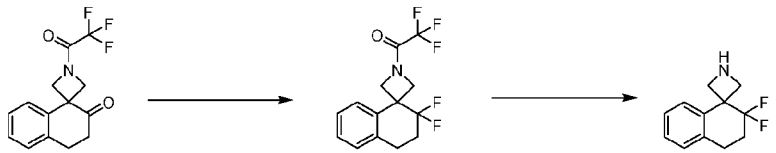
**[00567]** Step 2. Synthesis of 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbaldehyde (**Int-11b).** To a solution of [5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-2-yl]methanol (**Int-11a,** 850 mg, 2.41 mmol) in DMSO (8 mL) was added IBX (514.6 mg, 3.62 mmol) at 25 °C under argon. The mixture was stirred at 25 °C for 16 h. The mixture was filtered to afford a crude solution. The crude product was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ from 50% to 55%). 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbaldehyde (**Int-11b,** 570 mg, 1.59 mmol, 66.10 %yield) was obtained as white solid. LCMS calcld for $C_{14}H_{13}ClN_4O_5S$ $(M+H)^+$ m/z =351.1, found: 351.1.

**[00568]** Step 3. Synthesis of 2-(1-methylbenzimidazol-2-yl)-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine (**Int-11c**) **.** The solution of 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbaldehyde (**Int-11b,** 250 mg, 1 mmol) and N2-methylbenzene-1,2-diamine (244.34 mg, 2 mmol) in DMF (2 mL) was stirred at 100 °C for 18 h. The mixture was extracted with EtOAc and water, dried with brine and

$Na_2SO_4$, concentrated and purified by silica gel chromatography (DCM: MeOH= 50:1) to get the 2-(1-methylbenzimidazol-2-yl)-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine (**Int-11c**, 320 mg, 0.707 mmol, 70.72%yield). LCMS calcld for $C_{21}H_{20}N_6O_4S$ (M+H)+ m/z = 453.49, found: 453.3.

**[00569]** Step 4. Synthesis of 2-(1-methylbenzimidazol-2-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine **(Intermediate 11) .** A solution of $Cs_2CO_3$ (230.42 mg, 0.71 mmol), 2-(1-methylbenzimidazol-2-yl)-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine (**Int-11c,** 160 mg, 0.35 mmol) and 4-Methoxythiophenol (74.36 mg, 0.53 mmol) in $CH_3CN$ (5 mL) was stirred at 25 °C for 3h. The mixture was filtered and the solvent was removed and purified by silica gel chromatography (DCM: MeOH=11: 1) to get the 2-(1-methylbenzimidazol-2-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (**Intermediate 11**, 70 mg, 0.262 mmol, 74.05%yield). LCMS calcld for $C_{15}H_{17}N_5$ $(M+H)^+$ m/z = 268.33, found: 268.3.

**Intermediate 12.** Synthesis of 2',2'-difluorospiro[azetidine-3,1'-tetralin]

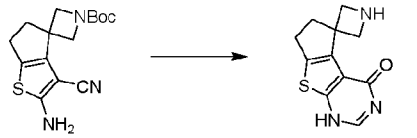



**[00570]** Step 1. Synthesis of 1-(2',2'-difluorospiro[azetidine-3,1'-tetralin]-1-yl)-2,2,2-trifluoro-ethanone (**Int-12b**). 1-(2,2,2-trifluoroacetyl)spiro[azetidine-3,1'-tetralin]-2'-one (**Int-12a** ref. *Angew. Chem. Int. Ed. 2021, 60, 7360–7365*, 120 mg, 0.42 mmol) was weighed in a vial and DCM (1.69 mL) was added. Diethylaminosulfur Trifluoride (0.11 mL, 0.85 mmol) was added, and mixture stirred at room temperature for 3 hrs. Reaction was purified by silica gel column eluting with 10% Ethyl Acetate/Hexanes to yield 1-(2',2'-difluorospiro[azetidine-3,1'-tetralin]-1-yl)-2,2,2-trifluoro-ethanone (**Int-12b,** 20 mg, 0.066 mmol, 15.47% yield). LCMS calculated for $C_{14}H_{12}F_5NO$ $(M+H)^+$ m/z =306.08; found: 306.1. $^1H$ NMR (500 MHz, $CD_3Cl$) δ ppm 2.18 - 2.30 (m, 2H) 3.06 (t, *J*=6.72 Hz, 2H) 4.17 (d, *J*=10.88 Hz, 1H) 4.42 (d, *J*=10.09 Hz, 1H) 4.58 (d, *J*=10.88 Hz, 1H) 4.79 - 4.88 (m, 1H) 7.17 (d, *J*=7.64 Hz, 1H) 7.28 - 7.32 (m, 1H) 7.36 - 7.42 (m, 1H) 7.56 - 7.60 (m, 1H).

**[00571]** Step 2. Synthesis of 2',2'-difluorospiro[azetidine-3,1'-tetralin]. (**Intermediate 12**). 1-(2',2'-difluorospiro[azetidine-3,1'-tetralin]-1-yl)-2,2,2-trifluoro-ethanone (**Int-12b,** 20 mg, 0.07 mmol) was weighed in a vial and Methanol (0.65 mL) was added. Potassium Carbonate (13.58 mg, 0.1 mmol) was added, and reaction was heated to reflux for 1 hour. Reaction was then

evaporated and redissolved in 10% MeOH/DCM. MeOH/DCM was then filtered and evaporated to yield crude product 2',2'-difluorospiro[azetidine-3,1'-tetralin] (**Intermediate 12,** 12 mg, 0.057 mmol, 87.53% yield) which was used without any further purification.

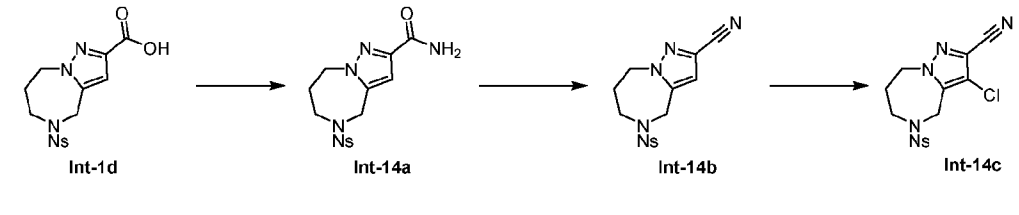
**Intermediate 13.** Synthesis of spiro[7-thia-9,11-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),10-triene-3,3'-azetidine]-12-one




Int-2a Intermediate 14

**[00572]** To a solution of tert-butyl 2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-2a**, 10 mg, 0.03 mmol) in Formic Acid (1 mL, 26.2 mmol) was added 1 drop $H_2SO_4$ and stirred at 105 °C for 3 h under argon. Then the reaction mixture was concentrated in vacuum to give the residue. The residue was recrystallized in ethanol to afford spiro[7-thia-9,11-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),10-triene-3,3'-azetidine]-12-one (**Intermediate 13**, 7 mg, 0.03 mmol, 91.64% yield) as white solid. LCMS calcld for $C_{11}H_{11}N_3OS$ $(M+H)^+$ m/z = 234.1, found: 234.1.

**Intermediate 14.** Synthesis of 3-(3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)-5-methyl-1,2,4-oxadiazole




Int-1d Int-14a Int-14b Int-14c

Int-14d Int-14e Intermediate 14

**[00573]** Step 1. Synthesis of 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (Int-14a). To a solution of 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (Int-1d, 870 mg, 2.37 mmol) , DIEA (1.65 mL, 9.5 mmol) and HATU (1354.48 mg, 3.56 mmol) in DMF (2mL) was added $NH_4Cl$ (171.13 mg, 2.85 mmol) at 30 °C. The mixture was stirred at 30 °C for 2h. The mixture was diluted with DCM (30 x 2 mL), washed with water (40mL) and brine (40mL), dried over $Na_2SO_4$, concentrated. The mixture was concentrated to afford a crude product. The crude

product was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ from 5.0% to 95%) to afford 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (Int-14a, 760 mg, 2.08 mmol, 87.59 %yield) as yellow solid. LCMS calcld for $C_{14}H_{15}N_5O_5S$ $(M+H)^+$ m/z =366.0 , found: 366.0.

**[00574]** Step 2. Synthesis of 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbonitrile (**Int-14b**) . To a solution of 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Int-14a,** 1.5 g, 4.11 mmol) and

Pyridine (1 mL, 12.32 mmol) in THF (10mL) was added TFAA (2586.98 mg, 12.32 mmol) slowly at 25 °C. The mixture was stirred at 25 °C for 48 h. The mixture was quenched with $H_2O$ (20 mL) at 25 °C, extracted with EtOAC (20 x 3 mL), dried over $Na_2SO_4$, concentrated. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 10% to 90%) to afford 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbonitrile (**Int-14b,** 0.8 g, 2.303 mmol, 56.10% yield) as yellow solid. LCMS calcld for $C_{14}H_{14}N_5O_4S$ $(M+H)^+$ m/z = 348.35, found: 348.0.

**[00575]** Step 3. Synthesis of 3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbonitrile (**Int-14c**). To a solution of 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbonitrile (500 mg, 1.44 mmol)in MeCN (5mL) were added NCS (192.21 mg, 1.44 mmol), The mixture was stirred at 60 °C for 4h. The mixture was quenched with $H_2O$ (10 mL) at 25 °C, extracted with EtOAC (30 mL), dried over $Na_2SO_4$, concentrated. The crude product was purified by flash chromatography (eluted with EtOAc in petroleum ether from 10% to 90%). The product 3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbonitrile (**Int-14c**, 400 mg, 1.05 mmol, 72.78% yield) was obtained as white solid. LCMS calcld for $C_{14}H_{12}ClN_5O_4S$ $(M+H)^+$ m/z = 382.1, found :382.1.

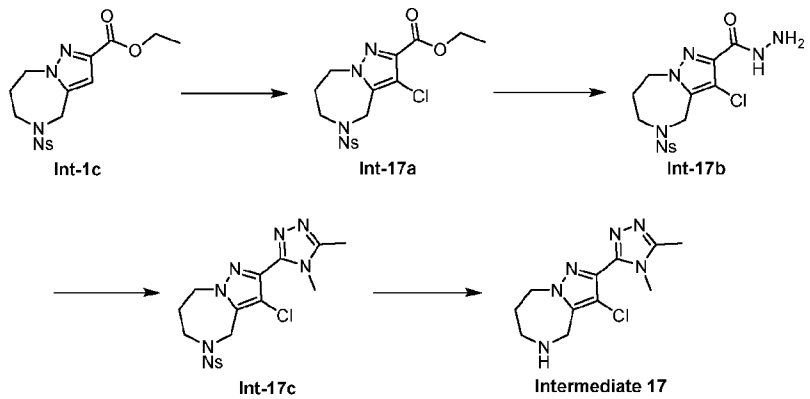
**[00576]** Step 4. Synthesis of 3-chloro-N-hydroxy-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamidine (**Int-14d**). To a solution of 3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbonitrile (**Int-14c**, 400 mg, 1.05mmol) and $K_2CO_3$ (433.75 mg, 3.14 mmol) in Ethanol (2 mL) was added HCl $NH_2OH$ (144.58 mg, 2.1 mmol) . The mixture was stirred at 80 °C for 12 h. The solution was concentrated. The crude product was washed with water 10 mL, filtrate to obtain a white solid. The product 3-chloro-N-hydroxy-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamidine (**Int-14d,** 183 mg, 0.441 mmol, 42.11% yield) was obtained as white solid. LCMS calcld for $C_{14}H_{15}ClN_6O_5S$ $(M+H)^+$ m/z = 415.0, found:415.0.

**[00577]** Step 5. Synthesis of 3-[3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-2-yl]-5-methyl-1,2,4-oxadiazole (**Int-14e**). To a solution

of 3-chloro-N-hydroxy-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamidine (Int-14d, 183 mg, 0.441 mmol) in Acetic acid (2 mL) were added Acetic anhydride (67.56 mg, 0.66 mmol), The mixture was stirred at 100 °C for 16h. The mixture was filtered to afford a crude product. The crude product was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ from 5.0% to 43%). 3-[3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-2-yl]-5-methyl-1,2,4-oxadiazole (**Int-14e**, 163 mg, 0.371 mmol, 84.19% yield) was obtained as white solid. LCMS calcld for $C_{16}H_{15}ClN_6O_5S(M+H)^+$ m/z = 439.1, found: 439.1.

**[00578]** Step 6. Synthesis of 3-(3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)-5-methyl-1,2,4-oxadiazole. To a solution of 3-[3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-2-yl]-5-methyl-1,2,4-oxadiazole (**Int-14e**, 150 mg, 0.34 mmol) ,4-methoxybenzenethiol (0.13 mL, 1.03 mmol) and cesium carbonate (444.34 mg, 1.37 mmol) in $CH_3CN$ (4 mL). The mixture was stirred at 20 °C for 1 h. The mixture was filtrated and purified by prep-HPLC on a C18 column with mobile phase: $H_2O$ (0.1%$NH_4HCO_3$)/$CH_3CN$ to afford 3-(3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)-5-methyl-1,2,4-oxadiazole (**Intermediate 14**, 80 mg, 0.315 mmol, 92.26% yield) as white solid. LCMS calcld for $C^{10}H^{13}ClN^5O$ $(M+H)^+$ m/z = 254.07, found: 254.0.

**Intermediate 15.** Synthesis of 3-chloro-2-(4,5-dimethyl-1,2,4-triazol-3-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine




**[00579]** Step 1. Synthesis of ethyl 3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-17a**). A solution of ethyl 5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-1c** 1000 mg, 2.54 mmol) in DMF (10 mL) was added NCS (372.42 mg, 2.79 mmol) at 25 °C. Then the mixture was stirred at 80 °C for 1 h. The solution was extracted with EtOAc (10 ml), the organic phase was concentrated. The residue was purified by silica gel chromatography (eluting with EtOAc in PE from 5% to 85%). The product ethyl 3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-

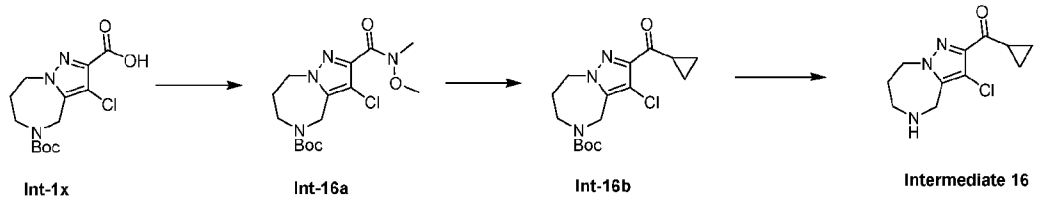
tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-17a,** 914 mg,2.131 mmol, 84.06% yield) was obtained as an oil. LCMS calcld for $C_{16}H_{17}ClN_4O_6S$ $(M+H)^+$ m/z =429.06, found: 429.2.

**[00580]** Step 2. Synthesis of 3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Int-17b**). A solution of ethyl 3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**Int-17a,** 500 mg, 1.17 mmol) in Ethanol (5 mL) was added $NH_2NH_2.H_2O$ (594.85 mg, 11.66 mmol) at 25 °C. Then the mixture was stirred at 85 °C for 2 h. The solution was extracted with EtOAc (5 ml), the organic phase was concentrated. The residue was purified by silica gel chromatography (eluting with EtOAc in PE from 5% to 95%). The product 3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbohydrazide (**Int-17b,** 300 mg,0.723 mmol, 62.03% yield) was obtained as a white solid. LCMS calcld for $C_{14}H_{15}ClN_6O_5S$ $(M+H)^+$ m/z =415.06, found: 415.0.

**[00581]** Step 3. Synthesis of 3-chloro-2-(4,5-dimethyl-1,2,4-triazol-3-yl)-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine (**Int-17c**). To a solution of 3-chloro-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carbohydrazide (**Int-17b,** 150 mg, 0.36 mmol) in 1,4-Dioxane (3 mL) was added 1,1,1-trimethoxyethane (65.17 mg, 0.54 mmol), Methylamine in EtOH (0.17mL, 1.08mmol) and a drop of AcOH (21.7mg, 0.36mmol) at rt. The mixture was stirred at 120 °C for 16 h in a sealed vial. The solution was extracted with EtOAc (2 ml), The water phase was concentrated. The residue was purified by silica gel chromatography (eluting with MeOH in DCM from 1 % to 3%). The product 3-chloro-2-(4,5-dimethyl-1,2,4-triazol-3-yl)-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine (**Int-17c,** 95 mg, 0.210 mmol, 58.14% yield) was obtained as a white solid. LCMS calcld for $C_{17}H_{18}ClN_7O_4S$ $(M+H)^+$ m/z =452.09, found: 452.2.

**[00582]** Step 4. Synthesis of 3-chloro-2-(4,5-dimethyl-1,2,4-triazol-3-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (**Intermediate 17**). To a solution of 3-chloro-2-(4,5-dimethyl-1,2,4-triazol-3-yl)-5-(2-nitrophenyl)sulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine (**Int-17c,** 75 mg, 0.17 mmol) in $CH_3CN$ (0.5 mL) was added 4-Methoxythiophenol (44.21 mg, 0.32 mmol) and $CS_2CO_3$ (137.07 mg, 0.42 mmol) at rt. The mixture was stirred at 25 °C for 2 h. The solution was concentrated. The residue was purified by silica gel on chromatography (eluting with MeOH in DCM from 3 % to 11%). The 3-chloro-2-(4,5-dimethyl-1,2,4-triazol-3-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine (**Intermediate 17**, 40 mg, 0.15 mmol, 71.33% yield) was obtained as a white solid. LCMS calcld for $C_{11}H_{15}ClN_6$ $(M+H)^+$ m/z =267.11, found: 267.1.

**Intermediate 16.** Synthesis of (3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)-cyclopropyl-methanone

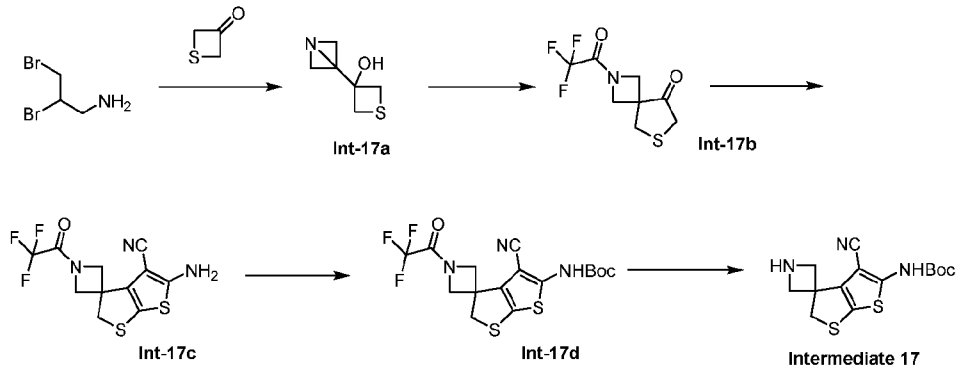



**[00583]** Step 1. Synthesis of tert-butyl 3-chloro-2-[methoxy(methyl)carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate. The mixture of 5-tert-butoxycarbonyl-3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (350 mg, 1.11 mmol) and HATU (0.41 mL, 1.66 mmol) in DMF (2mL) was added N,O-Dimethylhydroxylamine Hydrochloride (162.18 mg, 1.66 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 h. The mixture was filtered to afford a crude solution. The crude product was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ from51% to 72%). tert-butyl 3-chloro-2-[methoxy(methyl)carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (230 mg, 0.641 mmol, 57.83 %yield). LCMS calcld for $C_{15}H_{23}ClN_4O_4$ $(M+H)^+$ m/z =359.1 , found: 359.2.

**[00584]** Step 2. Synthesis of tert-butyl 3-chloro-2-(cyclopropanecarbonyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate. To a solution of tert-butyl 3-chloro-2-[methoxy(methyl)carbamoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (230 mg, 0.64 mmol) in THF (1.5mL) was added 1M bromo(cyclopropyl)magnesium in THF (372.49 mg, 2.56 mmol) at 0 °C under argon. The mixture was stirred at 0 °C for 2 h. The mixture was concentrated to afford a crude product. The crude product was used directly for the next step. tert-butyl 3-chloro-2-(cyclopropanecarbonyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (150 mg,0.441 mmol, 68.86% yield) was obtained as brown oil. LCMS calcld for $C_{16}H_{22}ClN_3O_3$ $(M+H)^+$ m/z = 340.1, found: 340.1.

**[00585]** Step 3. Synthesis of (3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)-cyclopropyl-methanone. To a solution of tert-butyl 3-chloro-2-(cyclopropanecarbonyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (150 mg, 0.44 mmol) in DCM (1mL) was added Trifluoroacetic Acid (0.3 mL, 3.89 mmol) at 25 °C under argon. The mixture was stirred at 25 °C for 2 h. The mixture was concentrated to afford a crude product. The crude product was purified by flash chromatography(eluted with $CH_3CN$ in $H_2O$ from 5.0% to 45%). (3-chloro-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)-cyclopropyl-methanone (100mg,0.4172mmol, 94.513% yield) was obtained as brown oil. LCMS calcld for $C_{11}H_{14}ClN_3O$ (M+H)+ m/z =240.3 , found: 240.3.

**Intermediate 17.** Synthesis of tert-butyl N-(4-cyanospiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-5-yl)carbamate




**[00586]** Step 1. Synthesis of 3-(1-azabicyclo[1.1.0]butan-3-yl)thietan-3-ol (**Int-17a**). 2,3-dibromopropan-1-amine;hydrobromide (5000 mg, 16.79 mmol) in THF (100mL) at -78 °C, Phenyllithium (50.37 mL, 50.37 mmol) was added, The mixture was stirred at -78 °C for 2h, After this time, the reaction mixture was removed from the cooling bath and warmed to room temperature over 10 minutes with stirring. After cooling back down to -78 °C, TMEDA (4877.27 mg, 41.97 mmol) was then added followed by s-BuLi (32.29 mL, 41.97 mmol) dropwise, and the resulting solution stirred for 1 hour at –78 °C. After this time, thietan-3-one (1479.63 mg, 16.79 mmol) was added dropwise in THF. The reaction was stirred for a further 1 hour at -78 °C. The mixture was diluted with EtOAC (100 mL x2), washed with water (100 mL), dried over Na2SO4, concentrated. The crude product was used directly for the next step. 3-(1-azabicyclo[1.1.0]butan-3-yl)thietan-3-ol (**Int-17a,** 4000 mg, 27.93 mmol, 166.36% yield) was obtained as crude yellow oil.

**[00587]** Step 2. Synthesis of 2-(2,2,2-trifluoroacetyl)-6-thia-2-azaspiro[3.4]octan-8-one (**Int-17b**). 3-(1-azabicyclo[1.1.0]butan-3-yl)thietan-3-ol (**Int-17a,** 3000 mg, 20.95 mmol) in DCM at -78 °C, TFAA (2.91 mL, 20.95 mmol) was added. The mixture was stirred at -78 °C for 2h. The mixture was quenched with $NaHCO_3$ (100 mL), extracted with DCM (100 mLx2), dried over $Na_2SO_4$, concentrated. The crude product was purified by flash chromatography (eluted with EtOAc in petroleum ether from 10% to 20%) to afford 2-(2,2,2-trifluoroacetyl)-6-thia-2-azaspiro[3.4]octan-8-one (**Int-17b,** 525 mg, 2.195 mmol, 10.48% yield) was obtained as crude yellow oil. LCMS calcld for $C_8H_8F_3NO_2S$ $(M+H)^+$ m/z = 239.21, found: 240.2.

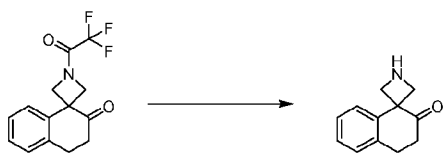
**[00588]** Step 3. Synthesis of 5-amino-1'-(2,2,2-trifluoroacetyl)spiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-4-carbonitrile (**Int-17c**). To a solution of 2-(2,2,2-trifluoroacetyl)-6-thia-2-azaspiro[3.4]octan-8-one (**Int-17b,** 500 mg, 2.09 mmol) L-Proline (240.65 mg, 2.09 mmol) propanedinitrile (207.12 mg, 3.14 mmol) in DMF (5mL), Sulfur (100.52 mg, 3.14 mmol)

was added. The mixture was stirred at 60 °C for 12h. The mixture was extracted with EtOAC (25 mL), dried over $Na_2SO_4$, concentrated. The crude product was purified by Flash chromatography eluted with $CH_3CN$ in $H_2O$ from 5.0% to 95%. 5-amino-1'-(2,2,2-trifluoroacetyl)spiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-4-carbonitrile (**Int-17c,** 330 mg, 1.03 mmol, 49.44 % yield) was reddish-brown solid. LCMS calcld for $C_{11}H_8F_3N_3OS_2$ $(M+H)^+$ m/z = 320.1, found: 320.1.

**[00589]** Step 4. Synthesis of tert-butyl N-tert-butoxycarbonyl-N-[4-cyano-1'-(2,2,2-trifluoroacetyl)spiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-5-yl]carbamate (**Int-17d**). To a solution of 5-amino-1'-(2,2,2-trifluoroacetyl)spiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-4-carbonitrile (**Int-17c,** 250 mg, 0.78 mmol) in MeCN (3 mL) was added $Boc_2O$ (341.73 mg, 1.57 mmol) and DMAP (9.56 mg, 0.08 mmol) at 25 °C. The reaction stirred at 25 °C for 1h. The mixture was concentrated. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 10% to 50%). tert-butyl N-tert-butoxycarbonyl-N-[4-cyano-1'-(2,2,2-trifluoroacetyl)spiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-5-yl]carbamate (300 mg,0.577 mmol, 73.75% yield) was obtained as brown solid. LCMS calculated for $C_{16}H_{16}F_3N_3O_3S_2$ $(M+Na)^+$ m/z = 442.2, found: 442.2.

**[00590]** Step 5. Synthesis of tert-butyl N-(4-cyanospiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-5-yl)carbamate (**Intermediate 17**). To a solution of tert-butyl N-[4-cyano-1'-(2,2,2-trifluoroacetyl)spiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-5-yl]carbamate (**Int-17d,** 300 mg, 0.58 mmol) in Methanol (3mL) was added $K_2CO_3$ (239.41 mg, 1.73 mmol) at 25 °C. The reaction stirred at 70 °C for 1 h. The mixture was filtered. The crude product was purified by silica gel chromatography (eluted with MeOH in DCM from 5% to 30%). tert-butyl N-(4-cyanospiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-5-yl)carbamate (**Intermediate 17,** 110 mg, 0.340 mmol, 58.90% yield) was obtained as yellow solid. LCMS calculated for $C_{14}H_{17}N_3O_2S_2$ $(M+H)^+$ m/z = 324.2, found: 324.2.

**Intermediate 18.** Synthesis of spiro[azetidine-3,1'-tetralin]-2'-one

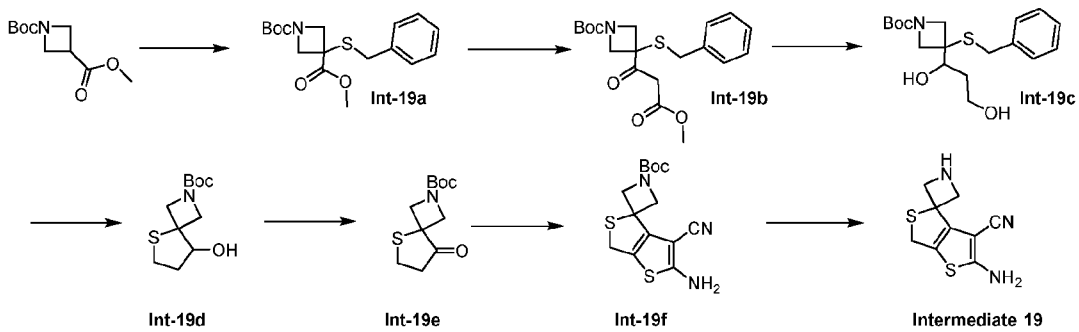



Int-12a Intermediate 18

**[00591]** 1-(2,2,2-trifluoroacetyl)spiro[azetidine-3,1'-tetralin]-2'-one (20 mg, 0.07 mmol) was weighed in a vial and Methanol was added. Potassium Carbonate (19.52 mg, 0.14 mmol) was added, and reaction stirred at 80 °C for 1 hour. Reaction was evaporated and redissolved in 10% MeOH/DCM and then filtered. MeOH/DCM was evaporated to yield product spiro[azetidine-3,1'-

tetralin]-2'-one (13 mg,0.069 mmol, 98.33% yield). $^1$H NMR (500 MHz, $CD_3Cl$) δ ppm 2.62 - 2.69 (m, 2H) 3.00 (t, *J*=6.66 Hz, 2H) 3.73 (d, *J*=8.07 Hz, 2H) 4.28 (d, *J*=8.07 Hz, 2H) 7.20 (s, 1H) 7.23 - 7.29 (m, 14H) 7.38 (s, 1H) 7.82 (d, *J*=7.82 Hz, 1H).

**Intermediate 19.** Synthesis of 2-aminospiro[6H-thieno[2,3-c]thiophene-4,3'-azetidine]-3-carbonitrile




**[00592]** Step 1. Preparation of O1-tert-butyl O3-methyl 3-benzylsulfanylazetidine-1,3-dicarboxylate (**Int-19a**). To a solution of O1-tert-butyl O3-methyl azetidine-1,3-dicarboxylate (1000 mg, 4.65 mmol) in THF (10 mL) was added 1M LDA in THF (4.65 mL, 9.29 mmol) at -78 °C, the mixture was then stirred at -78 °C for 1 h, then dibenzyldisulfide (2289.34 mg, 9.29 mmol) was added at -78 °C. The mixture was then stirred at -78 °C for 1 h. The reaction mixture was quenched by $NH_4Cl$ (5 mL), diluted with EtOAc (30 x 2 mL), washed with brine (20 ml), dried over $Na_2SO_4$, concentrated. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 0% to 10%). O1-tert-butyl O3-methyl 3-benzylsulfanylazetidine-1,3-dicarboxylate (**Int-19a,** 610 mg) was obtained as a crude yellow oil.

**[00593]** Step 2. Preparation of tert-butyl 3-benzylsulfanyl-3-(3-methoxy-3-oxo-propanoyl)azetidine-1-carboxylate (**Int-19b**). To a solution of methyl acetate (0.58 mL, 7.23 mmol) in THF (10 mL) was added 1M LiHMDS in THF (7.23 mL, 7.23 mmol) at -78 °C. The mixture was then stirred at -78 °C for 1 h before O1-tert-butyl O3-methyl 3-benzylsulfanylazetidine-1,3-dicarboxylate (**Int-19a,** 610 mg, 1.81 mmol) was added at -78 °C. The resulting mixture was stirred for 1h at -78 °C and then allowed to warm up to room temperature for 45 min. The reaction mixture was quenched by $NH_4Cl$ (5 mL), diluted with EtOAc (20 x 2 mL), washed with brine (10 ml), dried over $Na_2SO_4$, concentrated.

**[00594]** The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 0% to 20%) to afford tert-butyl 3-benzylsulfanyl-3-(3-methoxy-3-oxo-propanoyl)azetidine-1-carboxylate (**Int-19b** 270 mg,0.712mmol, 39.36% yield) as a colorless oil.

**[00595]** Step 3. Preparation of tert-butyl 3-benzylsulfanyl-3-(1,3-dihydroxypropyl)azetidine-1-carboxylate (**Int-19c**). To a solution of tert-butyl 3-benzylsulfanyl-3-(3-methoxy-3-oxo-propanoyl)azetidine-1-carboxylate (**Int-19b,** 1200 mg, 3.16 mmol) in DCM (10 mL) was added 1M DIBAL-H in PhMe (12.6 mL, 12.65 mmol) at -78 °C. The mixture was stirred at 25 °C for 16h under argon. The mixture was quenched with MeOH (20 mL) at 0 °C and filtered, extracted with EtOAC (30 x 3 mL), dried over $Na_2SO_4$, concentrated. The crude product was purified by silica gel chromatography (eluted with MeOH in DCM from 0% to 10%). The product tert-butyl 3-benzylsulfanyl-3-(1,3-dihydroxypropyl)azetidine-1-carboxylate (**Int-19c,** 350 mg, 0.99 mmol, 31.31% yield) was obtained as a colorless oil. LCMS calcld for $C_{18}H_{27}NO_4SNa$ $(M+Na)^+$ m/z = 376.2; found: 376.2.

**[00596]** Step 4. Preparation of tert-butyl 8-hydroxy-5-thia-2-azaspiro[3.4]octane-2-carboxylate (**Int-19d).**

**[00597]** To a solution of tert-butyl 3-benzylsulfanyl-3-(1,3-dihydroxypropyl)azetidine-1-carboxylate (**Int-19c,** 300 mg, 0.85 mmol) in pyridine (8 mL) was added TosCl (404.51 mg, 2.12 mmol) at 25 °C. The mixture was stirred at 25 °C for 16h. The mixture was concentrated to afford a crude product. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 10% to 40%) to afford tert-butyl 8-hydroxy-5-thia-2-azaspiro[3.4]octane-2-carboxylate (**Int-19d,** 130 mg, 0.530 mmol, 62.43% yield) as a colorless oil. LCMS calcld for $C_{11}H_{20}NO_3S$ (M+H)+ m/z = 246.1, found: 190.1 (-tBu).

**[00598]** Step 5. Preparation of tert-butyl 8-oxo-5-thia-2-azaspiro[3.4]octane-2-carboxylate (**Int-19e).** To a solution of tert-butyl 8-hydroxy-5-thia-2-azaspiro[3.4]octane-2-carboxylate (**Int-19d,** 350 mg, 1.43 mmol) in DCM (8 mL) and DMSO (2 mL) was added TEA (0.99 mL, 7.13 mmol) and pyridine sulfur trioxide (681.17 mg, 4.28 mmol) at 0 °C. The mixture was stirred at 25 °C for 16 h. The mixture was quenched with $H_2O$ at 25 °C, extracted with DCM, dried over $Na_2SO_4$ and concentrated. The crude product was purified by silica gel chromatography (eluted with EtOAc in petroleum ether from 10% to 25%). Tert-butyl 8-oxo-5-thia-2-azaspiro[3.4]octane-2-carboxylate (**Int-19e,** 260 mg, 1.07 mmol, 74.90% yield) was obtained as a white solid. LCMS calcld for $C_{11}H_{18}NO_3S$ (M+H)+ m/z = 244.1, found: 188.1 (-tBu).

**[00599]** Step 6. Preparation of tert-butyl 2-amino-3-cyano-spiro[6H-thieno[3,4-b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-19f)**

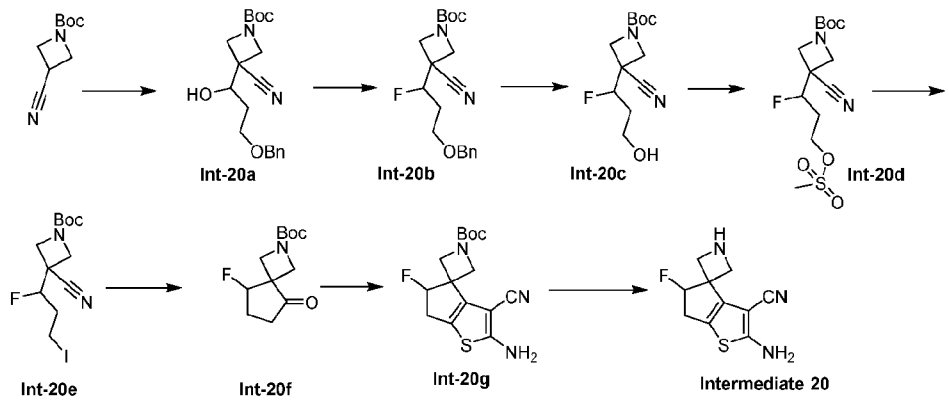
**[00600]** A solution of tert-butyl 8-oxo-5-thia-2-azaspiro[3.4]octane-2-carboxylate (**Int-19e,** 300 mg, 1.23 mmol), sulfur (63.03 mg, 1.85 mmol), $NH_4OAc$ (143.88 mg, 1.85 mmol) in ethanol (3 mL) was added propanedinitrile (122.17 mg, 1.85 mmol) slowly at 15 °C. Then the mixture was stirred at 60 °C for 16h. The crude product was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ from 5.0% to 95%). tert-butyl 2-amino-3-cyano-spiro[6H-thieno[3,4-

b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-19f,** 150 mg, 0.464 mmol, 37.62% yield) was obtained as a white solid. LCMS calcld for $C_{14}H_{17}N_3O_2S_2Na$ $(M+Na)^+$ m/z = 346.1, found: 346.1.

**[00601]** Step 7. Preparation of 2-aminospiro[6H-thieno[2,3-c]thiophene-4,3'-azetidine]-3-carbonitrile;2,2,2-trifluoroacetic acid (**Intermediate 19)**

**[00602]** A solution of trifluoroacetic acid (0.31 mL, 4.11 mmol) and tert-butyl 2-amino-3-cyano-spiro[6H-thieno[2,3-c]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-19f**, 50 mg, 0.15 mmol) in DCM (3 mL) was stirred at 25 °C for 1h. The solvent was removed to get 2-aminospiro[6H-thieno[2,3-c]thiophene-4,3'-azetidine]-3-carbonitrile (**Intermediate 19**, 52 mg, 99.71% -yield) as a crude brown oil. LCMS calculated for $C_9H_{10}N_3S_2$ $(M+H)^+$ m/z =224.1, found: 224.1.

**Intermediate 20.** Synthesis of 2-amino-5-fluoro-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile




**[00603]** Step 1. Preparation of tert-butyl 3-(3-benzyloxy-1-hydroxy-propyl)-3-cyano-azetidine-1-carboxylate (**Int-20a**). To a solution of tert-butyl 3-cyanoazetidine-1-carboxylate (500 mg, 2.74 mmol) in THF (5 mL) was added LDA (1.92 mL, 3.84mmol) portion wise at -70 °C under $N_2$. Then the mixture was stirred at -70 °C for 1h, and 3-benzyloxypropanal (630.78 mg, 3.84 mmol) was added at -70 °C.

**[00604]** The resulting mixture was stirred at -70 °C for 30min and warmed to rt for 1h. The reaction mixture was quenched with saturated $NH_4Cl$ solution, and then extracted with EtOAc. The organic layer was washed with water and brine, dried over $Na_2SO_4$, concentrated and purified by flash column chromatography (silica gel, eluting with 0% to 40% EtOAc/PE) to afford tert-butyl 3-(3-benzyloxy-1-hydroxy-propyl)-3-cyano-azetidine-1-carboxylate (**Int-20a,**

450 mg, 1.30 mmol, 47.34% yield) as a colorless oil. LCMS calculated for $C_{19}H_{27}N_2O_4$ $(M+H)^+$ m/z =347.20; found: 247.3 (-Boc).

**[00605]** Step 2. Preparation of tert-butyl 3-(3-benzyloxy-1-fluoro-propyl)-3-cyano-azetidine-1-carboxylate (**Int-20b**). To a solution of tert-butyl 3-(3-benzyloxy-1-hydroxy-propyl)-3-cyano-azetidine-1-carboxylate (**Int-20a,** 100 mg, 0.29 mmol) in DCM (2 mL) was added diethylaminosulfur trifluoride (0.08 mL, 0.58 mmol) portion-wise at -70 °C under $N_2$. The mixture was stirred at -70 °C for 30min, then warmed to rt for 4h. The reaction mixture was quenched with ice water and extracted with EtOAc. The organic layer was washed with water and brine, dried over $Na_2SO_4$, concentrated, and purified by flash column chromatography (silica gel, eluting with 0% to 40% EtOAc/PE) to afford tert-butyl 3-(3-benzyloxy-1-fluoro-propyl)-3-cyano-azetidine-1-carboxylate (**Int-20b,** 72 mg, 0.207 mmol, 71.59% yield) as a colorless oil. LCMS calculated for $C_{19}H_{26}FN_2O_3$ $(M+H)^+$ m/z =349.19; found: 249.3 (-Boc)

**[00606]** Step 3. Preparation of tert-butyl 3-cyano-3-(1-fluoro-3-hydroxy-propyl)azetidine-1-carboxylate (**Int-20c**). The mixture of tert-butyl 3-(3-benzyloxy-1-fluoro-propyl)-3-cyano-azetidine-1-carboxylate (**Int-20b,** 2000 mg, 5.74 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (5212.25 mg, 22.96 mmol) in DCM (20 mL) and water (3 mL) was stirred at 45 °C for 20h. The resulting mixture was filtered. The filtrate was treated with saturated $NaHCO_3$, extracted with DCM. The organic layer was washed with brine, dried over $Na_2SO_4$, concentrated and purified by flash column chromatography (silica gel, eluting with 0% to 60% EtOAc/PE) to afford tert-butyl 3-cyano-3-(1-fluoro-3-hydroxy-propyl)azetidine-1-carboxylate (**Int-20c,** 1090 mg, 4.22 mmol, 73.52% yield) as a brown oil. LCMS calculated for $C_{12}H_{20}FN_2O_3$ (M+H)+ m/z =259.2; found: 203.2 (-tBu).

**[00607]** Step 4. Preparation of tert-butyl 3-cyano-3-(1-fluoro-3-methylsulfonyloxy-propyl)azetidine-1-carboxylate (**Int-20d**). To a solution of tert-butyl 3-cyano-3-(1-fluoro-3-hydroxy-propyl)azetidine-1-carboxylate (**Int-20c,** 100 mg, 0.39 mmol) in DCM (2 mL) were added methanesulfonyl chloride (0.05 mL, 0.58 mmol) and TEA (0.11 mL, 0.77 mmol) at 0 °C. Then the mixture was stirred at rt for 1h. The resulting mixture was quenched with water, and then extracted with EtOAc. The organic layer was washed with brine, dried over $Na_2SO_4$, concentrated to afford tert-butyl 3-cyano-3-(1-fluoro-3-methylsulfonyloxy-propyl)azetidine-1-carboxylate (**Int-20d**, 130 mg, 0.387 mmol, 99.82% yield) as a green oil. LCMS calculated for $C_{13}H_{22}FN_2O_5S$ $(M+H)^+$ m/z =337.13; found: 281.0 (-tBu).

**[00608]** Step 5. Preparation of tert-butyl 3-cyano-3-(1-fluoro-3-iodo-propyl)azetidine-1-carboxylate (**Int-20e**). The mixture of tert-butyl 3-cyano-3-(1-fluoro-3-methylsulfonyloxy-propyl)azetidine-1-carboxylate (**Int-20d**, 130 mg, 0.39 mmol) and NaI (173.78 mg, 1.16 mmol) in acetone (2 mL) was stirred at rt overnight. The reaction mixture was stirred at 60 °C for 5h.

The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The mixture was diluted with water, extracted with EtOAc, washed with brine, dried over $Na_2SO_4$, concentrated and purified by flash column chromatography (silica gel, eluting with 0% to 70% EtOAc/PE) to afford tert-butyl 3-cyano-3-(1-fluoro-3-iodo-propyl)azetidine-1-carboxylate (**Int-20e,** 103 mg, 0.28 mmol, 72.39% yield) as a colorless oil. LCMS calculated for $C_{12}H_{19}FIN_2O_2$ $(M+H)^+$ m/z =369.05; found: 313.0 (-tBu).

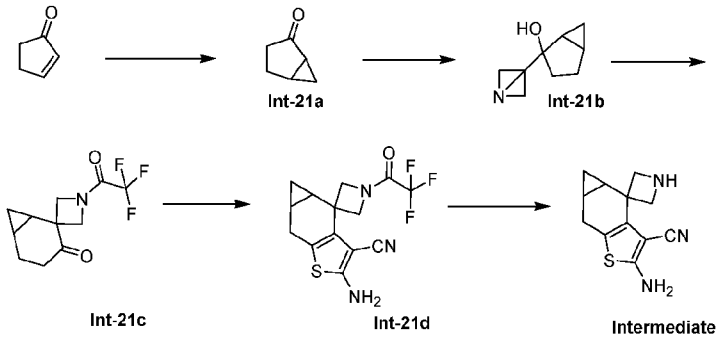
**[00609]** Step 6. Preparation of tert-butyl 5-fluoro-8-oxo-2-azaspiro[3.4]octane-2-carboxylate (**Int-20f**) To a solution of tert-butyl 3-cyano-3-(1-fluoro-3-iodo-propyl)azetidine-1-carboxylate (**Int-20e,** 1450 mg, 3.94 mmol) in THF (15 mL) was added n-butyllithium (504.56 mg, 7.88 mmol) at -78 °C under $N_2$. Then the mixture was stirred at -78 °C for 30min. After completion of the reaction, HOAc (0.68 mL, 11.81 mmol) was added dropwise at -78 °C. The resulting mixture was diluted with EtOAc and water was added. The organic layer was washed with brine, dried over $Na_2SO_4$, concentrated and purified by flash column chromatography (silica gel, eluting with 0% to 70% EtOAc/PE) to afford tert-butyl 5-fluoro-8-oxo-2-azaspiro[3.4]octane-2-carboxylate (**Int-20f,** 655 mg, 2.69 mmol, 68.37% yield) as a yellow oil. LCMS calculated for $C_{12}H_{19}FNO_3$ $(M+H)^+$ m/z =244.14; found: 188.0 (-tBu).

**[00610]** Step 7. Preparation of tert-butyl 2-amino-3-cyano-5-fluoro-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-20g**)

**[00611]** To a solution of tert-butyl 5-fluoro-8-oxo-2-azaspiro[3.4]octane-2-carboxylate (**Int-20f,** 600 mg, 2.47 mmol), sulfur (118.68 mg, 3.7 mmol), $NH_4OAc$ (287.83 mg, 3.7 mmol) in ethanol (12mL) was added propanedinitrile (244.4 mg, 3.7 mmol) at rt. Then the mixture was stirred at 30 °C for 3h. Diluted with water and extracted with EtOAc. The combined extracts were dried, filtered and concentrated and the crude product was purified to afford tert-butyl 2-amino-3-cyano-5-fluoro-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-20g,** 407 mg, 1.26 mmol, 51.03% yield) as a light-yellow solid. LCMS calculated for $C_{15}H_{19}FN_3O_2S$ $(M+H)^+$ m/z =324.12; found: 224.0 (-tBu).

**[00612]** Step 8. Preparation of 2-amino-5-fluoro-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile;hydrochloride (**Intermediate 20**). To a solution of tert-butyl 2-amino-3-cyano-5-fluoro-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-carboxylate (**Int-20g,** 360 mg, 1.11 mmol) in DCM (15mL) was added HCl in dioxane (3 mL, 12 mmol). Then the mixture was stirred at rt overnight. The resulting mixture was diluted with DCM, concentrated to afford 2-amino-5-fluoro-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile; hydrochloride (**Intermediate 20,** 322 mg, 1.103 mmol, 99.12% yield) as a brown solid. LCMS calculated for $C_{10}H_{11}FN_3S$ $(M+H)^+$ m/z =224.07; found: 224.2.

**Intermediate 21.** Synthesis of 2-aminospiro[4a,5,5a,6-tetrahydrocyclopropa[f]benzothiophene-4,3'-azetidine]-3-carbonitrile




**[00613]** Step 1. Preparation of bicyclo[3.1.0]hexan-2-one (**Int-21a**). NaH (4872.11 mg, 121.8 mmol) in DMSO (50mL) was added trimethylsulfoxonium iodide (26805.12 mg, 121.8 mmol) at 25 °C. Then the mixture was stirred at 25 °C for 1 h. The cyclopent-2-en-1-one (10.2 mL, 121.8 mmol) was added to the mixture at 25 °C for 30 mins. After 30 mins, the mixture was stirred at 50 °C for 2 h. The solution was extracted with MTBE (100 ml), the organic phase was concentrated. The residue was purified by silica gel on chromatography (eluting with 100% DCM). The product bicyclo[3.1.0]hexan-2-one (**Int-21a,** 2000 mg, 20.81 mmol, 17.08% yield) was obtained as a colorless oil. LCMS calculated for $C_6H_9O$ $(M+H)^+$ m/z =97.07, found: 97.2.

**[00614]** Step 2. Preparation of 2-(1-azabicyclo[1.1.0]butan-3-yl)bicyclo[3.1.0]hexan-2-ol (**Int-21b**). To a solution of 2,3-dibromopropan-1-amine; hydrobromide (4000 mg, 13.43 mmol) in THF (80 mL) at -78 °C, PhLi (3386.32 mg, 40.29 mmol) was added. The mixture was stirred at -78 °C for 2h. The reaction mixture was then removed from the cooling bath and warmed to rt for over 10 mins with stirring. After cooling back down to -78 °C, TMDEA (3901.82 mg, 33.58 mmol) was added, followed by the dropwise addition of s-BuLi (6703.94 mg, 33.58 mmol). The resulting solution was stirred for 1 hour at -78 °C. Then, bicyclo[3.1.0]hexan-2-one (**Int-21a,** 1291.16 mg, 13.43 mmol) was added dropwise in THF. The reaction was stirred for another 1 hour at -78 °C. The mixture was diluted with EtOAc (40 mL), washed with water (200 mL), dried over $Na_2SO_4$, concentrated to afford 2-(1-azabicyclo[1.1.0]butan-3-yl)bicyclo[3.1.0]hexan-2-ol (**Int-21b,** 3500 mg) as a crude yellow oil.

**[00615]** Step 3. Preparation of 1-(2,2,2-trifluoroacetyl)spiro[azetidine-3,2'-norcarane]-3'-one (**Int-21c**). A solution of 2-(1-azabicyclo[1.1.0]butan-3-yl)bicyclo[3.1.0]hexan-2-ol (**Int-21b,** 3500 mg, 23.15 mmol) in DCM (66 mL) was added TFAA (6.44 mL, 46.29 mmol) at -78 °C. Then the mixture was stirred at -78 °C for 1 h. The solution was added EtOAc (20 ml), washed with aqueous $NaHCO_3$ until pH=7. Then the organic phase was concentrated. The residue was purified by silica gel chromatography (eluting with EtOAc in PE from 17% to 50%). The product 1-(2,2,2-trifluoroacetyl)spiro[azetidine-3,2'-norcarane]-3'-one (**Int-21c,** 1000 mg, 4.05

mmol, 17% yield) was obtained as a brown oil. LCMS calculated for $C_{11}H_{13}F_3NO_2$ $(M+H)^+$ m/z =248.09, found:248.1.

**[00616]** Step 4. Preparation of 2-amino-1'-(2,2,2-trifluoroacetyl)spiro[4a,5,5a,6-tetrahydrocyclopropa[f]benzothiophene-4,3'-azetidine]-3-carbonitrile (**Int-21d)**

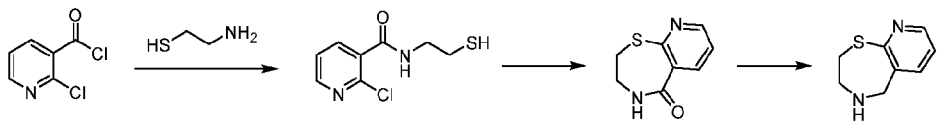
**[00617]** To a solution of 1-(2,2,2-trifluoroacetyl)spiro[azetidine-3,2'-norcarane]-3'-one (**Int-21c,** 180 mg, 0.73 mmol) in ethanol (2mL) was added $NH_4OAc$ (84.97 mg, 1.09 mmol), propanedinitrile (72.15 mg, 1.09 mmol) and S8 (34.95 mg, 1.09 mmol) at 25 °C. The reaction stirred at 55 °C for 16 h.

**[00618]** The solution was concentrated and purified by prep-HPLC (eluting with $CH_3CN$ in $H_2O$ from 5% to 95%). The product of 2-amino-1'-(2,2,2-trifluoroacetyl)spiro[4a,5,5a,6-tetrahydrocyclopropa[f]benzothiophene-4,3'-azetidine]-3-carbonitrile (**Int-21d,** 100 mg, 0.306 mmol, 41.96% yield) was obtained as a yellow solid. LCMS calculated for $C_{14}H_{13}F_3N_3OS$ $(M+H)^+$ m/z =328.1, found:328.0.

**[00619]** Step 5. Preparation of 2-aminospiro[4a,5,5a,6-tetrahydrocyclopropa[f]benzothiophene-4,3'-azetidine]-3-carbonitrile (**Intermediate 21**)

**[00620]** To a solution of 2-amino-1'-(2,2,2-trifluoroacetyl)spiro[4a,5,5a,6-tetrahydrocyclopropa[f]benzothiophene-4,3'-azetidine]-3-carbonitrile (**Int-21d,** 80 mg, 0.24 mmol) in methanol (5mL) was added $K_2CO_3$ (67.56 mg, 0.49 mmol) at 25 °C. The reaction stirred at 80 °C for 1h. The solution was concentrated, and the crude product was purified by silica gel chromatography (eluting with MeOH in DCM from 0% to 20%). The product of 2-aminospiro[4a,5,5a,6-tetrahydrocyclopropa[f]benzothiophene-4,3'-azetidine]-3-carbonitrile (**Intermediate 21**, 52 mg, 0.225 mmol, 91.98% yield) was obtained as a yellow solid. LCMS calculated for $C_{12}H_{14}N_3S$ $(M+H)^+$ m/z =232.1, found:232.1.

**Intermediate 22**. Synthesis of 2,3,4,5-tetrahydropyrido[3,2-f][1,4]thiazepine



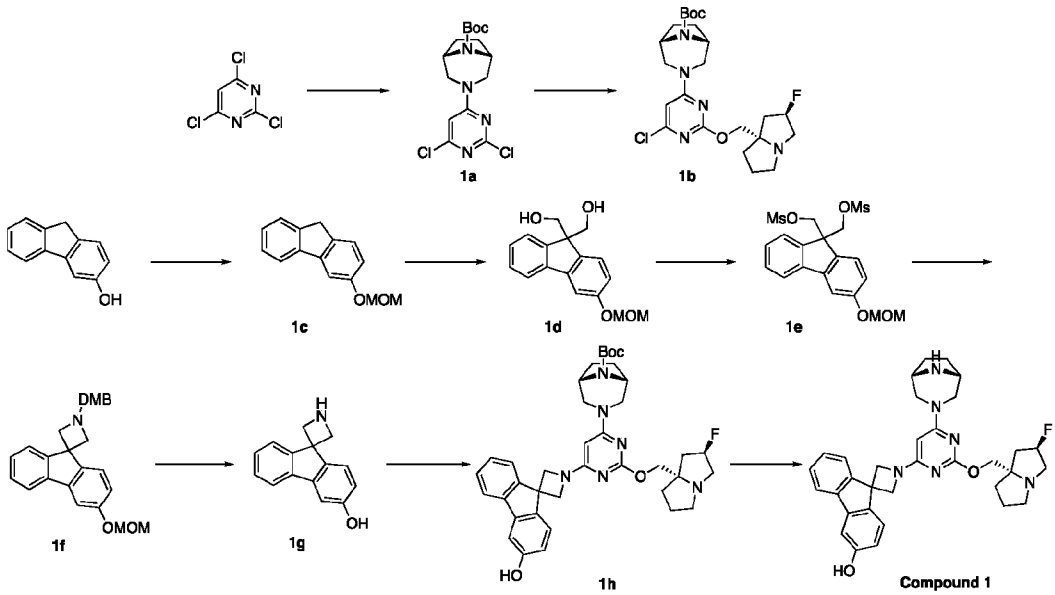

**[00621]** Step 1: Synthesis of 2-(2-aminoethylsulfanyl)pyridine-3-carboxamide (**Int-22a**)To the suspension of 2-aminoethanethiol;hydrochloride (4.25 g, 37.41 mmol) and 2-chloropyridine-3-carboxamide (3.91 g, 24.97 mmol) in Ethanol (50mL) was added the solution of KOH (4.2 g, 70 mmol) in Ethanol (25mL) at reflux dropwise over 0.5 h. The mixture was stirred for 1 h and cooled to rt. It was diluted with $Na_2CO_3$ solution (100 mL) and extracted with EtOAc (100 mL). It was dried over $Na_2SO_4$ and concentrated in vacuo to give the crude product 2-(2-

aminoethylsulfanyl)pyridine-3-carboxamide (**Int-22a**, 6.00 g) as a white solid. LCMS calculated for $C_8H_{12}N_3OS$ $(M+H)^+$ m/z =198.26; found: 198.4. $^1H$ NMR (400 MHz, DMSO) δ 8.48 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.00 (s, 1H), 7.81 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.54 (s, 1H), 7.16 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.18 – 3.06 (m, 2H), 2.74 (t, *J* = 6.9 Hz, 2H), 1.56 (br, 2H).

**[00622]** Step 2. Synthesis of 3,4-dihydro-2H-pyrido[3,2-f][1,4]thiazepin-5-one (**Int-22b**). The suspension of 2-(2-aminoethylsulfanyl)pyridine-3-carboxamide (**Int-22a,** 2 g, 8.11 mmol) and Benzoic Acid (0.2 g, 1.64 mmol) in m-Xylene (100mL) was heated to 120 °C for 16 h. It was cooled to rt and the solvent was removed in vacuo and the residue was diluted with DMSO (10 mL) and purified using reverse phase FC (eluant with MeCN in base water 5 to 20%), concentrated in vacuo to give the product 3,4-dihydro-2H-pyrido[3,2-f][1,4]thiazepin-5-one (**Int-22b,** 420 mg, 2.33 mmol, 28.73 %yield) as a white solid. LCMS calculated for $C_8H_8N_2OS$ $(M+H)^+$ m/z =181.04; found: 181.4. $^1H$ NMR (400 MHz, DMSO) δ 8.48 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.00 (s, 1H), 7.81 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.54 (s, 1H), 7.16 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.18 – 3.06 (m, 2H), 2.74 (t, *J* = 6.9 Hz, 2H), 1.56 (br, 2H).

**[00623]** Step 3: Synthesis of 2,3,4,5-tetrahydropyrido[3,2-f][1,4]thiazepine (**Intermediate 22**). A solution of $LiAlH_4$ (84.23 mg, 2.22 mmol) in THF (30mL) was cooled 0 °C, then a solution of 3,4-dihydro-2H-pyrido[3,2-f][1,4]thiazepin-5-one (**Int-22b,** 200 mg, 1.11 mmol) in THF (30 mL) was added dropwise. The reaction mixture was stirred at rt overnight and quenched with $10H_2O.Na_2SO_4$.The mixture was filtrated, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (DCM/MeOH, 20:1) to afford the title product 2,3,4,5-tetrahydropyrido[3,2-f][1,4]thiazepine, 82 mg, 44.45% yield as a colorless oil. LCMS calculated for $C_8H_{10}N_2S$ (M+H)+ m/z =167.06; found: 167.1.

**Example 1:** Exemplary synthesis of 1-[6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[azetidine-3,9'-fluorene]-3'-ol (**Compound 1**).




**[00624]** Step 1: Synthesis of *tert*-butyl (1*R*,5*S*)-3-(2,6-dichloropyrimidin4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**1a**). To a solution of *tert*-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.157g , 5.45 mmol) in DCM (20 mL) at -60 °C were added 2,4,6-trichloropyrimidine (1 g, 5.45 mmol) and DIEA (2.7 mL, 16.36 mmol) under $N_2$. Then the mixture was stirred at -60 °C for 1h. The resulting mixture was quenched with saturated aqueous $NH_4Cl$ (60 mL), and then extracted with DCM (60 mL × 2). The organic layer was washed with brine (50 mL), dried over $Na_2SO_4$, concentrated and purified by flash column chromatography (silica gel, eluting with 0% to 50% petroleum ether/EtOAc) to afford crude *tert*-butyl (1R,5S)-3-(2,6-dichloropyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**1a**, 1.566 g, 4.359 mmol, 79.9% yield) as a light white solid. LCMS calcld for $C_{15}H_{21}Cl_2N_4O_2$ $(M+H)^+$ m/z = 359.1; found: 359.2.

**[00625]** Step 2: Synthesis of *tert*-butyl (1*R*,5*S*)-3-(6-chloro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**1b**). The mixture of *tert*-butyl (1R,5S)-3-(2,6-dichloropyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**1a**, 700 mg, 1.95 mmol) and [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (931 mg, 5.85 mmol) in 1,4-dioxane (1 mL) was added DIEA (1.02 mL, 5.85 mmol) and it was stirred at 90 °C overnight. After the reaction was completed, the reaction mixture diluted with water, and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated to give the crude product. The crude product was purified by column chromatography on a silica gel column (DCM / MeOH = 20/1 to 10/1) to afford *tert*-butyl (1R,5S)-3-[6-chloro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**1b**, 501 mg, 1.04 mmol, 53.3% yield) and recovered

starting material (198 mg). LCMS calcld for $C_{23}H_{34}ClFN_5O_3$ $(M+H)^+$ m/z =482.23; found: 482.4.

**[00626]** Step 3: Synthesis of 3-(methoxymethoxy)-9H-fluorene (**1c**). To a solution of 9H-fluoren-3-ol (1.70 g, 9.33 mmol) and bromo(methoxy)methane (1.17 mL, 14.0 mmol) in acetonitrile (30 mL) was added DIEA (4.87 mL, 28.0 mmol). The mixture was stirred at rt for 1 h. The mixture was diluted with EtOAc (30 mL), washed with water (50 mL) and saturated brine (30 mL), dried over $Na_2SO_4$, concentrated, and purified by flash column chromatography (silica gel, eluting with EtOAc in petroleum ether 10% to 20%) to afford 3-(methoxymethoxy)-9H-fluorene (**1c**, 1.34 g, 5.92 mmol, 63.5% yield) as a white solid. LCMS calcld for $C_{15}H_{15}O_2$ $(M+H)^+$ m/z = 227.1; found: 227.1.

**[00627]** Step 4: Synthesis of (9-(hydroxymethyl)-3-(methoxymethoxy)fluoren-9-yl)methanol (**1d**). To a solution of paraformaldehyde (497mg, 5.52mmol, 2.5 eq) in DMF (3 mL) was added MeONa (29.8mg, 0.550mmol, 0.25 eq) at 0 °C. Then the mixture was stirred at 0 °C for 10 min, and 3-(methoxymethoxy)-9H-fluorene (**1c**, 500 mg, 2.21 mmol) in DMSO (1 mL) was added drop wise at 0 °C. The mixture was allowed to warm to rt and stirred for 2 h. The mixture was quenched with 1N HCl, diluted with water (30 mL), extracted with EtOAc (30 mL). The organic phase was dried and purified by flash column chromatography (silica gel, eluting with 5% MeOH in DCM) to afford (9-(hydroxymethyl)-3-(methoxymethoxy)fluoren-9-yl)methanol (**1d**, 400 mg, 1.40 mmol, 63.2% yield) as a yellow oil. LCMS calcld for $C_{17}H_{19}O_4$ $(M+H)^+$ m/z = 287.1; found: 287.1.

**[00628]** Step 5: Synthesis of (3-(methoxymethoxy)-9-(methylsulfonyloxymethyl)fluoren-9-yl)methyl methanesulfonate (**1e**). To the solution of (9-(hydroxymethyl)-3-(methoxymethoxy)fluoren-9-yl)methanol (**1d**, 100 mg, 0.35 mmol, 1 eq) and $Et_3N$ (0.22 mL, 1.57 mmol) in DCM (3 mL) was added MsCl (160 mg, 1.40 mmol, 4 eq) at 0 °C and the mixture was stirred for 2 h. Then the mixture was partitioned between with EtOAc/$H_2O$. The combined organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by FC (silica gel, eluting EtOAc in petroleum ether 0 to 50%) to afford (3-(methoxymethoxy)-9-(methylsulfonyloxymethyl)fluoren-9-yl)methyl methanesulfonate (**1e**, 150 mg, 0.339 mmol, 97.1% yield) as a colorless oil. LCMS calcld for $C_{19}H_{23}O_8S_2$ $(M+H)^+$ m/z = 443.1; found: 459.8.

**[00629]** Step 6: Synthesis of 1-(3,4-dimethylbenzyl)-3'-(methoxymethoxy)spiro[azetidine-3,9'-fluorene] (**1f**). A mixture of (3-(methoxymethoxy)-9-(methylsulfonyloxymethyl)fluoren-9-yl)methyl methanesulfonate (**1e**, 150 mg, 0.34 mmol) and 2,4-Dimethoxybenzylamine (1 mL) was stirred at 110 °C for 16 h. Then the mixture was cooled to rt and $NaHCO_3$ (5 mL) aqueous solution was added to quench the reaction. The mixture was extracted with EtOAc (10 mL). The

combined organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by FC (silica gel, eluting with EtOAc in petroleum ether 0 to 22%) to afford 1-(3,4-dimethylbenzyl)-3'-(methoxymethoxy)spiro[azetidine-3,9'-fluorene] (**1f**, 110 mg, 0.264 mmol, 77.7% yield) as a yellow oil. LCMS calcld for $C_{26}H_{28}NO_4$ $(M+H)^+$ m/z = 418.2; found: 417.8.

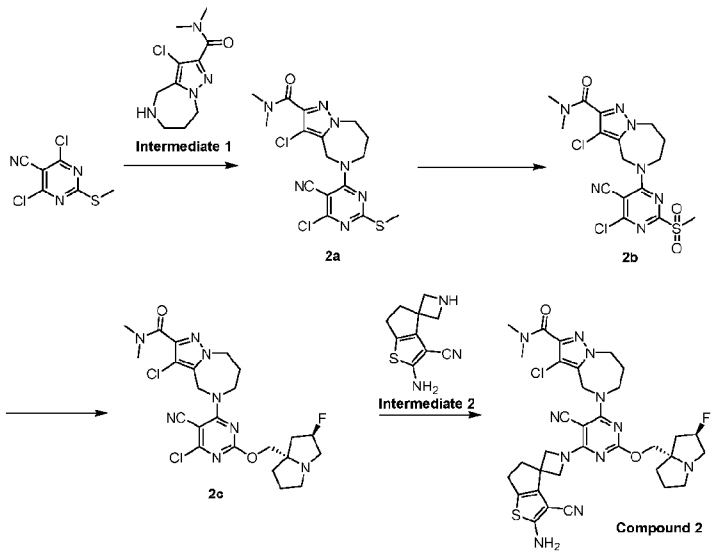
**[00630]** Step 7: Synthesis of spiro[azetidine-3,9'-fluorene]-3'-ol (**1g**). To a solution of 1-(3,4-dimethylbenzyl)-3'-(methoxymethoxy)spiro[azetidine-3,9'-fluorene] (450 mg, 1.08 mmol) in DCE (5 mL) was added 1-chloroethyl carbonochloridate (462 mg, 3.23 mmol) and the reaction was stirred at 100 °C for 6h. Then the mixture was concentrated in vacuo to dry. Methanol (5 mL) was added and the mixture was heated to 70 °C for 4 h. The mixture was filtered and purified by prep-HPLC on a C18 column (5 um, 50 x 150 mm) with mobile phase: $H_2O$ (0.1% $NH_4HCO_3$ / MeOH) at flow rate: 35 mL/min to afford spiro[azetidine-3,9'-fluorene]-3'-ol (148 mg, 0.663 mmol, 61.5% yield) as a yellow solid. LCMS calcld for $C_{15}H_{14}NO$ $(M+H)^+$ m/z =224.1; found: 224.0.

**[00631]** Step 8: Synthesis of *tert*-butyl (1R,5S)-3-[6-(3'-hydroxyspiro[azetidine-3,9'-fluorene]-1-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**1h**). The mixture of *tert*-butyl (1R,5S)-3-[6-chloro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (30.0 mg, 0.06 mmol), spiro[azetidine-3,9'-fluorene]-3'-ol (69.5 mg, 0.31 mmol) and cesium carbonate (121 mg, 0.370 mmol) in NMP (1.5 mL) was irritated to 135 °C using microwave for 3 h under Ar. Then the mixture was purified by prep-HPLC on a C18 column (5 um, 50 x 150 mm) with mobile phase: $H_2O$ (0.1% $NH_4HCO_3$ / MeOH) at flow rate: 35 mL/min to afford *tert*-butyl (1R,5S)-3-[6-(3'-hydroxyspiro[azetidine-3,9'-fluorene]-1-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizi8-yl]methoxy]pyrimidi4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**1h**, 16 mg, 0.0239 mmol, 38.4% yield) as a white solid. LCMS calcld for $C_{38}H_{46}FN_6O_4$ $(M+H)^+$ m/z = 669.4; found: 669.0.

**[00632]** Step 9: Synthesis of 1-[6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octa3-yl]-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[azetidine-3,9'-fluorene]-3'-ol (**compound 1**). To a solution of *tert*-butyl (1R,5S)-3-[6-(3'-hydroxyspiro[azetidine-3,9'-fluorene]-1-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**1h**, 24.0 mg, 0.04 mmol) in 1,4-dioxane (1 mL) was added HCl in 1,4-dioxane (1 mL, 4.0 mmol) at 0 °C and the reaction was stirred at rt for 2 h. Then the mixture was dried by $N_2$ and then purified by prep-HPLC on a C18 column (5 um, 50 x 150 mm) with mobile phase: $H_2O$ (0.1% $NH_4HCO_3$ / MeOH) at flow rate: 35 mL/min to afford 1-[6-[(1R,5S)-3,8-

diazabicyclo[3.2.1]octa3-yl]-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[azetidine-3,9'-fluorene]-3'-ol (**1**, 12.3 mg, 0.0214 mmol, 59.7% yield) as a white solid. LCMS calcld for $C_{33}H_{38}FN_6O_2$ $(M+H)^+$ m/z = 569.3; found: 569.0. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.64 – 7.71 (m, 2 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.33 – 7.40 (m, 2 H), 7.15 (d, *J* = 2.4 Hz, 1 H), 6.81 (dd, *J* = 8.0, 2.4 Hz, 1 H), 5.34 (s, 0.5 H), 5.27 (s, 1 H), 5.20 (s, 0.5 H), 4.36 (s, 4 H), 4.15 (d, *J* = 10.4 Hz, 1 H), 3.97 – 4.07 (m, 3 H), 3.59 (s, 2 H), 3.14 – 3.27 (m, 3 H), 3.00 – 3.06 (m, 2 H), 2.94 – 3.00 (m, 1 H), 2.15 – 2.34 (m, 2 H), 2.08 – 2.14 (m, 1 H), 1.89 – 2.00 (m, 2 H), 1.79 – 1.88 (m, 3 H), 1.72 – 1.79 (m, 2 H).

**Example 2**. Exemplary synthesis of 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**compound 2**)




**[00633]** Step 1. Synthesis of 3-chloro-5-(6-chloro-5-cyano-2-methylsulfanyl-pyrimidin-4-yl)-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**2a**). The mixture of 3-chloro-*N*,*N*-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**Intermediate 1**, 1.7 g, 7 mmol), 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbonitrile (1.7 g, 7.7 mmol) and DIEA (2.71 mg, 21.0 mmol) in DCM (3 mL)was stirred at 25 °C for 0.5 h under argon. The mixture was concentrated, diluted with DCM (50 mL), washed with water (50 x 2 mL) and brine (50 ml), dried over $Na_2SO_4$, concentrated. The crude product 3-chloro-5-(6-chloro-5-cyano-2-methylsulfanyl-pyrimidin-4-yl)-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**2a**) was used without purification. LCMS calcld for $C_{16}H_{18}Cl_2N_7OS$ $(M+H)^+$ m/z = 426.1, found: 426.3.

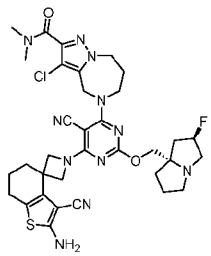
**[00634]** Step 2. Synthesis of (**2b**). The mixture of 3-chloro-5-(6-chloro-5-cyano-2-methylsulfanyl-pyrimidin-4-yl)-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**2a**, 2.9 g, 6.8 mmol), oxone (6.272 g, 10.2 mmol) , THF (20 mL) and water (10 mL) was stirred at 45 °C for 2 h under argon. The mixture was diluted with DCM (100 mL), washed with $H_2O$ (2 x 100 mL) and brine (100 mL), dried over $Na_2SO_4$ and concentrated to afford crude product 3-chloro-5-(6-chloro-5-cyano-2-methylsulfonyl-pyrimidin-4-yl)-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**2b**, 2.35 g, 5.13 mmol, 75.4% yield). LCMS calcld for $C_{16}H_{18}Cl_2N_7O_3S$ $(M+H)^+$ m/z = 458.1, found: 458.1.

**[00635]** Step 3. Synthesis of 3-chloro-5-[6-chloro-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**2c**). The mixture of 3-chloro-5-(6-chloro-5-cyano-2-methylsulfonyl-pyrimidin-4-yl)-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**2b**, 1.9 g, 4.15 mmol) and [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (1.98 g, 12.44 mmol) in DCM (20 mL) was stirred at 25 °C for 1 h under argon. The mixture was concentrated to afford a crude product. The crude product was purified by silica gel chromatography (eluted with MeOH in DCM from 3% to 10%) to afford 3-chloro-5-[6-chloro-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**2c**, 1.2 g, 1.85 mmol, 44.7% yield) LCMS m/z calcld for $C_{23}H_{28}Cl_2FN_8O_2$ $(M+H)^+$ m/z = 537.2, found: 537.2.

**[00636]** Step 4. Synthesis of 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**compound 2**).The mixture of 3-chloro-5-[6-chloro-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizi8-yl]methoxy]pyrimidin-4-yl]-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**2c**, 200 mg, 0.37 mmol), 2-aminospiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Intermediate 2**, 244 mg, 0.6 mmol), DIEA (192 g, 1.49 mmol) in 1,4-dioxane (5 mL) was stirred at 90 °C for 1.5 h under argon. The mixture was diluted with EtOAc (50 mL), washed with $H_2O$ (2 x 20 mL) and brine (50 mL), dried over $Na_2SO_4$ and concentrated. The crude product was purified by prep-HPLC (eluted with $CH_3CN$ in $H_2O$ from 5% to 95%) to afford 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (**compound 2**), 89 mg, 0.12 mmol, 32% yield) as yellow solid. LCMS calcld for

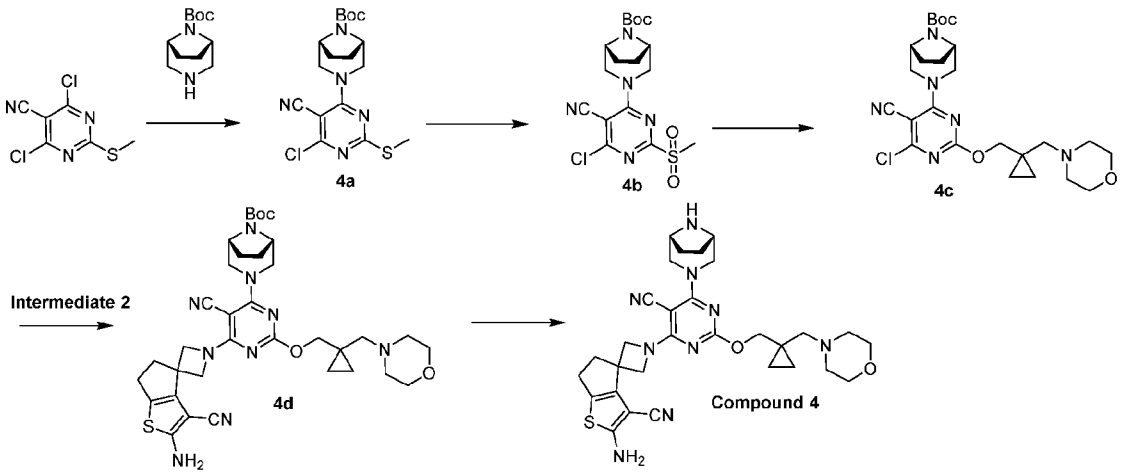
$C_{33}H_{38}ClFN_{11}O_2S$ $(M+H)^+$ m/z = 706.2, found: 706.2. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.94 (s, 2H), 5.17 (d, *J* = 52.4 Hz, 1H), 4.93 (s, 1H), 4.79 (d, *J* = 21.4 Hz, 2H), 4.61 (s, 2H), 4.54 (s, 1H), 4.35 (s, 2H), 4.17 – 3.87 (m, 4H), 3.13 (d, *J* = 14.8 Hz, 2H), 3.03 (d, *J* = 5.7 Hz, 6H), 2.87 (t, *J* = 7.2 Hz, 1H), 2.77 – 2.59 (m, 4H), 2.22 – 1.91 (m, 5H), 1.79 (ddd, *J* = 20.3, 19.1, 11.6 Hz, 4H).

**[00637]** **Compound 3**. 5-[6-(2-amino-3-cyano-spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-*N*,*N*-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



**[00638]** Compound **3** was prepared similarly to that of **Ex. 2** as a TFA salt using **Intermediate 3**. LCMS calcld for $C_{34}H_{40}ClFN_{11}O_2S$ $(M+H)^+$ m/z = 720.27; found: 720.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.55 (d, *J* = 52.0 Hz, 1H), 4.96 (s, 3H), 4.33 (m, 8H), 3.96 – 3.73 (m, 3H), 3.43 (m, 1H), 3.10 (m, 6H), 2.75 – 2.45 (m, 4H), 2.41 – 2.24 (m, 5H), 2.24 – 2.00 (m, 4H), 1.81 (s, 2H).

**Example 3.** Exemplary synthesis of 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-[-(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile **(Compound 4).**



**[00639]** Step 1. Preparation of tert-butyl (1R,5S)-3-(6-chloro-5-cyano-2-methylsulfanyl-pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4a**). To a solution of tert-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.93 g, 9.09 mmol) and 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbonitrile (2.0 g, 9.09 mmol) in DCM (20 mL) was added DIEA (4.75 mL, 27.26 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with EtOAc (50 mL), washed with $H_2O$ (2x30 mL) and brine (30 mL), dried over $Na_2SO_4$ and concentrated. The crude product was purified by silica gel chromatography (PE: EtOAc = 20:1 to 5:1). The product tert-butyl (1R,5S)-3-(6-chloro-5-cyano-2-methylsulfanyl-pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4a**, 3.35 g, 8.46 mmol, 93.11% yield) was obtained as white solid. LCMS calcld for $C_{17}H_{23}ClN_5O_2S$ $(M+H)^+$ m/z = 396.1, found: 396.0.

**[00640]** Step 2. Preparation of tert-butyl (1R,5S)-3-(6-chloro-5-cyano-2-methylsulfonyl-pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4b**). To a solution of tert-butyl (1R,5S)-3-(6-chloro-5-cyano-2-methylsulfanyl-pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4a**, 3.35 g, 8.46 mmol) in THF (35 mL)/Water (35 mL) was added oxone (5.2 g, 16.92 mmol) at 25°C. The mixture was stirred at 25°C for 3 h. The mixture was diluted with EtOAc (40 mL), washed with $H_2O$ (2x30 mL) and brine (30 mL), dried over $Na_2SO_4$ and concentrated. The crude product was used without purification. The product tert-butyl (1R,5S)-3-(6-chloro-5-cyano-2-methylsulfonyl-pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4b**, 3.40 g, 7.95 mmol, 93.90 % yield) was obtained as crude white solid. LCMS calcld for $C_{17}H_{23}ClN_5O_4S$ $(M+H)^+$ m/z = 428.1, found: 428.2.

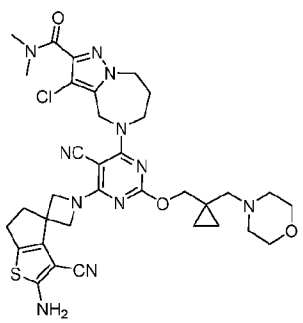
**[00641]** Step 3. Preparation of tert-butyl (1R,5S)-3-[5-cyano-2-methylsulfonyl-6-[[1(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4c**). To a solution of tert-butyl (1R,5S)-3-(6-chloro-5-cyano-2-methylsulfonyl-pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4b**, 3.4 g, 7.95 mmol) in DCM (34 mL) was added [1-(morpholinomethyl)cyclopropyl]methanol (2.72 g, 15.89 mmol) at 25°C. The mixture was stirred at 25°C for 3 h. The mixture was concentrated to afford a crude product. The crude product was purified by silica gel chromatography (PE: EtOAc = 10:1 to 1:1). The product tert-butyl (1R,5S)-3-[6-chloro-5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4c**, 2.10 g, 4.05 mmol, 50.92% yield) was obtained as yellow oil. LCMS calcld for $C_{25}H_{36}ClN_6O_4$ $(M+H)^+$ m/z = 519.2, found: 519.2.

**[00642]** Step 4. Preparation of tert-butyl (1R,5S)-3-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4d**). To a solution of 2-aminospiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-

azetidine]-3-carbonitrile (**Intermediate 2**, 1.0 g, 4.88 mmol) and tert-butyl (1R,5S)-3-[6-chloro-5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4c**, 1.95 g, 3.76 mmol) in 1,4-Dioxane (20 mL) was added DIEA (3.27 mL, 18.78 mmol) at 25°C. The mixture was stirred at 90°C for 2 h. The mixture was concentrated to afford a crude product. The crude product was purified by silica gel chromatography (PE: EtOAc = 1:1 to 1:5). The product tert-butyl (1R,5S)-3-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4d**, 1.80 g, 2.62 mmol, 69.65 % yield) was obtained as yellow oil. LCMS calcld for $C_{35}H_{46}N_9O_4S$ $(M+H)^+$ m/z = 688.3, found: 688.2.

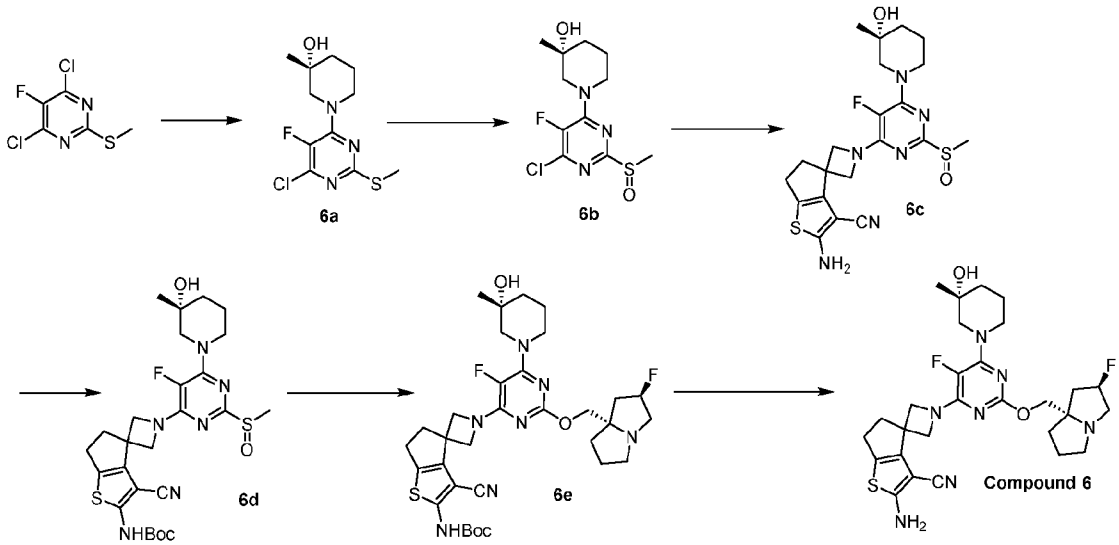
**[00643]** Step 5. Preparation of 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**4e**). To a solution of tert-butyl (1R,5S)-3-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (**4d**, 1.8 g, 2.62 mmol) and TFA (6.0 mL, 78.35 mmol) in THF (18 mL) at 25°C. The mixture was stirred at 25°C for 1 h. The mixture was concentrated to afford a crude product. The crude product was purified by Prep-HPLC (eluted with $CH_3CN$ in H2O (0.1 % NH3) from 5.0% to 95%). 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Compound 4**, 544.5 mg, 0.92 mmol, 35.16% yield) was obtained as white solid. LCMS calcld for $C_{30}H_{38}N_9O_2S$ $(M+H)^+$ m/z = 588.3, found: 588.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.68 – 4.13 (m, 8H), 3.68 (t, *J* = 4.6 Hz, 4H), 3.56 (s, 2H), 3.32 – 3.20 (m, 2H), 2.86 – 2.65 (m, 4H), 2.49 (s, 4H), 2.39 (s, 2H), 1.82 (s, 4H), 0.66 (t, *J* = 5.2 Hz, 2H), 0.46 (t, *J* = 5.2 Hz, 2H)

**[00644]** **Compound 5**. 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]-3-chloro-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



**[00645]** Compound **5** was prepared similarly to that of **Ex. 2**. LCMS calcld for $C_{34}H_{41}ClN_{11}O_3S$ $(M+H)^+$ m/z =718.3 found 718.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.08-5.01 (m, 2H), 4.62-4.40 (m, 5H), 4.29-4.14 (m, 5H), 4.81-471 (m, 4H), 3.15-3.03 (m, 6H), 2.88-2.64 (m, 10H), 2.31-2.21 (m, 2H), 0.76-0.53 (m, 4H).

**Example 4.** Exemplary synthesis of 2-amino-1'-[5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Compound 6).**




**[00646]** Step 1. Synthesis of (3R)-1-(6-chloro-5-fluoro-2-methylsulfanyl-pyrimidin-4-yl)-3-methyl-piperidin-3-ol (**6a**). A solution of 4,6-dichloro-5-fluoro-2-methylsulfanyl-pyrimidine (200 mg, 0.94 mmol) in DCM (8mL) was added (3R)-3-methylpiperidin-3-ol (108.11 mg, 0.94 mmol) and DIEA (0.33 mL, 1.88 mmol) at 0 °C. Then the mixture was stirred at 0 °C for 1 h. The solution was extracted with EtOAc (20 ml x3), dried over $Na_2SO_4$ and concentrated. The residue was purified by silica gel chromatography (DCM:MeOH=30:1). The product of (3R)-1-(6-chloro-5-fluoro-2-methylsulfanyl-pyrimidin-4-yl)-3-methyl-piperidin-3-ol (210 mg, 0.720 mmol, 76.67% yield) was obtained. LCMS calculated for $C_{11}H_{16}ClFN_3OS$ $(M+H)^+$ m/z =292.3, found: 292.3.

**[00647]** Step 2. Synthesis of (3R)-1-(6-chloro-5-fluoro-2-methylsulfinyl-pyrimidin-4-yl)-3-methyl-piperidin-3-ol (**6b**). A solution of (3R)-1-(6-chloro-5-fluoro-2-methylsulfanyl-pyrimidin-4-yl)-3-methyl-piperidin-3-ol (**6a**, 170 mg, 0.58 mmol) in THF (5mL) and Water (2.5mL) was added oxone (302.4 mg, 0.87 mmol) at 25 °C. Then the mixture was stirred at 25 °C for 1 h. The solution was extracted with EtOAc (20 ml x3), dried over $Na_2SO_4$ and concentrated. The residue was purified by silica gel chromatography (eluting with MeOH in DCM from 3% to 6%). The product (3R)-1-(6-chloro-5-fluoro-2-methylsulfinyl-pyrimidin-4-yl)-3-methyl-piperidin-3-ol

(180 mg, 0.585 mmol, quantitative yield) was obtained as a white solid. LCMS calculated for $C_{11}H_{16}ClFN_3O_2S$ $(M+H)^+$ m/z =308.0, found: 308.0.

**[00648]** Step 3. Synthesis of 2-amino-1'-[5-fluoro-2-methylsulfinyl-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**6c**). The mixture of DIEA (0.12 mL, 0.71 mmol) 2-aminospiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Intermediate 2**, 146.74 mg, 0.71 mmol) and (3R)-1-(6-chloro-5-fluoro-2-methylsulfinyl-pyrimidin-4-yl)-3-methyl-piperidin-3-ol (**6b,** 110 mg, 0.36 mmol) in 1,4-Dioxane (1 mL) was stirred at 90 °C for 2 h under argon. The mixture was filtered to afford a crude solution. The crude product was purified by flash chromatography (eluted with $CH_3CN$ in $H_2O$ from 5.0% to 95%). The product 2-amino-1'-[5-fluoro-2-methylsulfinyl-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (80 mg, 0.168 mmol, 46.97% yield) was obtained as a white solid. LCMS calcld for $C_{21}H_{26}FN_6O_2S_2$ $(M+H)^+$ m/z =477.2, found: 477.2.

**[00649]** Step 4. Synthesis of tert-butyl N-tert-butoxycarbonyl-N-[3-cyano-1'-[5-fluoro-2-methylsulfinyl-6-[(3S)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**6d**). The mixture of 2-amino-1'-[5-fluoro-2-methylsulfinyl-6-[(3S)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**6c**, 70 mg, 0.15 mmol) $Boc_2O$ (70.52 mg, 0.32 mmol), DMAP (1.79 mg, 0.01 mmol) in $CH_3CN$ (0.5mL) was stirred at 25 °C for 0.2 h under argon. The mixture was concentrated to afford a crude product. The crude product was purified by flash chromatography $H_2O$:$CH_3CN$ = 90:10 to 50:50. tert-butyl N-[3-cyano-1'-[5-fluoro-2-methylsulfinyl-6-[(3S)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (80 mg, 0.139 mmol, 94.45% yield)) was obtained as yellow oil. LCMS calcld for $C_{26}H_{34}N_6O_4S_2$ $(M+H)^+$ m/z = 577.2, found: 577.2.

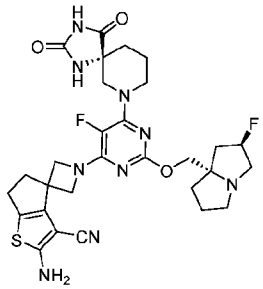
**[00650]** Step 5. Synthesis of tert-butyl N-[3-cyano-1'-[5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**6e**). The mixture of [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (44.17 mg, 0.28 mmol) and NaH (8.32 mg, 0.21 mmol) in DMF (0.5mL) was stirred at 25 °C for 0.2h under argon. Then, tert-butyl N-[3-cyano-1'-[5-fluoro-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]-2-methylsulfinyl-pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**6d**, 40 mg, 0.07 mmol) was added at 25 °C . The mixture was stirred at 25 °C for 0.2 h. The mixture was acidified with Acetic acid (1mol/L in $H_2O$) to pH=5,

extracted with EtOAc (3 x 10mL), dried over $Na_2SO_4$ and concentrated. The crude product was used directly for the next step. tert-butyl N-[3-cyano-1'-[5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**6e**, 40 mg,0.060 mmol) was obtained as yellow oil. LCMS calcld for $C_{33}H_{44}F_2N_7O_4$ $(M+H)^+$ m/z =672.2, found: 672.4.

**[00651]** Step 6. Synthesis of 2-amino-1'-[5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Compound 6**) . The mixture of tert-butyl N-[3-cyano-1'-[5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**6e**, 30 mg, 0.04 mmol) and TFA (0.1 mL, 1.31 mmol) in DCM (1mL) was stirred at 25 °C for 0.2h under argon. The mixture was stirred at 25 °C for 0.2 h. The mixture was concentrated to afford a crude product.

**[00652]** The crude product was purified by prep-HPLC (eluted with $CH_3CN$ in $H_2O$ (0.1 % TFA) from 5.0% to 95%). 2-amino-1'-[5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Compound 6**, 8.16 mg, 0.0089 mmol, 19.83% yield). LCMS calcld for $C_{28}H_{36}F_2N_7OS$ $(M+H)^+$ m/z =572.3, found: 572.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.64 – 5.44 (m, 1H), 4.51 – 4.41 (m, 2H), 4.41 – 4.36 (m, 1H), 4.28 – 4.16 (m, 2H), 4.06 – 3.71 (m, 4H), 3.69 – 3.60 (m, 1H), 3.52 – 3.35 (m, 4H), 3.35 – 3.33 (m, 2H), 2.82 – 2.66 (m, 4H), 2.63 – 2.44 (m, 1H), 2.40 – 2.03 (m, 4H), 1.92 – 1.78 (m, 1H), 1.73 – 1.62 (m, 2H), 1.62 – 1.46 (m, 1H), 1.20 (s, 3H).

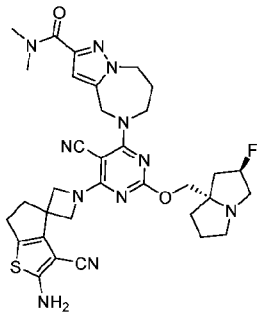
**Compound** 7. 2-amino-1'-[6-[(5R)-2,4-dioxo-1,3,9-triazaspiro[4.5]decan-9-yl]-5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00653]** Compound **7** was prepared similarly to that of **Ex. 4** as a TFA salt. LCMS calcld for $C_{29}H_{34}F_2N_9O_3S$ $(M+H)^+$ m/z = 626.2, found: 626.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.56 – 5.38

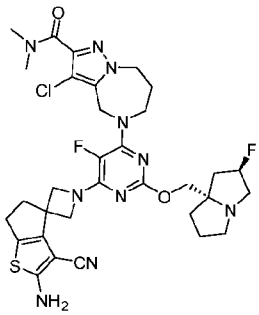
(m, 1H), 4.48 – 4.15 (m, 6H), 3.87 – 3.62 (m, 2H), 3.40 – 3.33 (m, 2H), 3.26 – 3.17 (m, 1H), 2.82 – 2.67 (m, 3H), 2.60 – 2.36 (m, 2H), 2.33 – 1.98 (m, 9H), 1.90 – 1.75 (m, 3H), 1.70 – 1.56 (m, 1H).

**Compound 8.** 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



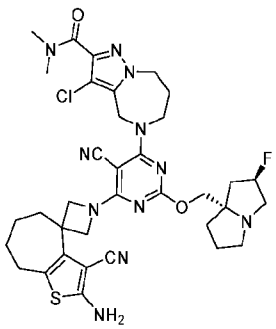
**[00654]** Compound **8** was prepared similarly to that of **Ex. 2** as a formate salt. LCMS calcld for $C_{33}H_{39}FN_{11}O_2S(M+H)^+$ m/z =672.3, found: 672.5. $^1$H NMR (400 MHz, $CD_3OD$) δ 6.67 (s, 1H), 5.29 (d, $J$ = 53.1 Hz, 1H), 5.07 (s, 2H), 4.52 – 4.46 (m, 5H), 4.22 – 4.07 (m, 5H), 3.26 – 3.23 (m, 6H), 3.17 – 2.97 (m, 4H), 2.77 – 2.70 (m, 4H), 2.28 – 1.86 (m, 8H).

**Compound 9.** 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



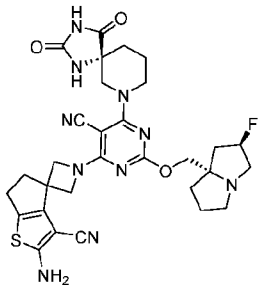
**[00655]** Compound **9** was prepared similarly to that of **Ex. 4** as a TFA salt. LCMS calcld for $C_{32}H_{38}ClF_2N_{10}O_2S$ $(M+H)^+$ m/z =699.2, found: 699.3. $^1$H NMR (400 MHz, $CD_3OD$) δ 5.54 (d, $J$ = 52.0 Hz, 1H), 4.92 – 4.88 (m, 1H), 4.83 – 4.75 (m, 1H), 4.55 – 4.40 (m, 4H), 4.38 (s, $J$ = 6.1 Hz, 2H), 4.30 – 4.18 (m, 2H), 4.14 – 3.73 (m, 5H), 3.41 (dd, $J$ = 16.2, 11.2 Hz, 1H), 3.09 (d, $J$ = 6.8 Hz, 6H), 2.83 – 2.69 (m, 4H), 2.69 – 2.42 (m, 2H), 2.31 (td, $J$ = 9.9, 4.1 Hz, 3H), 2.19 – 1.99 (m, 3H).

**Compound 10.** 5-[6-(2-amino-3-cyano-spiro[5,6,7,8-tetrahydrocyclohepta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



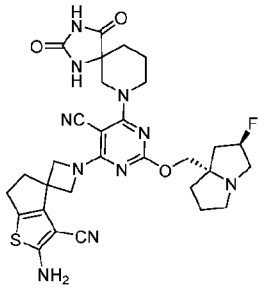
**[00656]** Compound **10** was prepared similarly to that of **Ex. 2**. LCMS calcld for $C_{35}H_{42}ClFN_{11}O_2S$ $(M+H)^+$ m/z =734.28; found: 734.3. $^1H$ NMR ($CDCl_3$, 500 MHz) δ 7.22 - 7.29 (m, 5H), 7.18 (d, *J* = 7.2 Hz, 1H), 5.39 - 5.52 (m, 1H), 5.23 - 5.39 (m, 1H), 4.67 - 5.09 (m, 4H), 4.42 (br. s., 6H), 3.98 - 4.22 (m, 3H), 3.50 - 3.83 (m, 2H), 3.20 - 3.48 (m, 1H), 2.94 - 3.18 (m, 6H), 2.49 - 2.66 (m, 3H), 1.30 - 2.40 (m, 31H), 0.65 - 0.92 (m, 3H).

**[00657]** **Compound 11.** 2-amino-1'-[5-cyano-6-[(5R)-2,4-dioxo-1,3,9-triazaspiro[4.5]decan-9-yl]-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



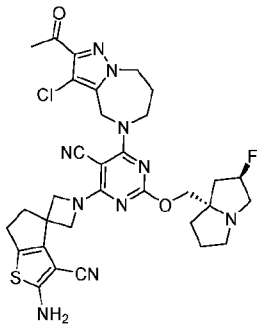
**[00658]** Compound **11** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calcld for $C_{30}H_{34}FN_{10}O_3S$ $(M+H)^+$ m/z = 633.2, found: 633.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.71 – 5.42 (m, 1H), 4.84 – 4.76 (m, 1H), 4.64 – 4.27 (m, 7H), 4.05 – 3.71 (m, 3H), 3.60 – 3.36 (m, 3H), 2.85 – 2.44 (m, 6H), 2.39 – 2.06 (m, 5H), 2.02 – 1.71 (m, 3H).

**[00659]** **Compound 12.** 2-amino-1'-[5-cyano-6-(2,4-dioxo-1,3,9-triazaspiro[4.5]decan-9-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



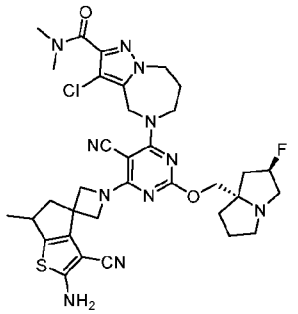
**[00660]** Compound **12** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calcld for $C_{30}H_{34}FN_{10}O_3S$ $(M+H)^+$ m/z = 633.2, found: 633.4. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.65 – 5.39 (m, 1H), 4.65 – 4.25 (m, 8H), 4.03 – 3.75 (m, 3H), 3.60 – 3.37 (m, 3H), 2.89 – 2.47 (m, 6H), 2.39 – 2.22 (m, 3H), 2.21 – 2.08 (m, 2H), 2.02 – 1.73 (m, 3H).

**[00661]** **Compound 13.** 1'-[6-(2-acetyl-3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-2-amino-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



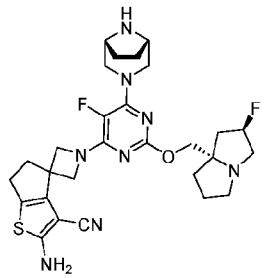
**[00662]** Compound **13** was prepared similarly to that of **Ex. 2** using **Intermediate 5**. LCMS calcld for $C_{32}H_{35}ClFN_{10}O_2S$ $(M+H)^+$ m/z = 677.2, found: 677.2. $^1H$ NMR (DMSO-d6, 400 MHz) δ 7.22 (s, 2H), 5.29 (d, $J$ = 52.8 Hz, 1H), 5.03 (s, 2H), 4.51 (s, 2H), 4.46-4.25 (m, 4H), 4.11 (s, 2H), 3.98 (d, $J$ = 10.4 Hz, 1H), 3.90 (d, $J$ = 10.4 Hz, 1H), 3.02 (br, 2H), 2.96-2.94 (m, 1H), 2.82-2.76 (m, 1H), 2.67-2.65 (m, 4H), 2.44 (s, 3H), 2.15 (br, 2H), 2.03 (s, 1H), 1.96 (s, 1H), 1.89-1.85 (m, 1H), 1.83-1.79 (m, 1H), 1.78-1.67 (m, 2H).

**[00663]** **Compound 14.** 5-[6-(2-amino-3-cyano-6-methyl-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



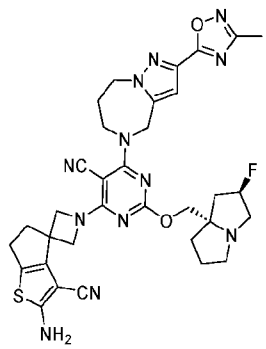
**[00664]** Compound **14** was prepared similarly to that of **Ex. 2** as a formate salt, using **Intermediate 6**. LCMS calcld for $C_{34}H_{40}ClFN_{11}O_2S$ $(M+H)^+$ m/z =720.3 , found: 720.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.66 – 8.46 (s, 1H), 5.38 – 5.19 (m, 1H), 5.10 – 5.01 (m, 2H), 4.62 – 4.41 (m, 4H), 4.25 – 4.07 (m, 4H), 3.27 – 3.11 (m, 4H), 3.09 (d, $J$ = 4.1 Hz, 6H), 3.06 – 2.97 (m, 2H), 2.97 – 2.88 (m, 1H), 2.41 – 1.69 (m, 10H), 1.17 (d, $J$ = 6.8 Hz, 3H).

**[00665]** **Compound 15.** 2-amino-1'-[6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



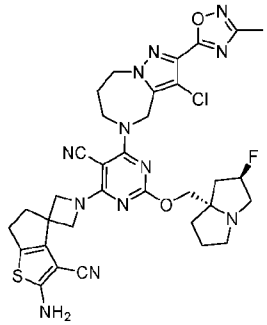
**[00666]** Compound **15** was prepared similarly to that of **Ex. 4** as a TFA salt. LCMS calcld for $C_{28}H_{35}F_2N_8OS$ $(M+H)^+$ m/z = 569.3, found: 569.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.51 – 5.29 (m, 1H), 4.51 – 4.41 (m, 2H), 4.30 – 4.12 (m, 6H), 4.08 – 3.99 (m, 2H), 3.66 – 3.46 (m, 3H), 3.38 – 3.32 (m, 2H), 3.27 – 3.15 (m, 1H), 2.83 – 2.63 (m, 4H), 2.53 – 1.91 (m, 10H).

**[00667]** **Compound 16.** 2-amino-1'-[5-cyano-6-[2-(3-methyl-1,2,4-oxadiazol-5-yl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile.



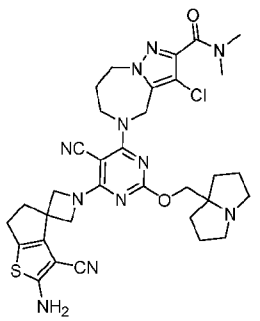
**[00668]** Compound **16** was prepared similarly to that of **Ex. 2** as a formate salt using **Intermediate** 7. LCMS calcld for $C_{33}H_{36}FN_{12}O_2S$ $(M+H)^+$ m/z =683.3, found: 683.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.03 (s, 1H), 5.39-5.07 (m, 3H), 4.65-4.02 (m, 10H), 3.29-3.09 (m, 3H), 3.08-2.97 (m, 1H), 2.78-2.68 (m, 4H), 2.40 (s, 3H), 2.28-1.80 (m, 8H).

**[00669]** **Compound 17.** 2-amino-1'-[6-[3-chloro-2-(3-methyl-1,2,4-oxadiazol-5-yl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile.



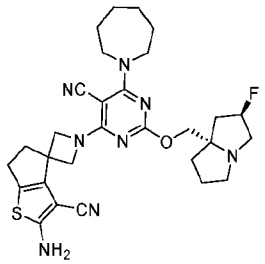
**[00670]** Compound **17** was prepared similarly to **Compound 16** as a formate salt. LCMS calcld for $C_{33}H_{35}ClFN_{12}O_2S$ $(M+H)^+$ m/z =717.2, found: 717.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.46-5.26 (m, 1H), 5.16-4.97 (m, 2H), 4.59-4.14 (m, 10H), 3.55-3.36 (m, 3H), 3.20-3.08 (m, 1H), 2.82-2.66 (m, 4H), 2.44 (s, 3H), 2.40-2.00 (m, 7H), 1.95-1.85 (m, 1H).

**[00671]** **Compound 18.** 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrimidin-4-yl]-3-chloro-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



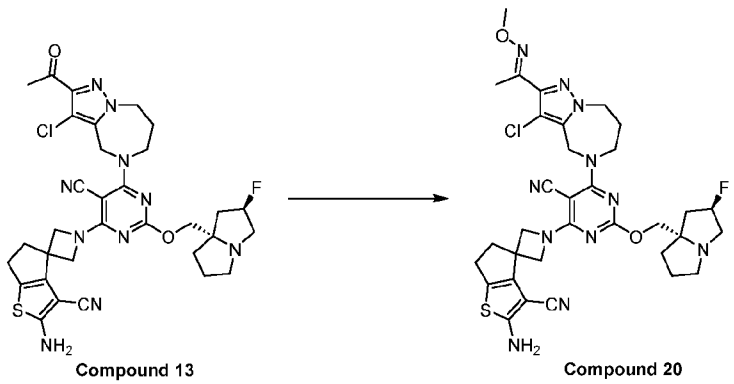
**[00672]** Compound **18** was prepared similarly to that of **Ex. 2** as a formate salt. LCMS calcld for $C_{33}H_{39}ClN_{11}O_2S$ $(M+H)^+$ m/z = 688.3; found : 688.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.01 (s, 2H), 4.62 – 4.47 (m, 2H), 4.47 – 4.40 (m, 2H), 4.35 (s, 2H), 4.21 (dd, J = 3.5, 2.9 Hz, 2H), 3.53 – 3.44 (m, 2H), 3.37 – 3.33 (m, 2H), 3.15 – 3.10 (m, 2H), 3.09 (dd, J = 5.5, 2.1 Hz, 6H), 2.82 – 2.65 (m, 4H), 2.37 – 1.85 (m, 10H).

**[00673]** **Compound 19.** 2-amino-1'-[6-(azepan-1-yl)-5-cyano-2-[[(2R)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00674]** Compound **19** was prepared similarly to that of **Ex. 2** as a formate salt. LCMS calcld for $C_{29}H_{36}FN_8OS$ $(M+H)^+$ m/z = 563.3; found :563.4. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.27 (d, *J* = 33.7, 23.2 Hz, 1H), 4.69 – 4.45 (m, 2H), 4.51 – 4.26 (m, 2H), 4.14 (dd, *J* = 46.1, 10.8 Hz, 2H), 3.92 – 3.75 (m, 4H), 3.30 – 3.19 (m, 3H), 3.10 – 2.97 (m, 1H), 2.84 – 2.62 (m, 4H), 2.41 – 1.92 (m, 5H), 1.86 (d, *J* = 5.3 Hz, 5H), 1.67 – 1.50 (m, 4H).

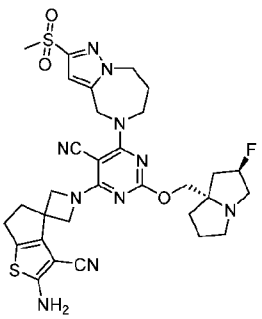
**Example 5**. Exemplary synthesis of 2-amino-1'-[6-[3-chloro-2-[(E)-N-methoxy-C-methyl-carbonimidoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile **(Compound 20)**




**[00675]** Preparation of 2-amino-1'-[6-[3-chloro-2-[(E)-N-methoxy-C-methyl-carbonimidoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile **(Compound 20).** To a solution of Methoxyammonium chloride (1.23 mg, 0.01 mmol) and 1'-[6-(2-acetyl-3-chloro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-2-amino-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Compound 13**, 5 mg, 0.01 mmol) in Ethanol (1 mL) AcONa (1.21 mg, 0.01 mmol) was added. The mixture was stirred at rt for 3h. The mixture was diluted with EtOAC (5 mL),

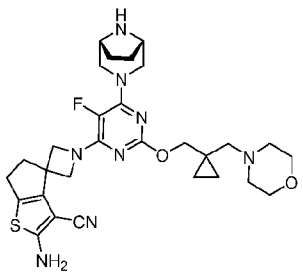
washed with water (5 mL), dried over $Na_2SO_4$, concentrated. The crude product was purified by Prep-HPLC (eluted with $CH_3CN$ in $H_2O$ (0.1 % $NH_4HCO_3$) from 5.0% to 95%). 2-amino-1'-[6-[3-chloro-2-[(E)-N-methoxy-C-methyl-carbonimidoyl]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (**Compound 20,** 3.12 mg,0.0038 mmol, 51.09% yield) was obtained as white solid. LCMS calcld for $C_{33}H_{38}ClFN_{11}O_2S$ $(M+H)^+$ m/z = 706.3, found: 706.1. $^1H$ NMR (DMSO-d6, 400 MHz) δ 7.22 (s, 2H), 5.24 (d, *J* = 56.0 Hz, 1H), 5.00 (br, 2H), 4.43-4.41 (m, 2H), 4.37-4.17 (m, 2H), 4.09 (m, 2H), 4.00 (m, 1H), 3.91 (m, 1H), 3.88 (s, 3H), 3.04 (br, 2H), 2.95 (br, 1H), 2.82-2.76 (m, 1H), 2.68-2.63 (m, 5H), 2.15-2.12 (m, 1H), 2.11 (s, 3H), 2.05-2.03 (m, 1H), 2.01-1.96 (m, 3H), 1.90-1.87 (m, 1H), 1.82-1.78 (m, 1H), 1.74-1.70 (m, 2H).

**[00676]** **Compound 21.** 2-amino-1'-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(2-methylsulfonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl)pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



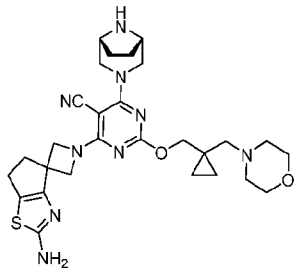
**[00677]** Compound **21** was prepared similarly to that of **Ex. 2** using **Intermediate 8**. LCMS calcld for $C_{31}H_{36}FN_{10}O_3S_2$ $(M+H)^+$ m/z = 679.2, found: 679.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ 6.87 (s, 1H), 5.36 – 5.15 (m, 1H), 5.15 – 4.97 (m, 2H), 4.64 – 4.42 (m, 6H), 4.29 – 4.21 (m, 2H), 4.13 – 4.01 (m, 2H), 3.21 (m, 2H), 3.16 (s, 3H), 3.15 (s, 2H), 2.75 (dd, *J* = 9.1, 5.2 Hz, 4H), 2.23 – 2.11 (m, 4H), 2.10 – 1.77 (m, 4H).

**[00678]** **Compound 22.** 2-amino-1'-[6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-5-fluoro-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



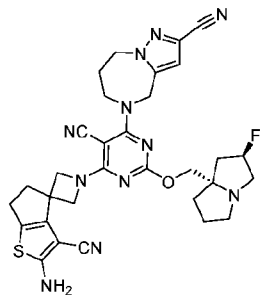
**[00679]** Compound **22** was prepared similarly to that of **Ex. 4** as a TFA salt. LCMS calcld for $C_{29}H_{38}FN_8O_2S$ $(M+H)^+$ m/z = 581.3, found: 581.4. $^1$H NMR (400 MHz, $CD_3OD$) δ 4.49 – 4.41 (m, 2H), 4.29 – 4.22 (m, 4H), 4.19 (d, *J* = 12.4 Hz, 2H), 4.14 – 4.07 (m, 2H), 3.91 – 3.78 (m, 4H), 3.39 – 3.33 (m, 2H), 3.18 – 2.89 (m, 6H), 2.82 – 2.70 (m, 4H), 2.15 – 2.05 (m, 4H), 0.80 (s, 2H), 0.69 (s, 2H).

**[00680]** **Compound 23.** 4-(2-aminospiro[5,6-dihydrocyclopenta[d]thiazole-4,3'-azetidine]-1'-yl)-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidine-5-carbonitrile



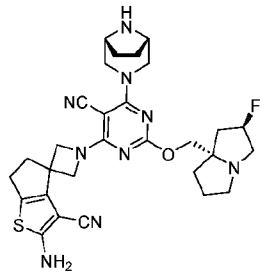
**[00681]** Compound **23** was prepared similarly to that of **Ex. 3** using **Intermediate 9**. LCMS calcld for $C_{28}H_{38}N_9O_2S$ $(M+H)^+$ m/z =564.3, found: 564.2. $^1$H NMR (400 MHz, $CD_3OD$) δ 4.45 (s, 6H), 4.24 (s, 2H), 3.98 (s, 2H), 3.67 (t, *J* = 4.5 Hz, 4H), 3.42 (d, *J* = 13.9 Hz, 2H), 2.89 – 2.69 (m, 4H), 2.51 (s, 4H), 2.41 (s, 2H), 2.01 (s, 4H), 0.64 (t, *J* = 5.2 Hz, 2H), 0.47 (t, *J* = 5.2 Hz, 1H).

**[00682]** **Compound 24.** 2-amino-1'-[5-cyano-6-(2-cyano-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



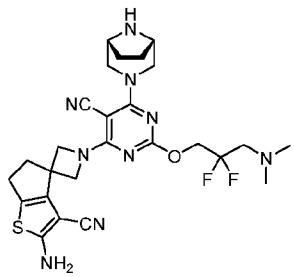
**[00683]** Compound **24** was prepared similarly to that of **Ex. 2** using **Intermediate 10**. LCMS calcld for $C_{31}H_{33}FN_{11}OS$ $(M+H)^+$ m/z = 626.3, found: 626.2. $^1$H NMR (400 MHz, $CD_3OD$) δ 6.87 (s, 1H), 5.26 (d, *J* = 53.8 Hz, 1H), 5.05 (s, 2H), 4.55 (m, 5H), 4.22 (s, 2H), 4.06 (m, 2H), 3.23 (s, 2H), 3.15 (m, 1H), 2.99 (s, 1H), 2.83 – 2.64 (m, 4H), 2.25 – 1.78 (m, 9H).

**[00684]** **Compound 25.** 2-amino-1'-[5-cyano-6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



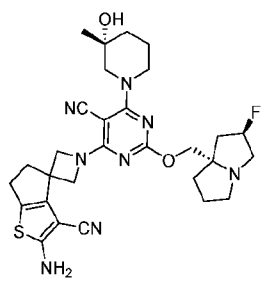
**[00685]** Compound **25** was prepared similarly to that of **Ex. 3** as a formate salt. LCMS calcld for $C_{29}H_{35}FN_9OS$ $(M+H)^+$ m/z = 576.3, found: 576.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.43 (s, 1H), 5.55 – 5.29 (m, 1H), 4.77 – 4.18 (m, 8H), 4.12 – 4.01 (m, 2H), 3.76 – 3.39 (m, 5H), 3.29 – 3.16 (m, 1H), 2.82 – 2.70 (m, 4H), 2.55 – 1.96 (m, 10H).

**[00686]** **Compound 26.** 2-amino-1'-[5-cyano-6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[3-(dimethylamino)-2,2-difluoro-propoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00687]** Compound **26** was prepared similarly to that of **Ex. 3** as a formate salt. LCMS calcld for $C_{26}H_{32}F_2N_9OS$ $(M+H)^+$ m/z = 556.2, found: 556.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.40 (s, 1H), 4.75-4.20 (m, 8H), 4.11 (s, 2H), 3.54-3.44 (m, 2H), 2.95-2.68 (m, 5H), 2.35 (s, 6H), 2.07 (s, 4H).

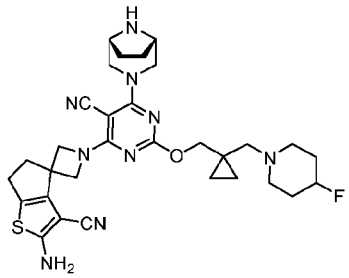
**[00688]** **Compound 27.** 2-amino-1'-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00689]** Compound **27** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS m/z calcd for $C_{29}H_{36}FN_8O_2S$ $(M+H)^+$ m/z = 579.3, found 579.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.63 – 5.38 (m, 1H), 4.93 – 4.87 (m, 1H), 4.67 – 4.32 (m, 5H), 4.12 – 3.79 (m, 5H), 3.60 – 3.37 (m,

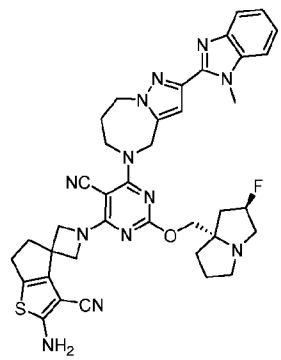
3H), 2.86 – 2.70 (m, 4H), 2.69 – 2.46 (m, 2H), 2.41 – 2.23 (m, 3H), 2.21 – 2.06 (m, 1H), 2.00 – 1.85 (m, 1H), 1.81 – 1.55 (m, 3H), 1.21 (s, 3H).

**[00690]** **Compound 28.** 2-amino-1'-[5-cyano-6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[[1-[(4-fluoro-1-piperidyl)methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



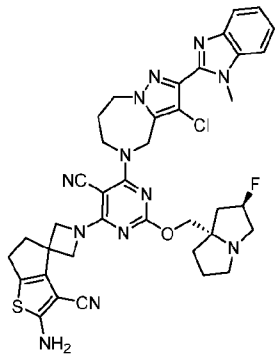
**[00691]** Compound **28** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{31}H_{39}FN_9OS$ $(M+H)^+$ m/z = 604.3, found:604.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.00 (d, *J* = 41.6 Hz, 1H), 4.82 – 4.33 (m, 6H), 4.28 (s, 2H), 4.16 (s, 2H), 3.79 – 3.61 (m, 2H), 3.56 – 3.44 (m, 2H), 3.29 – 3.22 (m, 2H), 2.86 – 2.65 (m, 4H), 2.42 – 2.13 (m, 4H), 2.14 – 1.94 (m, 6H), 0.90 (d, *J* = 3.5 Hz, 2H), 0.86 – 0.78 (m, 2H).

**[00692]** **Compound 29.** 2-amino-1'-[5-cyano-6-[2-(1-methylbenzimidazol-2-yl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



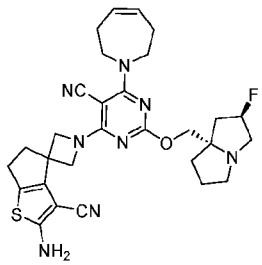
**[00693]** Compound **29** was prepared similarly to that of **Ex. 2** as a formate salt using **Intermediate 11**. LCMS calcld for $C_{38}H_{40}FN_{12}OS$ $(M+H)^+$ m/z = 731.3, found: 731.4. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.26 (m, 2H), 7.05 (s, 1H), 5.43 – 5.25 (m, 1H), 5.24 – 5.13 (m, 2H), 4.76 – 4.38 (m, 5H), 4.34 – 3.99 (m, 8H), 3.32 – 3.19 (m, 3H), 3.10 – 2.98 (m, 1H), 2.82 – 2.68 (m, 4H), 2.40 – 1.83 (m, 8H).

**[00694]** **Compound 30.** 2-amino-1'-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(2,3,6,7-tetrahydroazepin-1-yl)pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



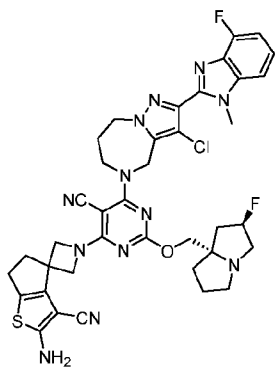
**[00695]** Compound **30** was prepared similarly to **Compound 29** as a formate salt. LCMS calcld for $C_{38}H_{39}FN_{12}OS$ $(M+H)^+$ m/z = 765.3, found: 765.5. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.47 (s, 2H), 5.80 – 5.71 (m, 2H), 5.55 – 5.37 (m, 1H), 4.72 – 4.21 (m, 8H), 4.02 – 3.93 (m, 2H), 3.76 – 3.58 (m, 3H), 3.27 – 3.18 (m, 1H), 2.84 – 2.71 (m, 4H), 2.57 – 2.00 (m, 10H).

**[00696]** **Compound 31.** 2-amino-1'-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(2,3,6,7-tetrahydroazepin-1-yl)pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



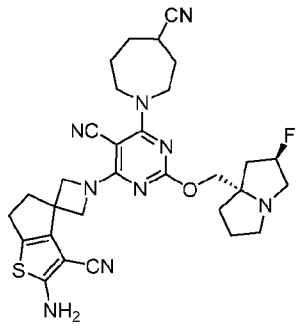
**[00697]** Compound **31** was prepared similarly to that of **Ex. 2** as a formate salt. LCMS calcld for $C_{29}H_{34}FN_8OS$ $(M+H)^+$ m/z = 561.3, found: 561.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.47 (s, 2H), 5.80 – 5.71 (m, 2H), 5.55 – 5.37 (m, 1H), 4.72 – 4.21 (m, 8H), 4.02 – 3.93 (m, 2H), 3.76 – 3.58 (m, 3H), 3.27 – 3.18 (m, 1H), 2.84 – 2.71 (m, 4H), 2.57 – 2.00 (m, 10H).

**[00698]** **Compound 32.** 2-amino-1'-[6-[3-chloro-2-(4-fluoro-1-methyl-benzimidazol-2-yl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



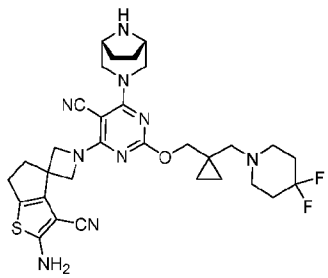
**[00699]** Compound **32** was prepared similarly **Compound 29** as a formate salt. LCMS calcld for $C_{38}H_{38}ClF2N_{12}OS$ $(M+H)^+$ m/z = 783.3, found:783.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.46-7.29 (m, 2H), 7.11-7.01 (m, 1H), 5.67-5.47 (m, 1H), 5.18-4.90 (m, 3H), 4.61-4.22 (m, 9H), 4.00-3.76 (m, 6H), 3.50-3.36 (m, 1H), 2.83-2.47 (m, 6H), 2.43-2.10 (m, 6H).

**[00700]** **Compound 33.** 2-amino-1'-[5-cyano-6-(4-cyanoazepan-1-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



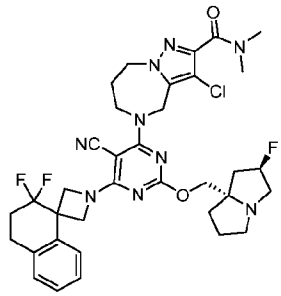
**[00701]** Compound **33** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calcld for $C_{30}H_{35}FN_9OS$ $(M+H)^+$ m/z =588.3, found: 588.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ: 5.55 (d, *J*=51.6 Hz, 1H), 4.55-4.36 (m, 6H), 4.02-3.81 (m, 7H), 3.48-3.40 (m, 1H), 3.08-3.04 (m, 1H), 2.80-2.70 (m, 4H), 2.68-2.49 (m, 2H), 2.37- 1.91 (m, 10H).

**[00702]** **Compound 34.** 2-amino-1'-[5-cyano-6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[[1-[(4,4-difluoro-1-piperidyl)methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



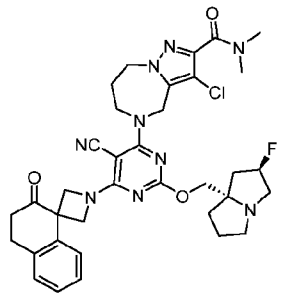
**[00703]** Compound **34** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{31}H_{38}F_2N_9OS$ $(M+H)^+$ m/z =622.3 , found: 622.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.69 – 4.27 (m, 6H), 4.26 – 4.19 (m, 2H), 3.59 – 3.48 (m, 2H), 3.29 – 3.13 (m, 2H), 2.81 – 2.37 (m, 10H), 1.99 – 1.88 (m, 4H), 1.85 – 1.75 (m, 4H), 0.69 – 0.61 (m, 2H), 0.50 – 0.41 (m, 2H).

**[00704]** **Compound 35.** 3-chloro-5-[5-cyano-6-(2',2'-difluorospiro[azetidine-3,1'-tetralin]-1-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



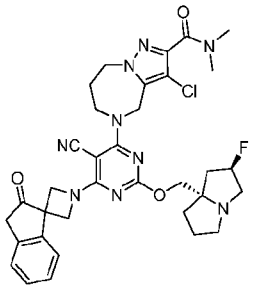
**[00705]** Compound **35** was prepared similarly to that of **Ex. 2** using **Intermediate 12**. LCMS calcld for $C_{35}H_{40}ClF_3N_9O_2$ $(M+H)^+$ m/z =710.3; found: 710.3. $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 2.07 - 2.67 (m, 12 H) 2.99 - 3.07 (m, 3 H) 3.10 (d, *J*=10.03 Hz, 6 H) 3.14 - 3.24 (m, 1 H) 3.35 - 3.47 (m, 2 H) 3.78 - 4.01 (m, 2 H) 4.01 - 4.32 (m, 3 H) 4.32 - 4.49 (m, 4 H) 4.54 (d, *J*=11.55 Hz, 2 H) 4.59 - 5.14 (m, 5 H) 5.32 - 5.57 (m, 1 H) 7.13 (d, *J*=7.64 Hz, 1 H) 7.22 - 7.26 (m, 1 H) 7.32 - 7.37 (m, 1 H) 7.65 (d, *J*=7.89 Hz, 1 H)

**[00706]** **Compound 36.** 3-chloro-5-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(2'-oxospiro[azetidine-3,1'-tetralin]-1-yl)pyrimidin-4-yl]-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



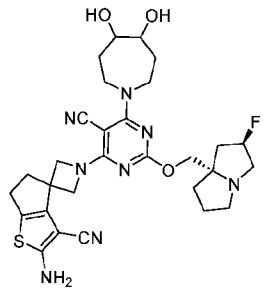
**[00707]** Compound **36** was prepared similarly to that of **Ex. 2** using **Intermediate 18**. LCMS calcld for $C_{35}H_{40}ClFN_9O_2(M+H)^+$ m/z =688.3; found: 688.3. $^1H$ NMR (500 MHz, $CDCl_3$) δ 2.02 - 2.13 (m, 3 H) 2.19 - 2.29 (m, 3 H) 2.30 - 2.47 (m, 2 H) 2.71 (t, *J*=6.79 Hz, 2 H) 3.06 (t, *J*=6.79 Hz, 2 H) 3.10 (s, 3 H) 3.11 (s, 3 H) 3.27 - 3.43 (m, 1 H) 3.59 - 3.80 (m, 2 H) 4.04 - 4.21 (m, 2 H) 4.32 (d, *J*=11.19 Hz, 1 H) 4.37 - 4.49 (m, 3 H) 4.69 - 5.12 (m, 4 H) 5.31 - 5.48 (m, 1 H) 7.20 - 7.24 (m, 1 H) 7.29 (td, *J*=7.47, 0.76 Hz, 1 H) 7.38 (t, *J*=7.27 Hz, 1 H) 7.63 (d, *J*=7.64 Hz, 1 H)

**[00708]** **Compound 37.** 3-chloro-5-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(2'-oxospiro[azetidine-3,1'-indane]-1-yl)pyrimidin-4-yl]-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



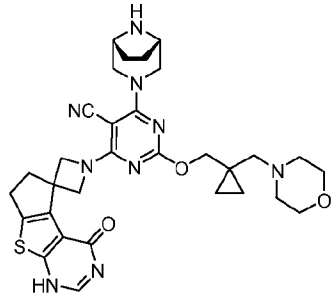
**[00709]** Compound **36** was prepared similarly to that of **Ex. 2** using 5-oxo-2-azaspiro[3.4]octane (*Angew. Chem. Int. Ed. 2021, 60, 7360–7365*). LCMS calcld for $C_{34}H_{38}ClFN_9O_3$ $(M+H)^+$ m/z =674.3; found: 674.3. $^1$H NMR ($CDCl_3$) d: 7.79 (d, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.39 - 7.44 (t, *J* = 7.5 Hz, 1H), 5.32 - 5.49 (d, *J* = 55 Hz, 1H), 4.80 - 5.08 (dd, *J* = 15 Hz , 1H), 3.99 - 4.72 (m, 10H), 3.73 - 3.94 (m, 2H), 3.54 (s, 2H), 3.46 (d, J = 1.4 Hz, 1H), 3.38 (t, *J* = 16.0 Hz, 1H), 3.12 (s, 2H), 3.09 (s, 3H), 2.32 - 2.56 (m, 2H), 2.20 - 2.31 (m, 3H), 2.13 (br. s., 3H).

**[00710]** **Compound 38.** 2-amino-1'-[5-cyano-6-(4,5-dihydroxyazepan-1-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



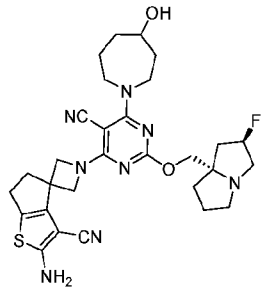
**[00711]** Compound **38** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calcld for $C_{29}H_{36}FN_8O_3S$ $(M+H)^+$ m/z = 595.3, found: 595.3. $^1$H NMR (400 MHz, $CD_3OD$) δ 5.55 (d, *J* = 51.6 Hz, 1H), 4.61 – 4.22 (m, 6H), 4.03 – 3.55 (m, 9H), 3.50 – 3.39 (m, 1H), 2.82 – 2.48 (m, 6H), 2.40 – 2.10 (m, 6H), 1.97 – 1.84 (m, 2H).

**[00712]** **Compound 39.** 2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-4-(12-oxospiro[7-thia-9,11-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),10-triene-3,3'-azetidine]-1'-yl)-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidine-5-carbonitrile



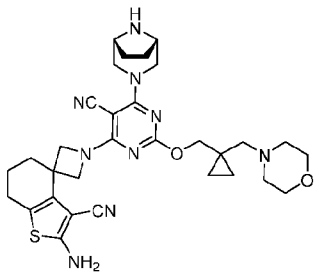
**[00713]** Compound **39** was prepared similarly to that of **Ex. 3** using **Intermediate 13** as a TFA salt. LCMS calcld for $C_{31}H_{38}N_9O_3S$ $(M+H)^+$ m/z = 616.3, found: 616.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.01 (s, 1H), 4.75-4.58 (m, 3H), 4.44-4.14 (m, 6H), 4.10-4.00 (m, 2H), 3.88-3.63 (m, 4H), 3.60-3.31 (m, 4H), 3.29-3.04 (m, 5H), 2.99-2.90 (m, 2H), 2.15-2.03 (m, 4H), 0.95-0.80 (m, 4H).

**[00714]** **Compound 40.** 2-amino-1'-[5-cyano-6-(4-hydroxyazepan-1-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



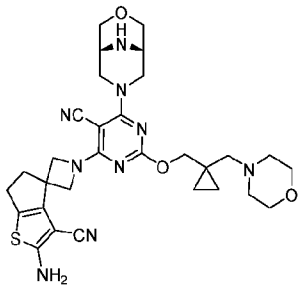

**[00715]** Compound **40** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calcld for $C_{29}H_{36}FN_8O_2S$ $(M+H)^+$ m/z = 579.3, found: 579.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.66 – 5.40 (m, 1H), 4.64 – 4.29 (m, 6H), 4.02 – 3.72 (m, 8H), 3.52 – 3.38 (m, 1H), 2.82 – 2.47 (m, 6H), 2.41 – 2.24 (m, 3H), 2.18 – 2.01 (m, 3H), 1.93 – 1.60 (m, 4H).

**[00716]** **Compound 41.** 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-3-carbonitrile



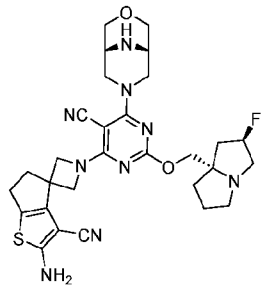

**[00717]** Compound **41** was prepared similarly to that of **Ex. 3**. LCMS calcld for $C_{31}H_{40}N_9O_2S$ $(M+H)^+$ m/z =602.3, found: 602.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ: 4.75-4.72 (m, 1H), 4.51-4.21 (m, 6H), 4.03-4.00 (m, 1H), 3.69-3.67 (m, 4H), 3.56-3.56 (m, 2H), 3.28-3.20 (m, 2H), 2.54- 2.35 (m, 8H), 2.17-2.10 (m, 2H), 1.85-1.78 (m, 6H), 0.69-0.65 (m, 2H), 0.51-0.45 (m, 2H).

**[00718]** **Compound 42.** 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



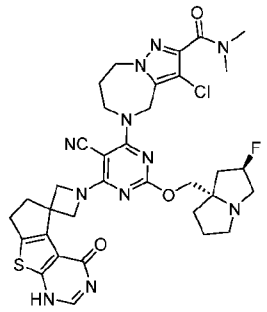
**[00719]** Compound **42** was prepared similarly to that of **Ex. 3**. LCMS calcld for $C_{30}H_{38}N_9O_3S$ $(M+H)^+$ m/z = 604.3, found: 604.4. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.78 (d, *J* = 13.2 Hz, 2H), 4.65 – 4.47 (m, 2H), 4.48 – 4.31 (m, 2H), 4.25 (s, 2H), 4.03 – 3.93 (m, 2H), 3.92 – 3.82 (m, 2H), 3.66 (t, *J* = 4.4 Hz, 4H), 3.52 (d, *J* = 13.4 Hz, 2H), 2.91 (s, 2H), 2.81 – 2.67 (m, 4H), 2.48 (s, 4H), 2.38 (s, 2H), 0.64 (t, *J* = 5.2 Hz, 2H), 0.44 (t, *J* = 5.2 Hz, 2H).

**[00720]** **Compound 43.** 2-amino-1'-[5-cyano-2-[[(2S,8R)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



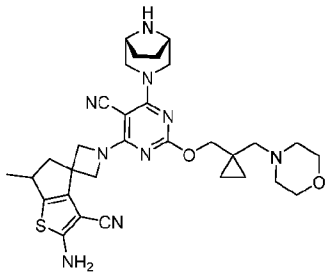
**[00721]** Compound **43** was prepared similarly to that of **Ex. 3**. LCMS calcld for $C_{29}H_{35}FN_9O_2S$ (M+H)+ m/z = 592.3, found: 592.2. $^1H$ NMR (DMSO-d6, 400 MHz) δ 7.23 (s, 2H), 5.25 (d, *J* = 52.0 Hz, 1H), 4.60-4.57 (m, 2H), 4.34 (br, 4H), 3.97 (d, *J* = 12.0 Hz, 1H), 3.84 (d, *J* = 12.0 Hz, 1H), 3.80 (d, *J* = 8.0 Hz, 2H), 3.70 (d, *J* = 8.0 Hz, 2H), 3.41-3.89 (m, 2H), 3.05 (br, 2H), 3.01-2.93 (m, 1H), 2.84-2.79 (m, 3H), 2.67 (br, 4H), 2.07-2.05 (m, 1H), 1.99-1.98 (m, 1H), 1.95-1.93 (m, 1H), 1.83-1.80 (m, 1H), 1.75-1.71 (m, 2H).

**[00722]** **Compound 44.** 3-chloro-5-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(12-oxospiro[7-thia-9,11-diazatricyclo[6.4.0.02,6]dodeca-1(8),2(6),10-triene-3,3'-azetidine]-1'-yl)pyrimidin-4-yl]-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



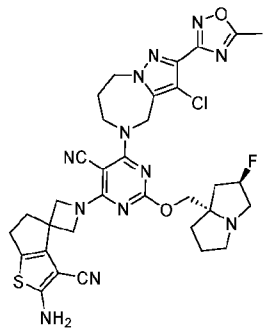
**[00723]** Compound **44** was prepared similarly to that of **Ex. 2** as a formate salt using **Intermediate 13**. LCMS calcld for $C_{34}H_{38}ClFN_{11}O_3S$ $(M+H)^+$ m/z = 734.3, found: 734.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.52 (s, 2H), 7.99 (s, 1H), 5.26 (d, $J$ = 56.2 Hz, 2H), 4.74 – 4.41 (m, 4H), 4.15 (m, 5H), 3.17 (m, 3H), 3.08 (m, 8H), 3.01 – 2.88 (m, 3H), 2.30 – 1.76 (m, 10H).

**[00724]** **Compound 45.** 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]-6-methyl-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



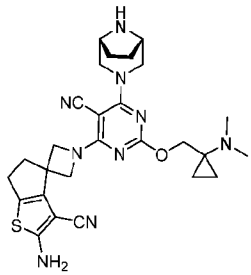
**[00725]** Compound **45** was prepared similarly to that of **Ex. 2** as a TFA salt using **Intermediate 6 (Compound 14)**. LCMS calcld for $C_{31}H_{40}N_9O_2S$ $(M+H)^+$ m/z = 602.2, found: 602.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.66-4.01 (m, 12H), 3.93-3.68 (m, 4H), 3.57-3.42 (m, 2H), 3.30-3.10 (m, 3H), 3.01-2.89 (m, 1H), 2.29-2.19 (m, 1H), 2.14-2.02 (m, 4H), 1.18 (d, $J$ = 6.8 Hz, 3H), 0.95-0.78 (m, 4H).

**[00726]** **Compound 46.** 2-amino-1'-[6-[3-chloro-2-(5-methyl-1,2,4-oxadiazol-3-yl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



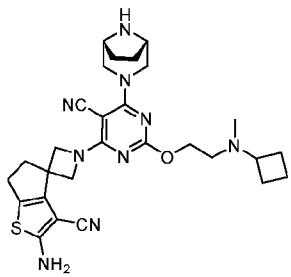
**[00727]** Compound **46** was prepared similarly to **Ex. 2** as a formate salt using **Intermediate 14**. LCMS calcld for $C_{33}H_{35}ClFN_{12}O_2S$ $(M+H)^+$ m/z = 717.2, found: 717.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.34 (dd, *J* = 35.3, 18.5 Hz, 1H), 5.12 – 5.02 (m, 2H), 4.74 – 4.44 (m, 6H), 4.29 – 4.09 (m, 5H), 3.47 – 3.33 (m, 2H), 3.15 – 3.00 (m, 1H), 2.79 – 2.68 (m, 4H), 2.66 (s, 3H), 2.43 – 1.78 (m, 9H).

**[00728]** **Compound 47.** 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-(dimethylamino)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



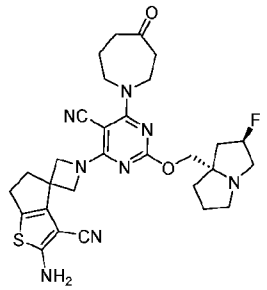
**[00729]** Compound **47** was prepared similarly to that of **Ex. 3** as a TFA. LCMS calcld for $C_{27}H_{34}N_9OS$ $(M+H)^+$ m/z =532.3, found:532,2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.66 – 4.53 (m, 4H), 4.44 – 4.37 (s, 2H), 4.35 – 4.16 (m, 2H), 3.62 – 3.48 (m, 2H), 3.29 – 3.10 (m, 2H), 2.83 – 2.67 (m, 4H), 2.46 (s, 6H), 1.89 – 1.71 (m, 4H), 0.80 – 0.66 (m, 4H).

**[00730]** **Compound 48.** 2-amino-1'-[5-cyano-2-[2-[cyclobutyl(methyl)amino]ethoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



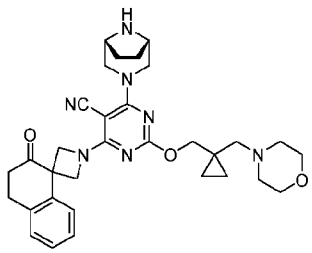
**[00731]** Compound **48** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{28}H_{36}N_9OS$ $(M+H)^+$ m/z = 546.3, found: 546.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.75 – 4.33 (m, 7H), 4.23 – 4.15 (m, 2H), 3.89 – 3.78 (m, 1H), 3.66 – 3.43 (m, 3H), 3.43 – 3.34 (m, 2H), 2.85 (s, 3H), 2.83 – 2.70 (m, 4H), 2.45 – 2.17 (m, 4H), 2.11 (s, 4H), 1.96 – 1.79 (m, 2H).

**[00732]** **Compound 49.** 2-amino-1'-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(4-oxoazepan-1-yl)pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



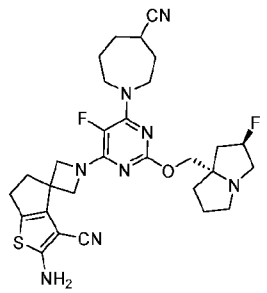
**[00733]** Compound **49** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calcld for $C_{29}H_{34}FN_8O_2S$ $(M+H)^+$ m/z =577.2, found: 577.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.57 (d, *J*=52 Hz, 1H), 4.57-4.39 (m, 6H), 4.21-4.18 (m, 2H), 4.12-4.01 (m, 2H), 4.00-3.83 (m, 4H), 3.50-3.41 (m, 2H), 2.81-2.51 (m, 10H), 2.40- 2.31 (m, 3H), 2.29-1.89 (m, 3H).

**[00734]** **Compound 50.** 4-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-(2'-oxospiro[azetidine-3,1'-tetralin]-1-yl)pyrimidine-5-carbonitrile



**[00735]** Compound **50** was prepared similarly to that of **Ex. 3** using **Intermediate 18**. LCMS calcld for $C_{32}H_{40}N_7O_3$ $(M+H)^+$ m/z = 570.3, found: 570.2. $^1H$ NMR (400 MHz, DMSO-d6) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.39-7.35 (m, 1H), 7.31-7.30 (m, 2H), 4.69 (br, 2H), 4.23-4.20 (m, 2H), 4.15 (s, 4H), 3.58 (br, 2H), 3.53 (br, 5H), 3.23 (d, *J* = 12.0 Hz, 2H), 3.04 (m, 2H), 2.70 (m, 2H), 2.35 (br, 4H), 2.24 (s, 2H), 1.69-1.62 (m, 4H), 0.57(s, 2H), 0.38 (s, 2H).

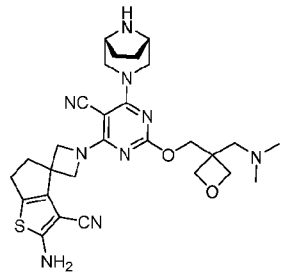
**[00736]** **Compound 51.** 2-amino-1'-[6-(4-cyanoazepan-1-yl)-5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00737]** Compound **51** was prepared similarly to that of **Ex. 4** as a TFA salt. LCMS calcld for $C_{29}H_{35}F_2N_8OS$ $(M+H)^+$ m/z =581.3, found:581.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.54 (dt, *J* = 51.6, 3.5 Hz, 1H), 4.52 – 4.30 (m, 4H), 4.24 (d, *J* = 8.8 Hz, 2H), 4.04 – 3.86 (m, 2H), 3.85 – 3.68

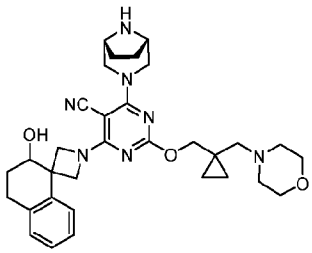
(m, 5H), 3.49 – 3.39 (m, 1H), 3.04 (d, $J$ = 11.3 Hz, 1H), 2.82 – 2.71 (m, 4H), 2.70 – 2.45 (m, 2H), 2.39 – 2.24 (m, 3H), 2.22 – 1.90 (m, 7H).

**[00738]** **Compound 52.** 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[3-[(dimethylamino)methyl]oxetan-3-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



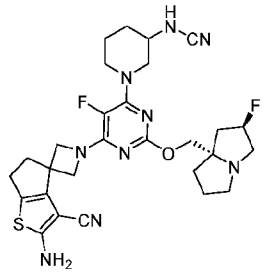
**[00739]** Compound **52** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{28}H_{36}N_9O_2S$ $(M+H)^+$ m/z =562.3, found:562.2. 1H NMR (400 MHz, $CD_3OD$) δ 4.83 – 4.61 (m, 6H), 4.60 – 4.35 (m, 6H), 4.24 – 4.10 (m, 2H), 3.79 – 3.62 (m, 2H), 3.60 – 3.42 (m, 2H), 2.91 (s, 6H), 2.81 – 2.68 (m, 4H), 2.19 – 1.99 (m, 4H).

**[00740]** **Compound 53.** 4-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-(2'-hydroxyspiro[azetidine-3,1'-tetralin]-1-yl)-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidine-5-carbonitrile



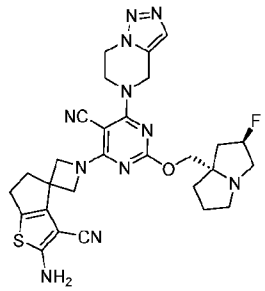
**[00741]** Compound **53** was prepared similarly to that of **Ex. 3** as a TFA salt using **Intermediate 18**. LCMS calcld for $C_{32}H_{42}N_7O_7$ $(M+H)^+$ m/z = 572.3, found: 572.2. $^1$H NMR (DMSO-d6, 400 MHz) δ 7.58 (d, $J$ = 8.0 Hz, 1H), 7.26 (t, $J$ = 8.0 Hz, 1H), 7.19 (t, $J$ = 8.0 Hz, 1H), 7.10 (m, 1H), 5.38 (m, 1H), 4.34 (br, 3H), 4.16 (s, 2H), 4.06 (br, 2H), 3.93-3.90 (m, 1H), 3.54 (m, 5H), 3.43-3.41 (m, 3H), 2.91-2.84 (m, 1H), 2.78-2.63 (m, 1H), 2.37-2.33 (m, 5H), 2.25 (br, 2H), 1.91-1.82 (m, 6H), 1.66 (br, 1H) 0.57 (s, 2H), 0.40 (s, 2H).

**[00742]** **Compound 54.** [1-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-piperidyl]cyanamide



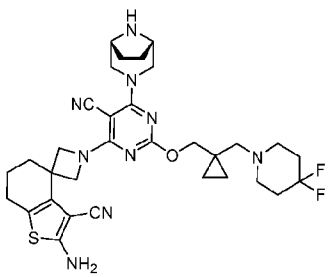
**[00743]** Compound **54** was prepared similarly to that of **Ex. 4** as a TFA salt. LCMS calcd for $C_{28}H_{34}F_2N_9OS$ $(M+H)^+$ m/z: 582.3, found: 582.4. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.54 (d, $J$ = 52.1 Hz, 1H), 4.51 – 4.33 (m, 4H), 4.26 - 4.15 (m, 3H), 4.03 – 3.70 (m, 4H), 3.46 - 3.39 (m, 1H), 3.27 – 3.22 (m, 3H), 2.90 – 1.98 (m, 12H), 1.82 (s, 1H), 1.60 (s, 1H).

**[00744]** **Compound 55.** 2-amino-1'-[5-cyano-6-(6,7-dihydro-4H-triazolo[1,5-a]pyrazin-5-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



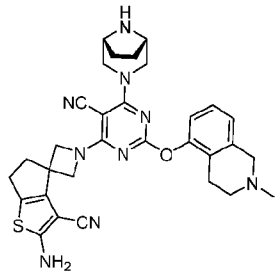
**[00745]** Compound **55** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calculated for $C_{28}H_{31}FN_{11}OS$ $(M+H)^+$ m/z =588.2, found: 588.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.65 (s, 1H), 5.65-5.46 (m, 1H), 5.12 (s, 2H), 4.75-4.20 (m, 9H), 4.00-3.82 (m, 3H), 3.50-3.40 (m, 1H), 2.82-2.50 (m, 6H), 2.41-2.26 (m, 3H), 2.20-2.10 (m, 1H).

**[00746]** **Compound 56.** 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-[(4,4-difluoro-1-piperidyl)methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-3-carbonitrile



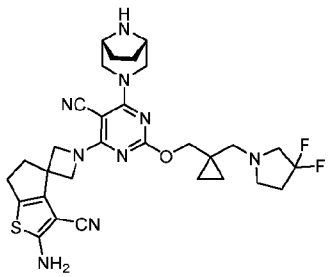
**[00747]** Compound **56** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{32}H_{40}F_2N_9OS$ $(M+H)^+$ m/z =636.3 , found: 636.2.. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.71 – 4.56 (m, 2H), 4.52 (s, 1H), 4.40 (s, 2H), 4.29 (d, $J$ = 16.0 Hz, 2H), 4.16 (s, 2H), 4.00 (s, 1H), 3.61 – 3.38 (m, 3H), 2.49 (m, 6H), 2.10 (m, 7H), 1.82 (s, 2H), 1.30 (s, 4H), 0.91 (s, 2H), 0.83 (s, 2H).

**[00748]** **Compound 57.** 2-amino-1'-[5-cyano-2-[(2-methyl-3,4-dihydro-1H-isoquinolin-5-yl)oxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



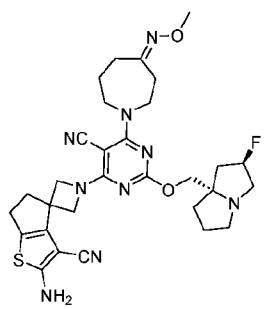
**[00749]** Compound **57** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{31}H_{34}N_9OS$ $(M+H)^+$ m/z: 580.3, found: 580.4. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.36 (t, $J$ = 7.9 Hz, 1H), 7.13 (dd, $J$ = 10.9, 7.9 Hz, 2H), 4.73 – 4.17 (m, 7H), 4.10 (s, 3H), 3.62 – 3.33 (m, 4H), 3.04 (s, 5H), 2.74 - 2.70 (m, 4H), 2.04 (s, 4H).

**[00750]** **Compound 58**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-[(3,3-difluoropyrrolidin-1-yl)methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



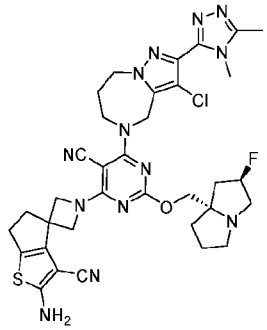
**[00751]** Compound **58** was prepared similarly to that of **Ex. 3** as a formate salt. LCMS calcld for $C_{30}H_{36}F_2N_9OS$ $(M+H)^+$ m/z = 608.3, found: 608.4. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.58 (s, 6H), 4.24 (s, 2H), 3.63 (s, 2H), 2.88 (d, $J$ = 13.3 Hz, 2H), 2.79 – 2.67 (m, 6H), 2.47 (s, 2H), 2.22 – 2.15 (m, 3H), 2.03 – 1.98 (m, 2H), 1.84 (s, 3H), 0.63 (t, $J$ = 5.2 Hz, 2H), 0.45 (t, $J$ = 5.3 Hz, 2H).

**[00752]** **Compound 59.** 2-amino-1'-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-[(4Z)-4-methoxyiminoazepan-1-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



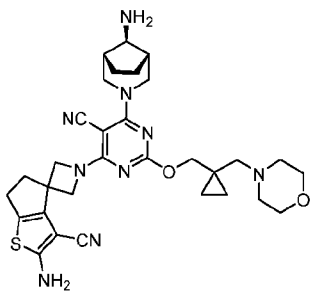
**[00753]** Compound **59** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calcld for $C_{30}H_{37}FN_9O_2S$ $(M+H)^+$ m/z =606.3, found: 606.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ: 5.54 (d, *J*=51.6 Hz, 1 H), 4.57-4.39 (m, 6 H), 4.07-3.84 (m, 7 H), 3.77-3.76 (m, 3 H), 3.48-3.41 (m, 1 H), 2.80-2.57 (m, 8 H), 2.38- 2.29 (m, 3 H), 2.27-2.10 (m, 1 H), 1.91-1.78 (m, 1H).

**[00754]** **Compound 60.** 2-amino-1'-[6-[3-chloro-2-(4,5-dimethyl-1,2,4-triazol-3-yl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



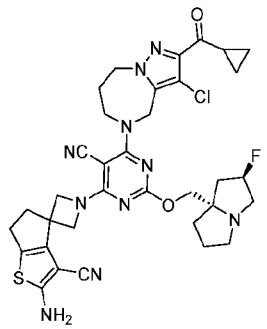
**[00755]** Compound **60** was prepared similarly to that of **Ex. 2** as a TFA salt using **Intermediate 15**. LCMS calcld for $C_{34}H_{38}ClFN_{13}OS$ $(M+H)^+$ m/z =730.3, found: 730.4. $^1H$ NMR (400 MHz, $CD_3OD$) δ: 5.58 (d, *J*=52 Hz, 1H), 5.14-5.01 (m, 2H), 4.59-4.43 (m, 8H), 4.34-4.25 (m, 2H), 3.98-3.85 (m, 3H), 3.808 (s, 3H), 3.50-3.41 (m, 1H), 2.79- 2.72 (m, 4H), 2.69-2.50 (m, 5H), 2.41 -2.11 (m, 6H).

**[00756]** **Compound 61**. 2-amino-1'-[6-[(1R,5S)-8-amino-3-azabicyclo[3.2.1]octan-3-yl]-5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



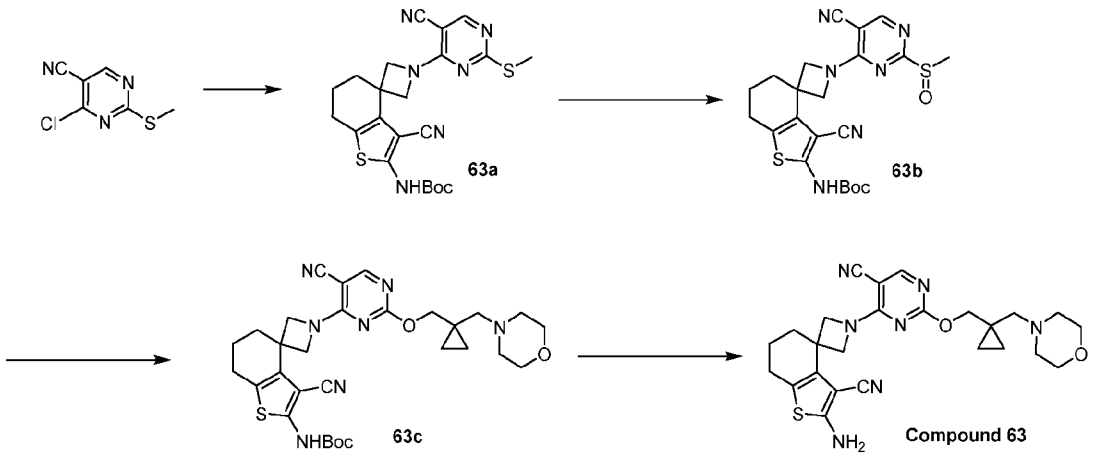
**[00757]** Compound **61** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calcld for $C_{31}H_{40}N_9O_2S$ $(M+H)^+$ m/z =602.2, found: 602.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ: 4.67 – 4.22 (m, 10H), 4.17 – 4.00 (m, 3H), 3.98 – 3.65 (m, 5H), 3.62 – 3.55 (m, 1H), 3.24 – 3.09 (m, 2H), 2.86 – 2.72 (m, 4H), 2.56 – 2.45 (m, 2H), 1.98 – 1.76 (m, 4H), 0.98 – 0.91 (m, 2H), 0.89 – 0.81 (m, 2H).

**[00758]** **Compound 62.** 2-amino-1'-[6-[3-chloro-2-(cyclopropanecarbonyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00759]** Compound **62** was prepared similarly to that of **Ex. 2** as a formate salt using **Intermediate 16**. LCMS calcld for $C_{34}H_{37}ClFN_{10}O_2S$ $(M+H)^+$ m/z =703.2, found:703.4. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.51 (s, 1H), 5.37 (d, $J$ = 51.0 Hz, 1H), 5.07 – 4.97 (m, 2H), 4.68 – 4.38 (m, 6H), 4.29 – 4.17 (m, 4H), 3.45 (m, 3H), 3.18 – 3.09 (m, 1H), 3.01 (m, 1H), 2.74 (m, 4H), 2.34 (m, 4H), 2.18 – 1.96 (m, 3H), 1.92 (s, 1H), 1.09 (m, 2H), 1.02 (m, 2H).

**Example 6.** Exemplary synthesis of 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-3-carbonitrile **(Compound 63).**




**[00760]** Step 1. Synthesis of tert-butyl N-[3-cyano-1'-(5-cyano-2-methylsulfanyl-pyrimidin-4-yl)spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (**63a**). The solution of 4-chloro-2-methylsulfanyl-pyrimidine-5-carbonitrile (43.59 mg, 0.23 mmol), $K_2CO_3$ (108.01 mg, 0.7 8mmol) and tert-butyl N-(3-cyanospiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl)carbamate (50 mg, 0.16 mmol) in IPA (5mL) was stirred at 50 °C for 1h. The solvent was

removed and purified by silica gel chromatography (PE: EtOAc=3:1) to get tert-butyl N-[3-cyano-1'-(5-cyano-2-methylsulfanyl-pyrimidin-4-yl)spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (**63a**, 45 mg, 0.0960 mmol, 61.35 %yield) (crude, white solid). LCMS calculated for $C_{22}H_{25}N_6O_2S_2$ $(M+H)^+$ m/z =469.1, found: 469.3.

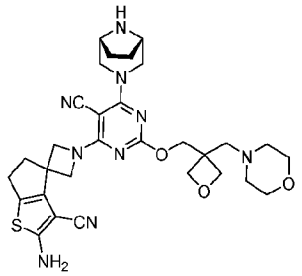
**[00761]** Step 2. Synthesis of tert-butyl N-[3-cyano-1'-(5-cyano-2-methylsulfinyl-pyrimidin-4-yl)spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (**63b**). The solution of oxone (118.07 mg, 0.19 mmol) and tert-butyl N-[3-cyano-1'-(5-cyano-2-methylsulfanyl-pyrimidin-4-yl)spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (45 mg, 0.1 mmol) in Water (2mL) and THF (2mL) was stirred at 25 °C for 18h. The mixture was extracted with EtOAc and water, dried with brine and $Na_2SO_4$, concentrated to get tert-butyl N-[3-cyano-1'-(5-cyano-2-methylsulfinyl-pyrimidin-4-yl)spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (**63b**, 25 mg, 0.0516 mmol, 53.72%yield) (crude, white solid) LCMS calculated for $C_{22}H_{24}N_6NaO_3S_2$ $(M+Na)^+$ m/z =507.1, found: 507.3.

**[00762]** Step 3. Synthesis of tert-butyl N-[3-cyano-1'-(5-cyano-2-hydroxy-pyrimidin-4-yl)spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (**63c**). The NaH (12 mg, 0.3 mmol) was put into the solution of [1-(morpholinomethyl)cyclopropyl]methanol (51.37 mg, 0.3 mmol) in DMSO (1.5mL) at 25 °C. After stirring for 1h, tert-butyl N-[3-cyano-1'-(5-cyano-2-methylsulfinyl-pyrimidin-4-yl)spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (**63b**, 25 mg) and tert-butyl N-[3-cyano-1'-(5-cyano-2-methylsulfonyl-pyrimidin-4-yl)spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (25 mg) in DMSO was added, and the mixture was stirred at rt for 1h. The mixture was quenched with water, extracted with EtOAc, dried with brine and $Na_2SO_4$, concentrated and purified by prep-HPLC (DCM: MeOH= 20:1) to get tert-butyl N-[3-cyano-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (**63c**, 30 mg, 0.0507 mmol, 98.27 %yield) (light yellow oil). LCMS calculated for $C_{30}H_{38}N_7O_4S$ $(M+H)^+$ m/z =592.3, found: 592.4.

**[00763]** Step 4. Synthesis of 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-3-carbonitrile (**Compound 63**). The solution of Trifluoroacetic acid (0.06 mL, 0.51 mmol) and tert-butyl N-[3-cyano-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-2-yl]carbamate (30 mg, 0.05 mmol) in DCM (3mL) was stirred at rt for 5h. The solvent was removed and purified by prep-HPLC (0.1% TFA) to get 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-3-carbonitrile (**Compound 63**, 10 mg, 0.0201 mmol, 39.72 %yield). LCMS

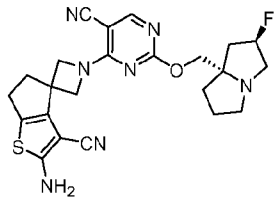
calculated for $C_{25}H_{30}N_7O_2S$ $(M+H)^+$ m/z =492.2, found: 492.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.39 (s, 1H), 4.87 - 4.85 (m, 1H), 4.50 (dd, *J* = 22.9, 9.9 Hz, 2H), 4.32 (s, 2H), 4.07 (m, 3H), 3.83 (m, 2H), 3.71 (m, 2H), 3.32 - 3.26 (m, 2H), 3.19 – 3.05 (m, 2H), 2.51 (t, J = 6.1 Hz, 2H), 2.15 (m, 2H), 1.98 – 1.75 (m, 2H), 1.02 – 0.76 (m, 4H).

**[00764]** **Compound 64.** 2-amino-1'-[5-cyano-2-[[3-(morpholinomethyl)oxetan-3-yl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



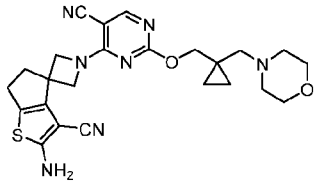
**[00765]** Compound **64** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{30}H_{38}N_9O_3S$ $(M+H)^+$ m/z =604.3, found:604.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.61 (s, 4H), 4.54 (dd, *J* = 14.8, 6.2 Hz, 6H), 3.61 (s, 4H), 3.56 (s, 2H), 2.76 (m, 6H), 2.38 (s, 4H), 1.81 (s, 4H), 1.31 (d, *J* = 17.6 Hz, 4H).

**[00766]** **Compound 65.** 2-amino-1'-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



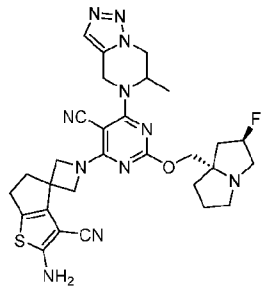
**[00767]** Compound **65** was prepared similarly to that of **Ex. 6** as a TFA salt. LCMS calcld for $C_{23}H_{25}FN_7OS$ $(M+H)^+$ m/z = 466.2, found: 466.3. $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 5.39 – 5.26 (m, 1H), 4.84 (s, 2H), 4.59 (s, 2H), 4.27 (s, 2H), 3.53 (s, 2H), 3.33 – 3.25 (m, 1H), 3.05 (s, 1H), 2.82 (d, *J* = 6.4 Hz, 2H), 2.74 (s, 2H), 2.38 – 2.15 (m, 5H), 2.08 – 1.98 (m, 3H).

**[00768]** **Compound 66.** 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



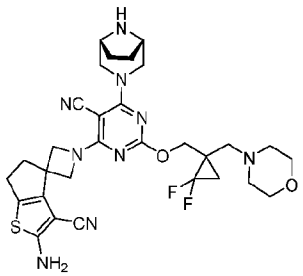
**[00769]** Compound **66** was prepared similarly to that of **Ex. 6** as a TFA salt. LCMS calcld for $C_{24}H_{28}N_7O_2S$ $(M+H)^+$ m/z =478.2, found: 478.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.40 (s, 1H), 4.75 – 4.67 (m, 2H), 4.33 (s, 6H), 4.07 (s, 2H), 3.82 (s, 2H), 3.73 – 3.66 (m, 2H), 3.13 (s, 2H), 2.78 (s, 4H), 0.95 (s, 2H), 0.84 (s, 2H).

**[00770]** **Compound 67.** 2-amino-1'-[5-cyano-6-(6-methyl-6,7-dihydro-4H-triazolo[1,5-a]pyrazin-5-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



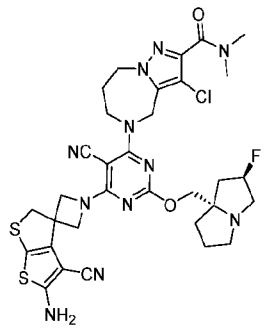
**[00771]** Compound **67** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calculated for $C_{29}H_{33}FN_{11}OS$ $(M+H)^+$ m/z =602.3, found: 602.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.64 (s, 1H), 5.66-5.46 (m, 1H), 5.33-5.22 (m, 1H), 4.86-4.75 (m, 1H), 4.64-4.40 (m, 6H), 4.04-3.81 (m, 4H), 3.51-3.38 (m, 1H), 2.84-2.50 (m, 7H), 2.41-2.24 (m, 3H), 2.20-2.09 (m, 1H), 1.69 (d, $J$ = 6.8 Hz, 3H).

**[00772]** **Compound 68.** 2-amino-1'-[5-cyano-2-[[2,2-difluoro-1-(morpholinomethyl)cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



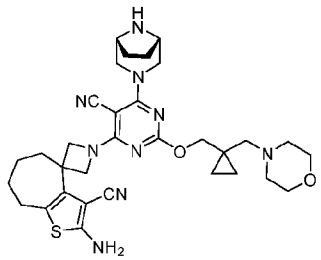
**[00773]** Compound **68** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcd for $C_{30}H_{36}F_2N_9O_2S$ $(M+H)^+$ m/z = 624.3. found: 624.4. 1H NMR (400 MHz, $CD_3OD$) δ 4.66 – 4.39 (m, 8H), 4.16 (s, 2H), 3.95 (s, 4H), 3.71 – 3.44 (m, 4H), 3.36 - 3.31 (m, 4H), 2.76 (d, $J$ = 5.9 Hz, 4H), 2.09 (s, 4H), 1.95 – 1.65 (m, 2H).

**[00774]** **Compound 69**. 5-[3-(5-amino-4-cyano-spiro[4,5-dihydro-2H-thieno[2,3-b]thiophene-3,3'-azetidine]-1'-yl)-2-cyano-5-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]phenyl]-3-chloro-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



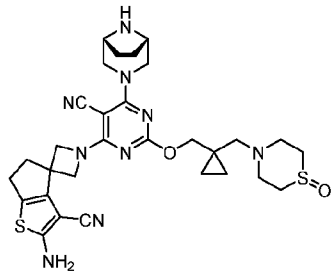
**[00775]** Compound **69** was prepared similarly to that of **Ex. 2** using **Intermediate 17.** LCMS calcld for $C_{32}H_{36}ClFN_{11}O_2S_2$ $(M+H)^+$ m/z = 724.2, found: 724.5.$^1$H NMR (400 MHz, $CD_3OD$) δ 5.25 (d, *J* = 54.6 Hz, 1H), 5.12 – 5.03 (m, 2H), 4.64 – 4.52 (m, 2H), 4.53 – 4.35 (m, 4H), 4.23 – 4.06 (m, 4H), 4.03 (s, 2H), 3.24 – 3.12 (m, 3H), 3.09 (s, 3H), 3.08 (s, 3H), 3.02 – 2.93 (m, 1H), 2.28 – 1.80 (m, 8H).

**[00776]** **Compound 70.** 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6,7,8-tetrahydrocyclohepta[b]thiophene-4,3'-azetidine]-3-carbonitrile



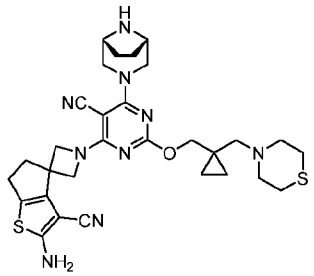
**[00777]** Compound **70** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{32}H_{42}N_9O_2S$ $(M+H)^+$ m/z = 616.3, found: 616.6. $^1$H NMR (400 MHz, $CD_3OD$) δ 4.80 – 4.24 (m, 7H), 4.19 – 4.00 (m, 5H), 3.93 – 3.67 (m, 4H), 3.60 – 3.43 (m, 2H), 3.39 – 3.31 (m, 2H), 3.21 – 3.06 (m, 2H), 2.85 – 2.58 (m, 2H), 2.38 – 2.23 (m, 2H), 2.15 – 1.99 (m, 4H), 1.93 – 1.72 (m, 4H), 0.98 – 0.79 (m, 4H).

**[00778]** **Compound 71**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-[(1-oxo-1,4-thiazinan-4-yl)methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



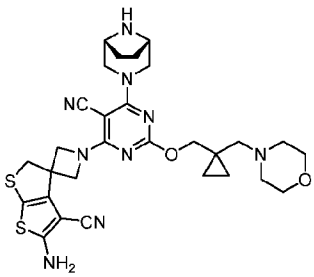
**[00779]** Compound **71** was prepared similarly to that of **Ex. 3.** LCMS calcld for $C_{30}H_{36}N_9O_2S$ $(M-H)^-$ m/z = 618.3, found:618.2.

**[00780]** **Compound 72**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-(thiomorpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



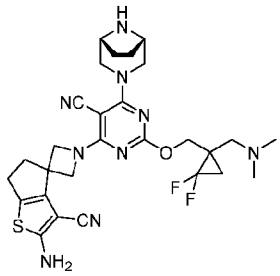
**[00781]** Compound **72** was prepared similarly to that of **Ex. 3.** LCMS calcld for $C_{30}H_{38}N_9OS_2$ $(M+H)^+$ m/z = 604.3, found:604.1.

**[00782]** **Compound 73**. 5-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[2H-thieno[2,3-b]thiophene-3,3'-azetidine]-4-carbonitrile



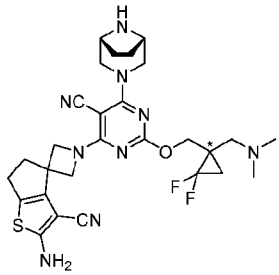
**[00783]** Compound **73** was prepared similarly to that of **Ex. 3** as a TFA salt**.** LCMS calcld for $C_{29}H_{36}N_9O_2S_2$ $(M+H)^+$ m/z = 606.2, found: 606.1. $^1$H NMR (400 MHz, $CD_3OD$) δ 4.95 – 4.86 (m, 2H), 4.74 – 4.44 (m, 5H), 4.30 – 4.15 (m, 4H), 4.12 – 3.97 (m, 4H), 3.93 – 3.62 (m, 4H), 3.55 – 3.38 (m, 3H), 3.26 – 3.01 (m, 2H), 2.13 – 2.03 (m, 4H), 0.95 – 0.77 (m, 4H).

**[00784]** **Compound 74**. 2-amino-1'-[5-cyano-6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[[1-[(dimethylamino)methyl]-2,2-difluoro-cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



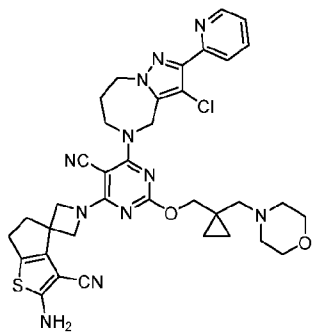
**[00785]** Compound **74** was prepared similarly to that of **Ex. 3.** LCMS calculated for $C_{28}H_{34}F_2N_9OS$ (m/z) =582.3; found:582.3. $^1$H NMR (400 MHz, $CD_3OD$) δ 4.16– 4.67 (m, 8H), 3.55 (s, 2H), 3.23 – 3.29 (m, 2H), 2.65-2.85 (m, 5H), 2.38 (d, *J* = 12.8 Hz, 1H), 2.24 (s, 6H), 1.73– 1.86 (m, 4H), 1.53 – 1.66 (m, 1H), 1.27 – 1.40 (m, 1H).

**[00786]** **Compound 74A and 74B.** 2-amino-1'-[5-cyano-6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-[[(1*)-1-[(dimethylamino)methyl]-2,2-difluoro-cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00787]** **Compound 74** was purified on an DAICELCHIRALCEL®AD (250*25 mm 10 mm) column on a Waters SFC 150 system (Mobile Phase A: Supercritical CO2, Mobile Phase B : EtOH [0.5%$NH_3$(7M in MeOH)] =75/25; Flow: 100ml/min to give faster eluting P1 (**74A**) and slower eluting P2 (**74B**).

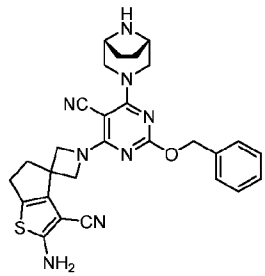
**[00788]** **Compound 75**. 2-amino-1'-[6-[3-chloro-2-(2-pyridyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00789]** Compound **75** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calcld for $C_{36}H_{39}ClN_{11}O_2S$ $(M+H)^+$ m/z = 724.3, found: 724.5. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.68 (m,

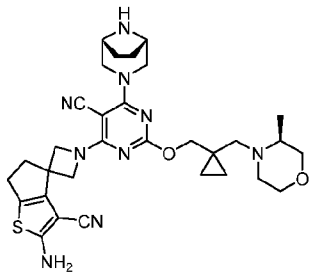
1H), 8.22 (m, 2H), 7.65 (m, 1H), 4.63 – 4.41 (m, 5H), 4.39 – 4.13 (m, 5H), 4.10 – 3.91 (m, 2H), 3.88 – 3.51 (m, 4H), 3.29 – 3.22 (m, 4H), 3.18 – 2.98 (m, 2H), 2.82 – 2.65 (m, 4H), 2.37 – 2.22 (m, 2H), 0.94 – 0.72 (m, 4H).

**[00790]** **Compound 76**. 2-amino-1'-[2-benzyloxy-5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



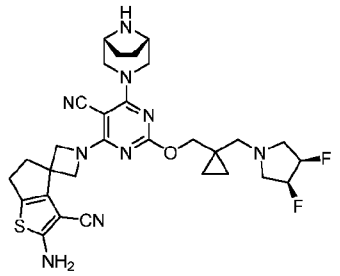
**[00791]** Compound **76** was prepared similarly to that of **Ex. 3.** LCMS calcld for $C_{28}H_{29}N_8OS$ $(M+H)^+$ m/z = 525.2, found: 525.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.45 – 7.37 (m, 2H), 7.37 – 7.32 (m, 2H), 7.32 – 7.26 (m, 1H), 5.33 (s, 2H), 4.73 – 4.11 (m, 6H), 3.63 – 3.44 (m, 2H), 3.25 (m, 2H), 2.81 – 2.63 (m, 4H), 1.89 – 1.55 (m, 4H).

**[00792]** **Compound 77**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-[[(3S)-3-methylmorpholin-4-yl]methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



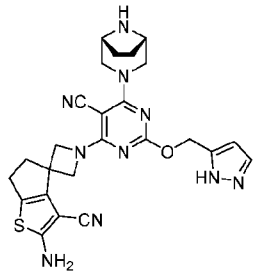
**[00793]** Compound 77 was prepared similarly to that of **Ex. 3.** LCMS calcld for $C_{31}H_{40}N_9O_2S$ $(M+H)^+$ m/z = 602.3, found: 602.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.51 (d, $J$ = 10.7 Hz, 4H), 4.32 (s, 3H), 3.92 (d, $J$ = 10.9 Hz, 1H), 3.72 (m, 3.1 Hz, 1H), 3.67 – 3.51 (m, 4H), 3.26 (s, 3H), 3.18 (m, 1H), 3.00 (m, 1H), 2.80 – 2.67 (m, 4H), 2.34 (m, 1H), 2.19 (m, 1H), 1.80 (s, 4H), 1.63 (d, $J$ = 12.6 Hz, 1H), 0.91 (d, $J$ = 6.3 Hz, 3H), 0.65 (m, 1H), 0.60 – 0.47 (m, 2H), 0.36 (m, 1H).

**[00794]** **Compound 78**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-[[(3S,4R)-3,4-difluoropyrrolidin-1-yl]methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



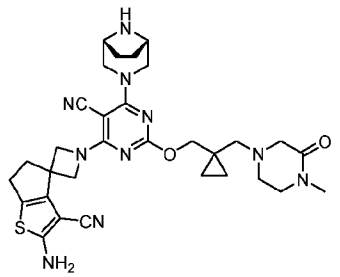
**[00795]** Compound **78** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{30}H_{36}F_2N_9OS$ $(M+H)^+$ m/z = 608.3, found: 608.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.56-5.33 (m, 2H), 4.75-4.20 (m, 5H), 4.27 (s, 2H), 4.19-3.93 (m, 4H), 3.89-3.63 (m, 2H), 3.57-3.32 (m, 5H), 2.83-2.68 (m, 4H), 2.08 (s, 4H), 0.94-0.79 (m, 4H).

**[00796]** **Compound 79**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-(1H-pyrazol-5-ylmethoxy)pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



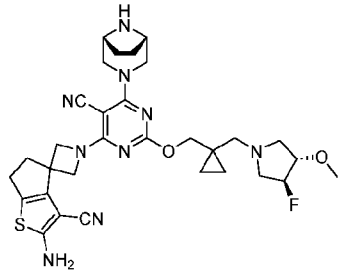
**[00797]** Compound **79** was prepared similarly to that of **Ex. 3.** LCMS calcld for $C_{25}H_{27}N_{10}OS$ $(M+H)^+$ m/z = 515.2, found: 515.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.59 (s, 1H), 6.39 (d, $J$ = 2.0 Hz, 1H), 5.35 (s, 2H), 4.46 (m, 6H), 3.54 (s, 2H), 3.26 (m, 2H), 2.82 – 2.62 (m, 4H), 1.87 – 1.64 (m, 4H), 1.30 (s, 1H).

**[00798]** **Compound 80**. 2-amino-1'-[5-cyano-2-[[1-[(4-methyl-3-oxo-piperazin-1-yl)methyl]cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



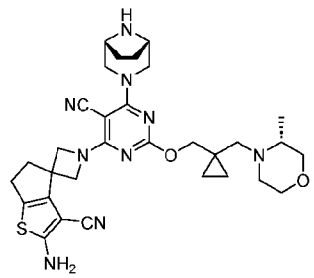
**[00799]** Compound **80** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{31}H_{39}N_{10}O_2S$ $(M+H)^+$ m/z = 615.3, found: 615.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.61 (s, 5H), 4.31 (s, 3H), 4.15 (s, 2H), 3.64 (s, 2H), 3.48 (t, J = 15.8 Hz, 2H), 2.99 (s, 3H), 2.94 – 2.84 (m, 2H), 2.82 – 2.70 (m, 2H), 2.09 (s, 4H), 0.83 – 0.77 (m, 2H), 0.77 – 0.71 (m, 2H).

**[00800]** **Compound 81**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-[[(3S,4S)-3-fluoro-4-methoxy-pyrrolidin-1-yl]methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



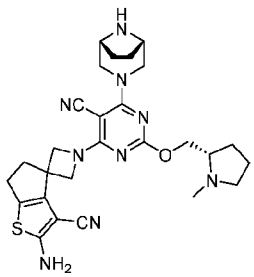
**[00801]** Compound **81** was prepared similarly to that of **Ex. 3** as a TFA salt of a mixture of diastereomers. LCMS calcld for $C_{31}H_{39}N_9O_2S$ $(M+H)^+$ m/z = 620.3, found: 602.3. $^1$H NMR (400 MHz, $CD_3OD$) δ 5.35 (d, *J* = 51.6 Hz, 1H), 4.72-4.40 (m, 5H), 4.38-4.12 (m, 4H), 3.57-3.42 (m, 6H), 3.60-3.42 (m, 7H), 3.33-3.20 (m, 4H), 2.81-2.70 (m, 4H), 0.96-0.76 (m, 4H).

**[00802]** **Compound 82**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-[[(3R)-3-methylmorpholin-4-yl]methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



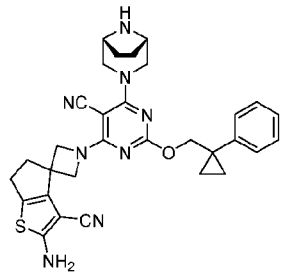
**[00803]** Compound **82** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{31}H_{40}N_9O_2S$ $(M+H)^+$ m/z = 602.3, found: 602.2. $^1$H NMR (400 MHz, $CD_3OD$) δ 4.76 – 4.39 (m, 5H), 4.38 – 4.21 (m, 3H), 4.16 (s, 2H), 4.12 – 3.77 (m, 5H), 3.67 – 3.55 (m, 1H), 3.56 – 3.44 (m, 2H), 3.49 – 3.35 (m, 2H), 3.27 – 3.09 (m, 1H), 2.81 – 2.69 (m, 4H), 2.08 (s, 3H), 2.07 – 1.98 (m, 1H), 1.49 – 1.32 (m, 3H), 1.07 – 0.67 (m, 4H).

**[00804]** **Compound 83**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



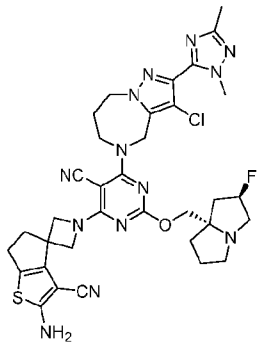
**[00805]** Compound **83** was prepared similarly to that of **Ex. 3** as a formate salt. LCMS calcld for $C_{27}H_{34}N_9OS$ (M+H)+ m/z = 532.3, found: 532.2. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.44 (s, 2H), 4.68 – 4.41 (m, 7H), 4.06 (s, 2H), 3.68 – 3.53 (m, 2H), 3.52 – 3.41 (m, 2H), 3.15 – 3.01 (m, 1H), 2.92 (s, 3H), 2.81 – 2.70 (m, 4H), 2.37 – 2.24 (m, 1H), 2.15 – 1.90 (m, 7H).

**[00806]** **Compound 84**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[(1-phenylcyclopropyl)methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



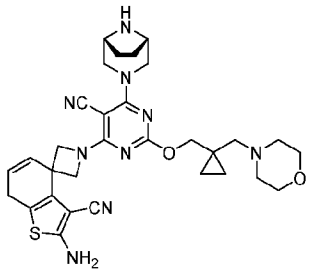
**[00807]** Compound **84** was prepared similarly to that of **Ex. 3.** LCMS calcld for $C_{31}H_{33}N_8OS(M+H)^+$ m/z =565.2 , found:565.2. $^1$H NMR (400 MHz, $CD_3OD$) δ 7.35 (d, $J$ = 7.3 Hz, 2H), 7.25 (t, $J$ = 7.5 Hz, 2H), 7.15 (t, $J$ = 7.2 Hz, 1H), 4.66 – 4.47 (m, 2H), 4.47 – 4.37 (m, 3H), 4.36 – 4.09 (m, 3H), 3.56 (s, 2H), 3.23 (m, 2H), 2.79 – 2.65 (m, 4H), 1.89 – 1.73 (m, 4H), 1.05 – 0.87 (m, 4H).

**[00808]** **Compound 85**. 2-amino-1'-[6-[3-chloro-2-(2,5-dimethyl-1,2,4-triazol-3-yl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



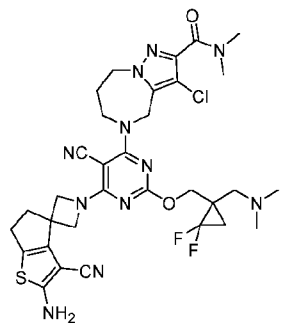
**[00809]** Compound **85** was prepared similarly to that of **Ex. 2** as a TFA salt. LCMS calculated for $C_{34}H_{38}ClFN_{13}OS$ $(M+H)^+$ m/z =730.3, found: 730.2. $^1$H NMR (400 MHz, $CD_3OD$) δ 5.55 (d, $J$ = 51.6 Hz, 1H), 5.17-4.98 (m, 2H), 4.70-4.17 (m, 10H), 3.99 (s, 3H), 3.98-3.79 (m, 3H), 3.51-3.35 (m, 1H), 2.82-2.44 (m, 6H), 2.40-2.22 (m, 8H), 2.17-2.04 (m, 1H).

**[00810]** **Compound 86**. 2-amino-1'-[5-cyano-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[7H-benzothiophene-4,3'-azetidine]-3-carbonitrile



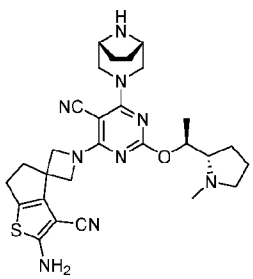
**[00811]** Compound **86** was prepared similarly to that of **Ex. 3.** LCMS calculated for $C_{31}H_{38}N_9O_2S$ $(M+H)^+$ m/z =600.3, found: 600.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ: 6.18-5.98 ( m, 2H), 4.84-4.77 (m, 1H), 4.60-4.57 (m, 1H), 4.49-4.40 (m, 1H), 4.24-4.18 (m, 2H), 4.17-4.12 (m, 1H), 3.66-3.57 (m, 8H), 3.27- 3.18 (m, 4H), 2.47-2.37 (m, 6H), 1.87- 1.80 (m, 4H), 0.65- 0.61 (m, 2H), 0.46- 0.43 (m, 2H).

**[00812]** **Compound 87**. 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[1-[(dimethylamino)methyl]-2,2-difluoro-cyclopropyl]methoxy]pyrimidin-4-yl]-3-chloro-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



**[00813]** Compound **87** was prepared similarly to that of **Ex. 2.** LCMS calculated for $C_{32}H_{37}ClF_2N_{11}O_2S$ $(M+H)^+$ m/z =712.2; found:712.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.08 (s, 2H), 4.58 (s, 2H), 4.45 – 4.49 (m, 2H), 4.42 (s, 2H), 4.19 (s, 2H), 3.08 (d, $J$ = 2.8 Hz, 6H), 2.69 – 2.79 (m, 4H), 2.45 (s, 1H), 2.28 (s, 7H), 1.60 (s, 2H), 1.26 – 1.38 (m, 5H), 0.86 – 0.99 (m, 1H).

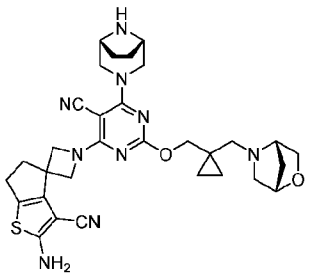
**[00814]** **Compound 88**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[(1S)-1-[(2S)-1-methylpyrrolidin-2-yl]ethoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00815]** Compound **88** was prepared similarly to that of **Ex. 3** as a formate salt**.** LCMS calcld for $C_{28}H_{36}N_9OS$ $(M+H)^+$ m/z = 546.3, found: 546.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.46 (s,

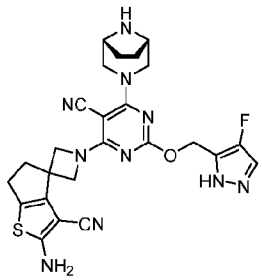
2H), 5.26 – 5.14 (m, 1H), 4.69 – 4.34 (m, 5H), 4.01 (s, 2H), 3.58 – 3.40 (m, 4H), 3.14 – 3.02 (m, 1H), 2.95 (s, 3H), 2.83 – 2.69 (m, 4H), 2.37 – 2.24 (m, 1H), 2.16 – 2.07 (m, 1H), 2.06 – 1.96 (m, 6H), 1.92 – 1.82 (m, 1H), 1.41 (d, $J$ = 6.1 Hz, 3H).

**[00816]** **Compound 89**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-[[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



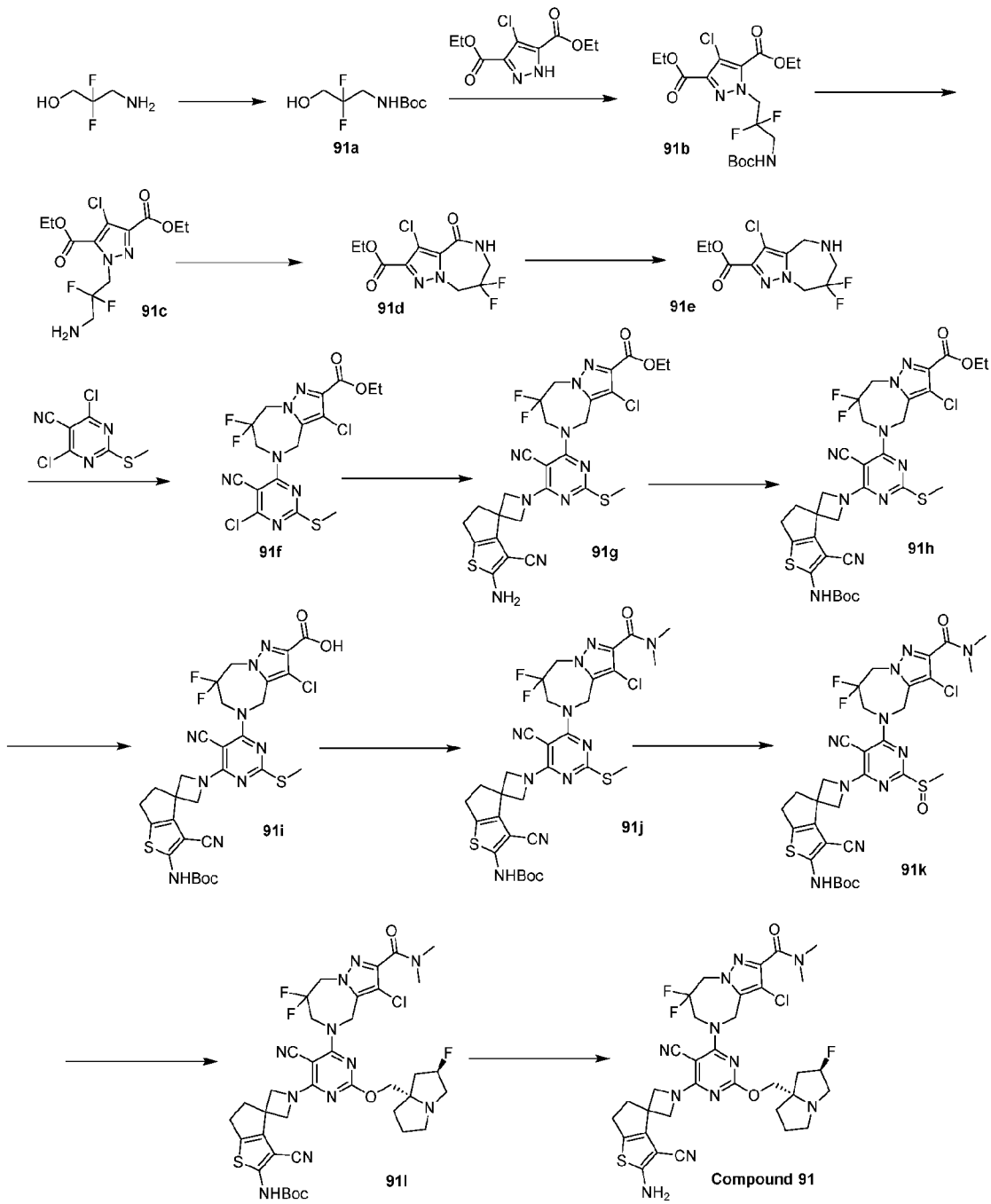
**[00817]** Compound **89** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{31}H_{38}N_9O_2S$ $(M+H)^+$ m/z = 600.3, found: 600.3. $^1$H NMR (400 MHz, $CD_3OD$) δ 5.05 – 4.88 (m, 2H), 4.74 – 4.44 (m, 6H), 4.40 – 4.07 (m, 5H), 4.01 – 3.75 (m, 2H), 3.67 – 3.41 (m, 3H), 3.22 – 2.94 (m, 2H), 2.85 – 2.62 (m, 4H), 2.32 – 1.98 (m, 6H), 1.10 – 0.74 (m, 4H).

**[00818]** **Compound 90**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[(4-fluoro-1H-pyrazol-5-yl)methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00819]** Compound **90** was prepared similarly to that of **Ex. 3**. LCMS calcld for $C_{25}H_{26}FN_{10}OS$ $(M+H)^+$ m/z = 533.2, found: 533.3. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.46 (d, $J$ = 4.6 Hz, 1H), 4.67 (s, 2H), 4.66 – 4.60 (m, 2H), 4.59 – 4.26 (m, 4H), 3.63 – 3.53 (m, 2H), 3.39 – 3.32 (m, 2H), 2.89 – 2.65 (m, 4H), 1.87 – 1.74 (m, 4H).

**[00820]** **Example 7.** preparation of 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-7,7-difluoro-N,N-dimethyl-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide TFA salt **Compound 91**.




**[00821]** Step 1. Preparation of tert-butyl N-(2,2-difluoro-3-hydroxy-propyl)carbamate (**91a**)

**[00822]** To a solution of 3-amino-2,2-difluoro-propan-1-ol (2 g, 18 mmol) in THF (20 mL) and water (20 mL), was added $Boc_2O$ (3.93 g, 18 mmol), and the reaction mixture was stirred at 25 °C for 16 h. The mixture was evaporated under reduced pressure to give crude product, and then the mixture was extracted by EtOAc (10 ml x3), washed by brine (10 ml x 2), dried over $Na_2SO_4$, concentrated. The crude product was washed with hexane to afford tert-butyl N-(2,2-difluoro-3-hydroxy-propyl)carbamate (3.10 g, 14.7 mmol, 81.53%) yield as white solid.

**[00823]** Step 2. Preparation of diethyl 1-[3-(tert-butoxycarbonylamino)-2,2-difluoro-propyl]-4-chloro-pyrazole-3,5-dicarboxylate (**91b**)

**[00824]** To a solution of diethyl 4-chloro-1H-pyrazole-3,5-dicarboxylate (1 g, 4.05 mmol) and PPh3 (2.12 g, 8.11 mmol) in THF (5 mL), was added tert-butyl N-(2,2-difluoro-3-hydroxy-propyl)carbamate (**91a**, 1.71 g, 8.11 mmol) and BTBAD (1867.1 mg, 8.11 mmol) , and the reaction mixture was stirred at 120 °C for 1h in microwave. The mixture was concentrated to afford a crude product diethyl 1-[3-(tert-butoxycarbonylamino)-2,2-difluoro-propyl]-4-chloro-pyrazole-3,5-dicarboxylate (**91b**, 1.50 g) as a yellow oil. LCMS calcld for $C_{17}H_{25}ClF_2N_3O_6$ $(M+H)^+$ m/z = 440.1, found: 384.0 (-tBu).

**[00825]** Step 3. Preparation of diethyl 1-(3-amino-2,2-difluoro-propyl)-4-chloro-pyrazole-3,5-dicarboxylate; hydrochloride (**91c**)

**[00826]** To a solution of diethyl 1-[3-(tert-butoxycarbonylamino)-2,2-difluoro-propyl]-4-chloro-pyrazole-3,5-dicarboxylate (**91b,** 3 g, 6.82 mmol) in 1,4-dioxane (45 mL), was added HCl/dioxane (4713.42 mg, 34.1 mmol), and the reaction mixture was stirred at 25 °C for 2h. The mixture was concentrated to afford the crude product diethyl 1-(3-amino-2,2-difluoro-propyl)-4-chloro-pyrazole-3,5-dicarboxylate;hydrochloride (**91c,** 2.50 g) as a yellow solid. LCMS calcld for $C_{12}H_{17}ClF_2N_3O_4$ $(M+H)^+$ m/z = 340.1, found:340.1.

**[00827]** Step 4. Preparation of N,N-diethylethanamine; ethyl 3-chloro-7,7-difluoro-4-oxo-6,8-dihydro-5H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate; hydrochloride (**91d)**

**[00828]** To a solution of diethyl 1-(3-amino-2,2-difluoro-propyl)-4-chloro-pyrazole-3,5-dicarboxylate; hydrochloride (**91c**, 2.77 g, 7.36 mmol) in ethanol (42 mL), was added $Et_3N$ (20.54 mL, 147.18 mmol), and the reaction mixture was stirred at 70 °C for 24h. The mixture was concentrated and then purified by silica gel chromatography (eluted with $CH_3CN$ in $H_2O$ from 5.0% to 95%) to afford N,N-diethylethanamine;ethyl 3-chloro-7,7-difluoro-4-oxo-6,8-dihydro-5H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate;hydrochloride (**91d,** 1.80 g, 2.24 mmol, 30.40% yield) as a white solid. LCMS calcld for $C_{10}H_{11}ClF_2N_3O_3$ $(M+H)^+$ m/z = 294.6, found: 294.6.

**[00829]** Step 5. Preparation of ethyl 3-chloro-7,7-difluoro-4,5,6,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91e**)

**[00830]** To a solution of ethyl 3-chloro-7,7-difluoro-4-oxo-6,8-dihydro-5H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91d,** 200 mg, 0.37 mmol) in THF (5mL), was added $BH_3$ in $SMe_2$ (55.42 mg, 1.46 mmol), and the reaction mixture was stirred at 60 °C for 3h. The mixture was diluted with $CH_3OH$ (5 mL), and then the mixture was stirred at 60 °C for 3h. The crude product was not purified. Ethyl 3-chloro-7,7-difluoro-4,5,6,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91e,** 35 mg) was obtained as a colorless oil. LCMS calcld for $C_{10}H_{13}ClF_2N_3O_2(M+H)^+$ m/z = 280.1, found: 280.1.

**[00831]** Step 6. Preparation of ethyl 3-chloro-5-(6-chloro-5-cyano-2-methylsulfanyl-pyrimidin-4-yl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91f**)

**[00832]** To a solution of ethyl 3-chloro-7,7-difluoro-4,5,6,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylate (200 mg, 0.72 mmol) in THF (10 mL), was added 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carbonitrile (**91e,** 157.39 mg, 0.72 mmol) and DIEA (138.63 mg, 1.07 mmol), and the reaction mixture was stirred at 40 °C for 3h . The mixture was concentrated to afford a crude product. The crude product was purified by silica gel chromatography/flash chromatography (eluted with $CH_3CN$ in $H_2O$ from 5.0% to 95%); ethyl 3-chloro-5-(6-chloro-5-cyano-2-methylsulfanyl-pyrimidin-4-yl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91f,** 270 mg, 0.583 mmol, 81.49% yield) was obtained as white solid. LCMS calcld for $C_{16}H_{15}Cl_2F_2N_6O_2S$ $(M+H)^+$ m/z = 463.02, found: 463.02.

**[00833]** Step 7. Preparation of ethyl 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-chloro-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91g)**

**[00834]** To a solution of ethyl 3-chloro-5-(6-chloro-5-cyano-2-methylsulfanyl-pyrimidin-4-yl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91f,** 100 mg, 0.22 mmol) in 1,4-dioxane (1mL) was added DIEA (55.79 mg, 0.43 mmol) and 2-aminospiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile (44.31 mg, 0.22 mmol) at 25 °C. The mixture was stirred at 50 °C for 1 h. The mixture was concentrated, then purified by silica gel on chromatography (eluting with EtOAc in PE from 0 % to 50 %). The product ethyl 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-chloro-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91g,** 135 mg, 0.214 mmol, 98.95% yield) was obtained as a white solid. LCMS calcld for $C_{26}H_{25}ClF_2N_9O_2S_2$$(M+H)^+$ m/z = 632.1, found: 632.0.

**[00835]** Step 8. Preparation of ethyl 5-[6-[2-(tert-butoxycarbonylamino)-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-chloro-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91h)**

**[00836]** To a solution of ethyl 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-chloro-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91g,** 135 mg, 0.21 mmol) in MeCN (1 mL) was added DMAP (2.61 mg, 0.02 mmol) and $Boc_2O$ (16.21 mg, 0.43 mmol) at 25 °C , The mixture was stirred at 25 °C for 1 h. The mixture was purified by silica gel on chromatography (eluting with EtOAc in PE from 0 % to 50 %). The mixture of product ethyl 5-[6-[2-(tert-butoxycarbonylamino)-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-chloro-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate (**91h,** 145

mg, 0.198 mmol, 92.72% yield). LCMS calcld for $C_{31}H_{33}ClF_2N_9O_4S_2$ $(M+H)^+$ m/z = 732.2, found: 732.0.

**[00837]** Step 9. Preparation of 5-[6-[2-(tert-butoxycarbonylamino)-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-chloro-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**91i)**

**[00838]** To a mixture of ethyl 5-[6-[2-(tert-butoxycarbonylamino)-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-chloro-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylate

**[00839]** (**91h,** 128.2 mg, 0.16 mmol) in THF (1 mL) and Water (1 mL) was added $LiOH.H_2O$ (10.31 mg, 0.25 mmol) and the mixture was stirred at 25 °C for 1h. The mixture was acidified with HCl (1 mol/L in $H_2O$) to PH=6, extracted with EtOAc (3 x 10mL), dried over $Na_2SO_4$, concentrated. The mixture was not purified and used in the next step directly. The mixture of 5-[6-[2-(tert-butoxycarbonylamino)-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-chloro-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**91i,** 110 mg) was obtained as a white solid. LCMS calcld for $C_{29}H_{29}ClF_2N_9O_4S_2$ $(M+H)^+$ m/z = 704.1, found:704.2.

**[00840]** Step 10. Preparation of tert-butyl N-[1'-[6-[3-chloro-2-(dimethylcarbamoyl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**91j**)

**[00841]** To a solution of 5-[6-[2-(tert-butoxycarbonylamino)-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-chloro-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (**91i,** 100 mg, 0.13 mmol) in DCM (2mL) was added Dimethylamine (0.01 mL, 0.15 mmol), DIEA (19.28 mg, 0.15 mmol) and HATU (56.73 mg, 0.15 mmol) at 25 °C , The mixture was stirred at 25 °C for 1 h. The mixture was extracted DCM (3 x 10mL), dried over $Na_2SO_4$, concentrated. The mixture was purified by silica gel (eluting with $CH_3OH$ in DCM from 0% to 10%). The mixture of tert-butyl N-[1'-[6-[3-chloro-2-(dimethylcarbamoyl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**91j,** 100 mg, 0.120 mmol, 97% yield) was obtained as a white solid. LCMS calcld for $C_{31}H_{34}ClF_2N_{10}O_3S_2$ $(M+H)^+$ m/z = 731.2, found: 731.1.

**[00842]** Step 11. Preparation of tert-butyl N-[1'-[6-[3-chloro-2-(dimethylcarbamoyl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-methylsulfinyl-

pyrimidin-4-yl]-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**91k**)

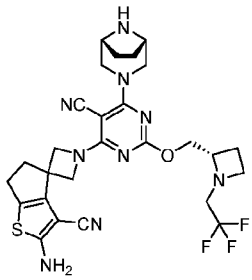
**[00843]** To a solution of tert-butyl N-[1'-[6-[3-chloro-2-(dimethylcarbamoyl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**91j,** 30 mg, 0.04 mmol) in THF (1 mL) and water (1 mL) was added oxone (18.92 mg, 0.06 mmol) at 25 °C , The mixture was stirred at 25 °C for 4 h. The mixture was extracted with EtOAc (3 ml x3), dried over $Na_2SO_4$, concentrated. The mixture was not purified and used to next step directly. Tert-butyl N-[1'-[6-[3-chloro-2-(dimethylcarbamoyl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-methylsulfinyl-pyrimidin-4-yl]-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**91k,** 30 mg) was obtained as a white solid. LCMS calcld for $C_{31}H_{34}ClF_2N_{10}O_4S_2(M+H)^+$ m/z = 747.2, found:747.1.

**[00844]** Step 12. Preparation of tert-butyl N-[1'-[6-[3-chloro-2-(dimethylcarbamoyl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**91l**)To a solution of tert-butyl N-[1'-[6-[3-chloro-2-(dimethylcarbamoyl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-methylsulfanyl-pyrimidin-4-yl]-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**91k,** 80 mg, 0.0 mmol) in THF (1mL) was added [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (6.39 mg, 0.04 mmol) at 0 °C , The mixture was added LiHDMS (0.04 mL, 0.04 mmol) at 0 °C for 1 h. The mixture was quenched with aqueous $NH_4Cl$ and extracted with EtOAc (3 x 5mL), dried over $Na_2SO_4$ and concentrated. The mixture was purified by silica gel chromatography (eluting with MeOH in DCM from 0% to 10%). The mixture of tert-butyl N-[1'-[6-[3-chloro-2-(dimethylcarbamoyl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**91l,** 85 mg, 0.101 mmol, 94% yield) was obtained as a white solid. LCMS calcld for $C_{38}H_{44}ClF_3N_{11}O_4S(M+H)^+$ m/z = 842.3, found: 842.4.

**[00845]** Step 13. Preparation of 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-7,7-difluoro-N,N-dimethyl-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide;2,2,2-trifluoroacetic acid (**Compound 91**).

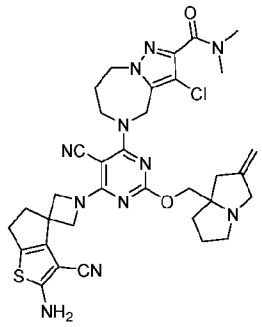
**[00846]** To a solution of tert-butyl N-[1'-[6-[3-chloro-2-(dimethylcarbamoyl)-7,7-difluoro-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5-yl]-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-2-yl]carbamate (**91l,** 65 mg, 0.08 mmol) in DCM (1 mL) was added TFA (0.2 mL, 2.61 mmol) at 25 °C , The mixture was stirred at 25 °C for 1h. The mixture was concentrated. The mixture was purified by prep-HPLC (eluting with $CH_3CN$ (0.1%) in $H_2O$ from 5% to 95%). The product of 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]-3-chloro-7,7-difluoro-N,N-dimethyl-6,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide;2,2,2-trifluoroacetic acid (**Compound 91**, 6.75 mg, 0.008 mmol, 10.19% yield) was obtained as a white solid. LCMS calcld for $C_{33}H_{36}ClF_3N_{11}O_2S(M+H)^+$ m/z = 742.2., found:742.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ: 5.57 ( d, *J*= 52 Hz, 1H), 4.95 (s, 2H), 4.88-4.67 (m, 2H), 4.82-4.82 (m, 2H), 4.75-4.69 (m, 2H),4.61-4.56 (m, 2H), 4.45 (s, 2H), 3.96-3.83 (m, 3H), 3.50-3.39 (m, 1H), 3.13-3.10 (m, 6H), 2.78- 2.69 (m, 4H), 2.68- 2.48 (m, 2H), 2.39- 2.25 (m, 3H), 2.19- 2.09 (m, 1H).

**[00847]** **Compound 92**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[(2S)-1-(2,2,2-trifluoroethyl)azetidin-2-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



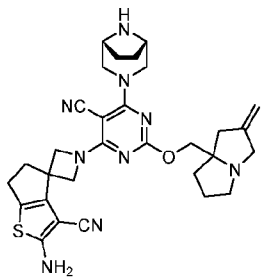
**[00848]** Compound **92** was prepared similarly to that of **Ex. 3.** LCMS calcld for $C_{27}H_{31}F_3N_9OS$ $(M+H)^+$ m/z = 586.2, found: 586.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.64 – 4.42 (m, 3H), 4.40 – 4.17 (m, 5H), 3.78 – 3.66 (m, 1H), 3.57 – 3.45 (m, 3H), 3.45 – 3.32 (m, 1H), 3.26 (m, 2H), 3.18 – 2.99 (m, 2H), 2.80 – 2.68 (m, 4H), 2.22 – 2.03 (m, 2H), 1.88 – 1.75 (m, 4H).

**[00849]** **Compound 93**. 5-[6-(2-amino-3-cyano-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[(6-methylene-2,3,5,7-tetrahydro-1H-pyrrolizin-8-yl)methoxy]pyrimidin-4-yl]-3-chloro-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



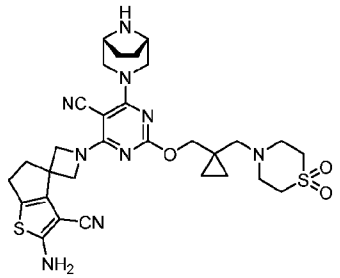
**[00850]** Compound **93** was prepared similarly to that of **Ex. 2**. LCMS calculated for $C_{34}H_{39}ClN_{11}O_2S$ $(M+H)^+$ m/z =700.3; found:700.0/702.0. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.08 (s, 2H), 4.97 (s, 3H), 4.42 – 4.67 (m, 6H), 4.16 (m, 5H), 3.71 (d, *J* = 14.8 Hz, 1H), 3.10 – 3.16 (m, 1H), 3.08 (s, 6H), 2.65 – 2.79 (m, 6H), 2.43 (d, *J* = 15.6 Hz, 1H), 2.15 – 2.28 (m, 2H), 1.73 – 2.10 (m, 5H)

**[00851]** **Compound 94**. 2-amino-1'-[5-cyano-2-[(6-methylene-2,3,5,7-tetrahydro-1H-pyrrolizin-8-yl)methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00852]** Compound **94** was prepared similarly to that of **Ex. 3**. LCMS calculated for $C_{30}H_{36}N_9OS$ $(M+H)^+$ m/z = 570.3, found: 570.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.96 (s, 2H), 4.43 (m, 6H), 4.02 – 4.11 (m, 2H), 3.65 (d, J = 14.0 Hz, 1H), 3.53 (s, 2H), 3.18 – 3.30 (m, 3H), 3.05 – 3.13 (m, 1H), 2.60 – 2.82 (m, 6H), 2.41 (d, J = 15.6 Hz, 1H), 1.72 – 2.11 (m, 8H).

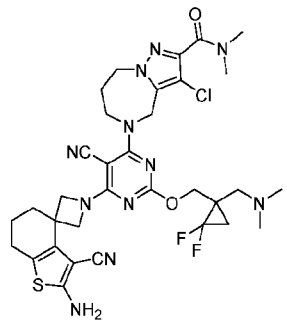
**[00853]** **Compound 95**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-[(1,1-dioxo-1,4-thiazinan-4-yl)methyl]cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00854]** Compound **95** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{30}H_{38}N_9O_3S_2$ $(M+H)^+$ m/z = 636.3, found: 636.1. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.55 - 4.15 (m,

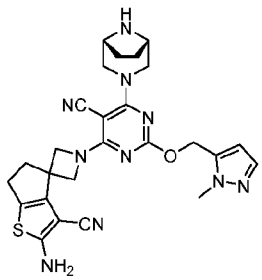
10H), 3.49 - 3.10 (m, 8H), 2.84 - 2.75 (m, 6H), 2.09 (s, 4H), 1.33 - 1.28 (d, 2H), 0.76 (s, 2H), 0.61 (s, 2H).

**[00855]** **Compound 96**. 5-[6-(2-amino-3-cyano-spiro[6,7-dihydro-5H-benzothiophene-4,3'-azetidine]-1'-yl)-5-cyano-2-[[1-[(dimethylamino)methyl]-2,2-difluoro-cyclopropyl]methoxy]pyrimidin-4-yl]-3-chloro-N,N-dimethyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide



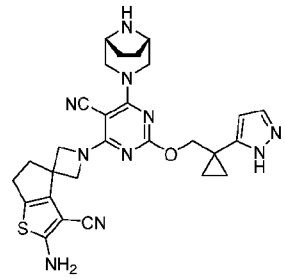
**[00856]** Compound **96** was prepared similarly to that of **Ex. 2**. LCMS calculated for $C_{33}H_{39}ClF_2N_{11}O_2S$ $(M+H)^+$ m/z =726.3, found: 726.3/728.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.11 – 5.26 (m, 1H), 5.01 (m, 1H), 4.59 (s, 6H), 4.47 (m, 4H), 4.36 (m, 1H), 3.08 (d, $J$ = 3.2 Hz, 6H), 2.75 (s, 1H), 2.49 (t, $J$ = 6.0 Hz, 2H), 2.31 – 2.41 (m, 1H), 2.20 – 2.28 (m, 8H), 2.08 – 2.14 (m, 2H), 1.76 – 1.85 (m, 2H), 1.53 – 1.62 (m, 1H), 1.27 – 1.39 (m, 2H).

**[00857]** **Compound 97**. 2-amino-1'-[5-cyano-2-[(2-methylpyrazol-3-yl)methoxy]-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



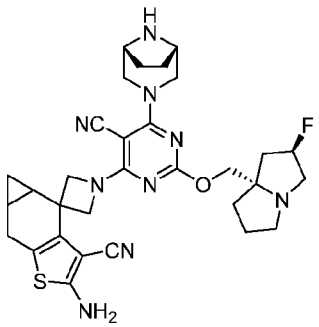
**[00858]** Compound **97** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{26}H_{29}N_{10}OS$ $(M+H)^+$ m/z = 529.2, found: 529.6. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.41 (d, $J$ = 1.8 Hz, 1H), 6.38 (d, $J$ = 1.8 Hz, 1H), 5.43 (s, 2H), 4.60 (m, 5H), 4.34 (s, 1H), 4.11 (m, 2H), 3.89 (m, 3H), 3.51 (s, 2H), 2.77 (dd, $J$ = 11.6, 8.0 Hz, 4H), 2.07 (s, 4H).

**[00859]** **Compound 98**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-(1H-pyrazol-5-yl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



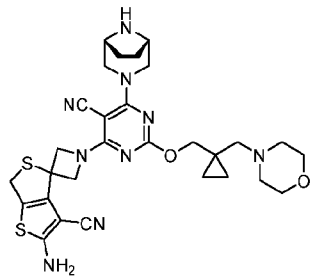
**[00860]** Compound **98** was prepared similarly to that of **Ex. 3**. LCMS calcld for $C_{28}H_{31}N_{10}OS$ $(M+H)^+$ m/z = 555.2, found: 555.6. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.47 (s, 1H), 6.18 (s, 1H), 4.39 (m, 8H), 3.55 (s, 2H), 3.25 (m, 2H), 2.79 – 2.67 (m, 4H), 1.85 – 1.72 (m, 4H), 1.05 (s, 4H).

**[00861]** **Compound 99.** 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[4a,5,5a,6-tetrahydrocyclopropa[f]benzothiophene-4,3'-azetidine]-3-carbonitrile



**[00862]** Compound **99** was prepared similarly to that of **Ex. 3** as a TFA salt using Intermediate 21. LCMS calcld for $C_{31}H_{37}FN_9OS$ $(M+H)^+$ m/z =602.3, found: 602.3. 1H NMR (400 MHz, $CD_3OD$) δ: 5.54 (d, *J*=52 Hz, 1H), 5.03-4.99 ( m, 1H), 4.75-4.28 ( m, 7H), 4.16 ( s, 2H), 3.97-3.80 ( m, 3H), 3.63-3.40 (m, 3H), 2.91-2.80 (m, 2H), 2.71-2.49 (m, 2H), 2.41-2.27 (m, 3H), 2.18-2.03 (m, 5H), 1.71-1.66 (m, 1H), 1.55-1.51 ( m, 1H), 0.80-0.74 (m, 1H), 0.19-0.16 (m, 1H).

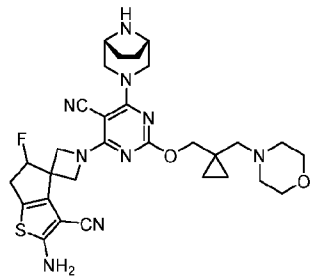
**[00863]** **Compound 100.** 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]spiro[6H-thieno[2,3-c]thiophene-4,3'-azetidine]-3-carbonitrile



**[00864]** Compound **100** was prepared similarly to that of **Ex. 3** as a formate salt using Intermediate 19.

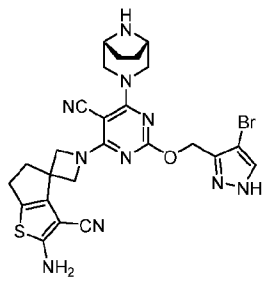
**[00865]** LCMS calcld for $C_{29}H_{36}N_9O_2S_2$ $(M+H)^+$ m/z =606.2, found: 606.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 4.84 – 4.30 (m, 6H), 4.25 (s, 2H), 4.10 (s, 2H), 4.07 (s, 2H), 3.71 (s, 4H), 3.58 – 3.38 (m, 2H), 2.66 (s, 4H), 2.56 (s, 2H), 2.06 (s, 4H), 0.69 (s, 2H), 0.53 (s, 2H).

**[00866]** **Compound 101.** 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[1-(morpholinomethyl)cyclopropyl]methoxy]pyrimidin-4-yl]-5-fluoro-spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



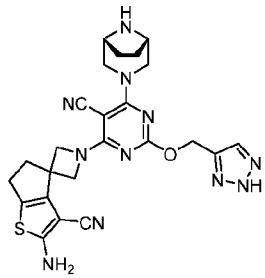
**[00867]** Compound **101** was prepared similarly to that of **Ex. 3** using Intermediate 20. LCMS calculated for $C_{30}H_{37}FN_9O_2S$ $(M+H)^+$ m/z = 606.6; found: 606.5. 1H NMR (400 MHz, $CD_3OD$) δ 5.60 (d, *J* = 52.3 Hz, 1H), 4.27 – 4.55 (m, 6H), 4.24 (s, 2H), 3.66 (m, 4H), 3.54 (s, 2H), 3.14 – 3.29 (m, 3H), 2.89 (m, 1H), 2.47 (s, 4H), 2.37 (s, 2H), 1.75 – 1.85 (m, 4H), 0.64 (m, 2H), 0.44 (m, 2H).

**[00868]** **Compound 102.** 2-amino-1'-[2-[(4-bromo-1H-pyrazol-3-yl)methoxy]-5-cyano-6-[(1S,5R)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



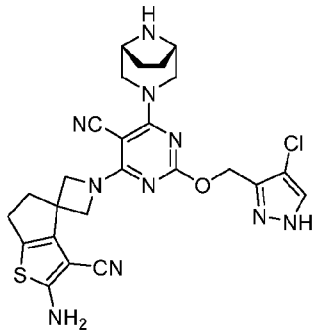
**[00869]** Compound **102** was prepared similarly to that of **Ex. 3** as a TFA and formate salt. LCMS calcld for $C_{25}H_{26}BrN_{10}OS$ $(M+H)^+$ m/z = 593.2, found: 593.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 8.53 – 8.45 (m, 1H), 7.79 – 7.60 (m, 1H), 5.34 (s, 2H), 4.74 – 4.18 (m, 6H), 4.15 – 3.98 (m, 2H), 3.60 – 3.38 (m, 2H), 2.82 – 2.69 (m, 4H), 2.03 (s, 4H).

**[00870]** **Compound 103.** 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-(2H-triazol-4-ylmethoxy)pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



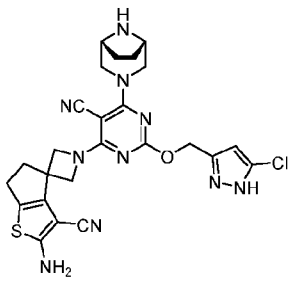
**[00871]** Compound **103** was prepared similarly to that of **Ex. 3** as a formate salt. LCMS calcld for $C_{24}H_{26}N_{11}OS$ $(M+H)^+$ m/z = 516.5, found: 516.5. $^1H$ NMR (DMSO-d6, 400 MHz) δ 8.34 (s, 2H), 7.90 (s, 1H), 7.23 (s, 2H), 5.33 (s, 2H), 4.19 (d, *J* = 12.0 Hz, 2H), 3.48 (s, 3H), 3.17 (d, *J* = 12.0 Hz, 2H), 2.68 (s, 4H), 1.62-1.56 (m, 4H).

**[00872]** **Compound 104.** 2-amino-1'-[2-[(4-chloro-1H-pyrazol-3-yl)methoxy]-5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00873]** Compound **104** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{25}H_{26}ClN_{10}OS$ $(M+H)^+$ m/z = 549.1, found: 549.2. $^1H$ NMR (400 MHz, $CD_3OD$) δ 7.68 (s, 1H), 5.35 (s, 2H), 4.76 – 4.21 (m, 6H), 4.14 (s, 2H), 3.60 – 3.38 (m, 2H), 2.82 – 2.67 (m, 4H), 2.08 (s, 4H).

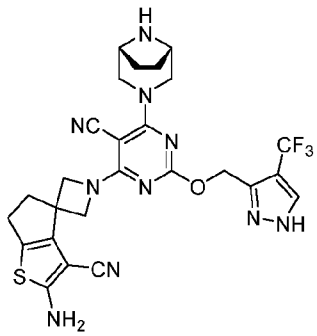
**[00874]** **Compound 105.** 2-amino-1'-[2-[(5-chloro-1H-pyrazol-3-yl)methoxy]-5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00875]** Compound **105** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{25}H_{26}ClN_{10}OS$ $(M+H)^+$ m/z = 549.2, found: 549.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 6.31 (s,

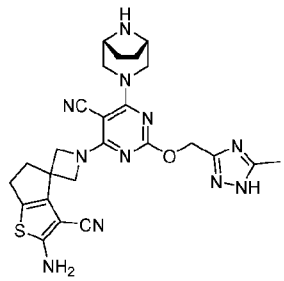
1H), 5.34 (s, 2H), 4.27 (s, 2H), 4.75-4.18 (m, 6H), 4.14 (s, 2H), 3.58-3.38 (m, 2H), 2.83-2.68 (m, 4H), 2.05 (s, 4H).

**[00876]** **Compound 106**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[4-(trifluoromethyl)-1H-pyrazol-3-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



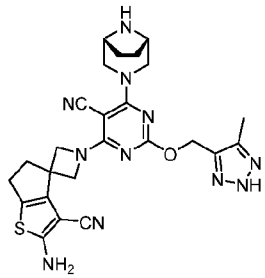
**[00877]** Compound **106** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{26}H_{26}F_3N_{10}OS$ $(M+H)^+$ m/z = 583.2, found: 583.2. $^1$H NMR (400 MHz, $CD_3OD$) δ 8.05 (s, 1H), 5.42 (s, 2H), 4.58 (s, 5H), 4.27 (s, 1H), 4.13 (s, 2H), 3.48 (s, 2H), 2.76 (dt, $J$ = 12.0, 6.8 Hz, 4H), 2.06 (s, 4H).

**[00878]** **Compound 107**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[(5-methyl-1H-1,2,4-triazol-3-yl)methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



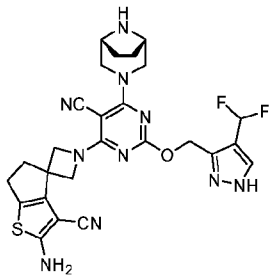
**[00879]** Compound **107** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{25}H_{28}N_{11}OS$ $(M+H)^+$ m/z = 530.3, found: 530.4. $^1$H NMR (400 MHz, $CD_3OD$) δ 5.35 (s, 2H), 4.75 – 4.18 (m, 6H), 4.17 – 4.09 (m, 2H), 3.56 – 3.42 (m, 2H), 2.85 – 2.66 (m, 4H), 2.43 (s, 3H), 2.12 – 1.97 (m, 4H).

**[00880]** **Compound 108**. 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[4-(trifluoromethyl)-1H-pyrazol-3-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



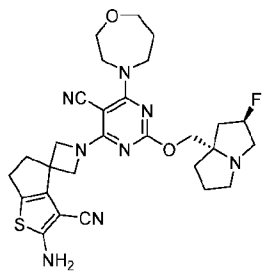
**[00881]** Compound **108** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{25}H_{28}N_{11}OS$ $(M+H)^+$ m/z = 530.6, found: 530.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.43 (s, 2H), 4.74 – 4.20 (m, 6H), 4.14 (s, 2H), 3.61 – 3.37 (m, 2H), 2.85 – 2.66 (m, 4H), 2.36 (s, 3H), 2.07 (s, 4H).

**[00882]** **Compound 109.** 2-amino-1'-[5-cyano-6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-2-[[4-(difluoromethyl)-1H-pyrazol-3-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



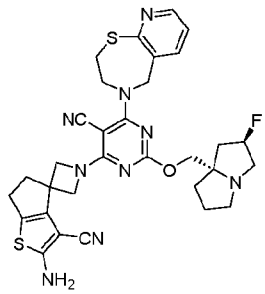
**[00883]** Compound **109** was prepared similarly to that of **Ex. 3** as a TFA salt. LCMS calcld for $C_{26}H_{27}F_2N_{10}OS$ $(M+H)^+$ m/z = 565.2, found: 565.2 .$^1H$ NMR (400 MHz, $CD_3OD$) δ 7.86 (s, 1H), 6.92 (t, $J$ = 55.9 Hz, 1H), 5.44 (s, 2H), 4.56 (s, 6H), 4.12 (s, 2H), 3.60 – 3.36 (m, 2H), 2.84 – 2.68 (m, 4H), 2.04 (s, 4H).

**[00884]** **Compound 110.** 2-amino-1'-[5-cyano-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-6-(1,4-oxazepan-4-yl)pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00885]** Compound **110** was prepared similarly to that of **Ex. 3**. LCMS calculated for $C_{28}H_{34}FN_8O_2S$ $(M+H)^+$ m/z = 565.24; found: 565.3. $^1H$ NMR (400 MHz, $CD_3OD$) δ 5.25 (d, $J$ = 53.6 Hz, 1H), 4.20 – 4.59 (m, 4H), 3.94 – 4.15 (m, 6H), 3.82 – 3.88 (m, 2H), 3.70 – 3.78 (m, 2H), 3.10 – 3.24 (m, 3H), 2.92 – 3.02 (m, 1H), 2.69 – 2.81 (m, 4H), 1.77 – 2.28 (m, 8H).

**[00886] Compound 111.** 2-amino-1'-[5-cyano-6-(3,5-dihydro-2H-pyrido[3,2-f][1,4]thiazepin-4-yl)-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrimidin-4-yl]spiro[5,6-dihydrocyclopenta[b]thiophene-4,3'-azetidine]-3-carbonitrile



**[00887]** Compound **111** was prepared similarly to that of **Ex. 3** using intermediate 22. LCMS calculated for $C_{31}H_{33}FN_9OS_2$ $(M+H)^+$ m/z =630.22; found:630.3. $^1H$ NMR (400 MHz, DMSO) δ 8.23 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.70 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.22 (s, 2H), 7.13 (dd, *J* = 7.6, 4.7 Hz, 1H), 5.21 (d, *J* = 54.4 Hz, 1H), 4.88 (s, 2H), 4.42 (s, 2H), 4.18 (tm, 3H), 3.65 (m, 2H), 3.45 (s, 2H), 3.03 (m, 2H), 2.93 (m, 1H), 2.82 – 2.74 (m, 1H), 2.66 (s, 4H), 1.98 (s, 1H), 1.94 – 1.87 (m, 1H), 1.86 – 1.75 (m, 2H), 1.68 (m, 2H).

**Example 8: Nucleotide Exchange Assay:**

**[00888]** Ras proteins cycle between an active, GTP bound state, and an inactive GDP-bound state. This activity is tightly regulated by GTPase activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs). GEFs, such as SOS1/2, activate Ras proteins by exchanging GDP for GTP, thus returning Ras to its active conformation (Simanshu, Nissley, & McCormick, 2017). Therefore, a small molecule that binds K-Ras in a manner that prevents SOS-mediated nucleotide exchange locks KRas in its inactive state. Homogenous time resolved fluorescence (HTRF) was used to detect SOS-mediated binding of a fluorescent GTP analog, GTP-DY-647P1 (Jena Biosciences NU-820-647P1) to GST-tagged KRAS-G12D (2-169, Reaction Biology, MSC-11-539) or to GST-tagged KRAS-G12V (2-169, Reaction Biology, MSC-11-540).

**[00889]** GST-tagged KRAS-G12D (2-169) and anti-GST MAb Tb Cryptate Gold (CisBio 61GSTTLB) were diluted into assay buffer (20 mM HEPES, pH 7.3, 150 mM NaCl, 5 mM MgCl2, 0.05% BSA 0.0025% NP40, 1 mM DTT) to prepare a 2.5X donor solution. 5X compound was added to the protein mixture and incubated for 1 h at RT. 2.5X acceptor solution containing SOS1cat (564-1049, Reaction Biology MSC-11-502) and GTP-DY-647P1 were then added to the donor KRAS mixture such that the final concentration of the reaction contained 5 nM GST-tagged KRAS-G12D (2-169), 20 nM SOScat, and 150 nM GTP. The reaction was monitored using at RT with the Envision multimode plate reader (Ex/Em 337/665, 620 nM) up to 90 minutes at 5 minute

intervals. To monitor KRAS-G12V Sos-mediated nucleotide exchange, 80 nM SOS was added to reaction instead of 20 nM. All other components were the same as previously described. Data was blanked to reactions without SOS1 and % inhibition was calculated such that DMSO only = 0% and blank = 100%. Curve fitting was done using a 4 parameter fit. Reported IC50 values were extracted at 30 min and 90 min for the KRAS-G12D and KRAS-G12V assays, respectively.

**[00890]** Curve fitting was done using a 4 parameter fit. NEA KRAS G12D $IC_{50}$ (uM) values of selected compounds are depicted in Table **2** with compounds having a value <0.01 uM as ++++; > 0.01 uM to 0.1 uM as +++; > 0.1 uM to 1 uM as ++; > 1 uM to 20 uM as +; and >20 uM as NA.

**Example 9: Protein Constructs for Protein-Protein Interaction:**

**Table 1**: Assay, Protein construct, and protein construct sequences

| Assay | Protein Construct | Protein Construct Sequence |
|---|---|---|
| PPI | Biotinylated Avi-KRAS-G12D (1-169) | SGLNDIFEAQKIEWHEMTEYKLVVVGADGVGKSALTIQLIQ NHFVDEYDPTIEDSYRKQVVIDGETCLLDILDTAGQEEYSA MRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDS EDVPMVLVGNKCDLPSRTVDTKQAQDLARSYGIPFIETSAK TRQGVDDAFYTLVREIRKHKEK |
| PPI | Biotinylated Avi-KRAS-G12V (1-169) | SGLNDIFEAQKIEWHEMTEYKLVVVGAVGVGKSALTIQLIQ NHFVDEYDPTIEDSYRKQVVIDGETCLLDILDTAGQEEYSA MRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDS EDVPMVLVGNKCDLPSRTVDTKQAQDLARSYGIPFIETSAK TRQGVDDAFYTLVREIRKHKEK |
| PPI | Biotinylated Avi-KRAS wt (1-169) | SGLNDIFEAQKIEWHEMTEYKLVVVGAGGVGKSALTIQLI QNHFVDEYDPTIEDSYRKQVVIDGETCLLDILDTAGQEEYSA MRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDS EDVPMVLVGNKCDLPSRTVDTKQAQDLARSYGIPFIETSAK TRQGVDDAFYTLVREIRKHKEK |
| PPI | Biotinylated Avi-NRAS (1-169) | SGLNDIFEAQKIEWHEMTEYKLVVVGAGGVGKSALTIQLI QNHFVDEYDPTIEDSYRKQVVIDGETCLLDILDTAGQEEYSA MRDQYMRTGEGFLCVFAINNSKSFADINLYREQIKRVKDS DDVPMVLVGNKCDLPTRTVDTKQAHELAKSYGIPFIETSAK TRQGVEDAFYTLVREIRQYRMK |
| PPI | His8-RAF1 RBD (52-131) | SHHHHHHHHSKTSNTIRVFLPNKQRTVVNVRNGMSLHDC LMKALKVRGLQPECCAVFRLLHEHKGKKARLDWNTDAASL IGEELQVDFL |

**Example 10.** Recombinant Protein Production:

**[00891]** Biotinylated KRAS wt and KRAS G12D/V proteins were expressed and purified in conditions similar to those previously reported (Tran, et al., 2021) (Zhang, et al., 2020). Briefly, KRAS (1-169) proteins were expressed in E. coli at 18°C with an upstream TEV cleavage site (ENLFYQS) followed an Avi tag sequence (GLNDIFEAQKIEWHE). KRAS expression

constructs contained both a His6 and maltose-binding protein (MBP) tags at the N-terminus for Ni-NTA column purification prior to overnight TEV cleavage and MBP column purification. The avi-tagged NRAS expression construct contained both a His6 tag and SUMO cleavage sige at the N-terminus for Ni-NTA column purification followed by His-ULP1 digestion overnight. All avi-tagged RAS proteins were dialyzed into buffer containing ATP, biotin, and BirA followed by purification over a second Ni-NTA column and then run over a size exclusion HiLoad™ 26/600 Superdex™ column in 20 mM HEPES, pH 7.5, 300 mM NaCl, 5 mM $MgCl_2$, and 1 mM TCEP. Fractions containing the protein of interest were pooled, concentrated, and confirmed by intact mass spectrometry. To prepare 'GTP' loaded KRAS and NRAS, biotinylated KRAS or NRAS was nucleotide exchanged from GDP-bound protein to GppNHp-bound (Jena Biosciences, NU-401-50) protein in the presence of alkaline phosphatase and excess GppNHp as previously described and the resulting nucleotide content was confirmed by HPLC reverse phase analytical chromatography (Donohue, et al., 2019) (Tran, et al., 2021).

**[00892]** His-tagged RAF1 (52-131) was similarly expressed in E. coli at 18°C overnight with an upstream TEV cleavage site. His-tagged RAF1 expression construct contained both a His6 and MBP tags at the N-terminus for Ni-NTA column purification followed by MBP-tagged TEV digestion overnight. RAF1 protein samples were further purified over a MBP column followed by a Ni-NTA column and a second MBP column. The fractions containing the protein of interest were pooled, concentrated, and further purified over a HiLoad™ 16/600 Superdex™ 75 pg size exclusion column into 20mM HEPES, pH8.0, 200mM NaCl, 5mM TCEP.

**Example 11: Protein-Protein Interaction (PPI) Assay:**

**[00893]** When RAS proteins are in the active GTP-bound conformation, they bind the effector protein RAF1 at the N-terminus Ras-binding domain (RBD, residues 52-131) (Tran, et al., 2021). Homogenous time resolved fluorescence (HTRF) was used to monitor the interaction between wt or mutant KRAS and RAF1 or wt NRAS and RAF1. Compounds were assayed in the presence of KRAS G12D/V and RAF1 versus wt KRAS to assess activity against mutant and w.t. KRAS. Similarly, compounds were then assayed in the presence of w.t. NRAS and RAF1 to assess RAS isoform selectivity. In all assay formats, His-tagged RAF1 protein was incubated with the HTRF donor, anti-6His Tb Cryptate gold (Cisbio 61DB10RDF), and biotinylated RAS proteins were incubated with the HTRF acceptor, streptavidin-d2 (CisBio 610SADLA). The intensity of the fluorescence signal emitted is proportional to binding between the two proteins. The donor solution was prepared by mixing 16 nM His-tagged RAF1 in protein dilution buffer with 1:100 anti-6His Tb cryptate in PPI-Terbium detection buffer. 16 nM biotinylated RAS protein was diluted into protein dilution buffer (50 mM Tris-HCl pH 7.5, 150 mM NaCl, 0.1 mM

MgCl2, 1 mM TCEP, 0.005% Tween20) and mixed with 1:2000 Streptavidin-d2 diluted in PPI-Terbium detection buffer (CisBio 61DB10RDF). 50X compound in DMSO was mixed with 16 nM KRAS-acceptor solution and incubated for 30 minutes at room temperature. After compound pre-incubation with KRAS, the RAF1 donor solution was added to the KRAS-acceptor solution and incubated for 1 hour at room temperature. The fluorescence signal emitted was monitored at 665 nm and 615 nm using an Envision multimode plate reader. The HTRF ratio (665/615) was calculated and normalized to 0% inhibition in the absence of compound and 100% inhibition in the presence of untagged RAF1 protein. PPI KRAS G12D/RAF1, KRAS G12V/RAF1, w.t.KRAS/RAF1 and NRAS/RAF1 $IC_{50}$ (uM) values of selected compounds are depicted in Table **3** with compounds having a value <0.1 uM as ++++; > 0.1 uM to 1 uM as +++; > 1 uM to 10 uM as ++; > 10 uM to 100 uM as +; and >100 uM as NA.

**[00894]** Compounds described herein are active against KRAS G12 mutant and other alleles representative by PPI-G12D, PPI-G12V and PPI-w.t.KRAS potency for broad activity against mutant KRAS and wtKRAS amplification driven malignancies. Compounds described herein are selective for the KRAS isoform representative by lack of activity in the PPI-NRAS assay.

**Example 12.** pERK Inhibition cellular HTRF assay in AGS Cell Lines (Method A)

**[00895]** The Phospho-ERK cellular HTRF assay measures ERK protein phosphorylated at Thr202/Tyr204 as a readout of MAPK pathway activation (Cisbio 64ERKPEH). AGS cells (ATCC CRL-1739) are cultured in the complete medium containing 10% fetal bovine serum and 1x Penicillin/Streptomycin at 37°C in a humid atmosphere of 5% $CO_2$ in the air (AGS cells: RPMI 1640 medium).

**[00896]** On day 1, the cells are plated in tissue-culture treated 96-well plates at the specified densities and allowed to attach for overnight (AGS: 30,000 cells/well). On day 2, the cells are treated with the serially diluted compound solutions in a final concentration of 0.5 % DMSO. After the treatment for the specified time (AGS cells: 3 hours), the supernatant is removed, and the cells are lysed by the lysis buffer supplied with the kit. Then, the cell lysates are treated with the detection reagents overnight at 4°C in darkness. On day 3, the fluorescence intensities at the wavelengths 665 and 620 nm are measured by the Envision plate reader (Perkin Elmer). The data are processed and fitted to a 4-parameter logistic model for $IC_{50}$ calculations (GraphPad Prism 9).

**Example 13.** pERK In Cell Western (ICW) assay (Method B)

**[00897]** pERK ICW is a high throughput screening assay to evaluate the cellular potency of mutant KRAS small molecule inhibitors. KRAS mutant cell lines AGS and GP2D ($KRAS^{G12D}$)

were purchased from ATCC and maintained respectively in RPMI and DMEM medium supplemented with 10% fetal bovine serum and Penicillin/Streptomycin.

**[00898]** Cells grown in exponential phase were trypsinized, resuspended in fresh media, and viable cells were counted using a cell counter with Trypan Blue (BioRad TC20). Cells were seeded into 384-well plate (Greiner 781091) at density of 5,000 cells/well for AGS and 10,000 cells/well for GP2D and allowed to grow overnight in a 37°C $CO_2$ incubator. The next day, compounds were dispensed into wells with a ½ log, 10-point serial dilution and top concentration of 10 μM using Tecan D300e dispenser and incubated for 3 hours in a 37 °C CO2 incubator. Cells were then fixed with paraformaldehyde (Electron Microscopy Sciences, 15710, 4% final concentration) for 30 min, permeabilized with wash buffer (1X PBS + 0.1% Triton X-100) for 30 min and blocked with Odyssey blocking buffer (Li-COR 927-70001) for 1 hour, all at room temperature (RT). Phospho-ERK antibody (CST 4370L) was diluted 1:500 in Odyssey blocking + 0.2% Tween 20 and incubated with cells overnight at 4 °C. The next day, plates were washed 5x with wash buffer, incubated with IRDye 800 CW, Goat anti-Rabbit secondary antibody (Li-COR 926-32211, 1:500) and DRAQ5 (CST 4084L, 1:5,000) diluted in in Odyssey blocking + 0.2% Tween 20 for 1 hour, washed 5x, and imaged on an Odyssey CLx imaging system.

**[00899]** For data analysis, signal intensities from 800 (phosphor-ERK) and 700 (DRAQ5) channels were extracted, and phospho-ERK signals were normalized to DRAQ5 signals for each well and percent of DMSO control values were computed. Data were then imported into Graphpad Prism to compute half-maximal inhibitory concentrations ($IC_{50}$) using a 4-parameter variable slope model. Z-factor for each plate was computed from signals derived from wells treated with either DMSO or 5 μM of Trametinib. AGS pERK ICW (Method B) $IC_{50}$ (uM) values of selected compounds are depicted in Table **2** with compounds having a value 0.001 uM to 0.01 uM as ++++; > 0.01 uM to 0.1 uM as +++; > 0.1 uM to 1 uM as ++; 1 uM to 10 uM as + and > 10 uM as NA.

**[00900]** **Table 2** includes NEA KRAS G12D $IC_{50}$ (uM) values (<0.01 uM as ++++; > 0.01 uM to 0.1 uM as +++; > 0.1 uM to 1 uM as ++; > 1 uM to 20 uM as +; and >20 uM as NA), PPI KRAS G12D/RAF1 $IC_{50}$ (uM) values (<0.1 uM as ++++; > 0.1 uM to 1 uM as +++; > 1 uM to 10 uM as ++; > 10 uM to 100 uM as +; and >100 uM as NA), AGS pERK HTRF (Method A) $IC_{50}$ (uM) values (<0.01 uM as ++++; > 0.01 uM to 0.1 uM as +++; 0.1 uM to 1 uM as ++; 1 uM to 20 uM as + and >20 uM as NA), and AGS pERK ICW (Method B) $IC_{50}$ (uM) values (0.001 uM to 0.01 uM as ++++; > 0.01 uM to 0.1 uM as +++; > 0.1 uM to 1 uM as ++; 1 uM to 10 uM as + and > 10 uM as NA) of selected compounds. ND indicates not determined.

**Table 2:** $IC_{50}$ (uM) values for various assays

| cpd# | NEA-G12D (uM) | PPI-G12D (uM) | pERK-AGS (uM) Method B |
|---|---|---|---|
| 1 | ++ | + | ND |
| 2 | ++++ | +++ | +++ |
| 3 | ++++ | + | ND |

**[00901]** **Table 3** includes KRASG12V/RAF1, wtKRAS/RAF1 and wtNRAS/RAF1 PPI $IC_{50}$ (uM) values of selected compounds; with compounds having a value <0.1 uM as ++++; 0.1 uM to 1 uM as +++; >1 uM to 10 uM as ++; >10 uM to 100 uM as +; and >100 uM as NA.

**Table 3:** $IC_{50}$ (uM) values for KRASG12V/RAF1, wtKRAS/RAF1 and wtNRAS/RAF1 PPI

| cpd# | PPI-G12V (uM) | PPI-w.t.KRAS (uM) | PPI-w.t.NRAS (uM) |
|---|---|---|---|
| 2 | ++ | ++ | NA |
| 3 | + | ND | NA |

**[00902]** **Table 4** includes NEA KRAS G12D $IC_{50}$ (uM) values (<0.01 uM as ++++; > 0.01 uM to 0.1 uM as +++; > 0.1 uM to 1 uM as ++; > 1 uM to 20 uM as +; and >20 uM as NA), PPI KRAS G12D/RAF1 $IC_{50}$ (uM) values (<0.1 uM as ++++; > 0.1 uM to 1 uM as +++; > 1 uM to 10 uM as ++; > 10 uM to 100 uM as +; and >100 uM as NA), AGS and GP2D pERK ICW $IC_{50}$ (uM) values (0.001 uM to 0.01 uM as ++++; > 0.01 uM to 0.1 uM as +++; > 0.1 uM to 1 uM as ++; 1 uM to 10 uM as + and > 10 uM as NA) of selected compounds. ND indicates not determined.

**Table 4:**

| # | NEA G12D | PPI G12D | ICW-AGS | ICW-GP2D |
|---|---|---|---|---|
| 1 | ++ | + | ND | ND |
| 2 | ++++ | +++ | +++ | ++++ |
| 3 | ++++ | ++ | +++ | ++++ |
| 4 | ++++ | ++++ | ++++ | ++++ |
| 5 | ++++ | ++ | +++ | ++++ |
| 6 | ++ | + | ND | ND |
| 7 | ++++ | +++ | + | ++ |
| 8 | ++++ | ++ | +++ | ++++ |
| 9 | ++++ | ++ | ++ | +++ |
| 10 | ++++ | ++ | +++ | +++ |
| 11 | ++++ | +++ | + | + |
| 12 | ++++ | +++ | + | + |
| 13 | ++++ | ++ | +++ | ++++ |
| 14 | ++++ | +++ | +++ | ++++ |
| 15 | ++++ | +++ | +++ | +++ |
| 16 | ++++ | + | ++ | ++ |
| 17 | ++++ | ++ | ++ | +++ |

| | | | | |
|---|---|---|---|---|
| 18 | ++++ | +++ | ++ | +++ |
| 19 | +++ | ++ | + | ++ |
| 20 | ++++ | ++ | ND | ND |
| 21 | ++++ | ++ | ++ | +++ |
| 22 | ++++ | +++ | +++ | +++ |
| 23 | ++++ | ++ | ++ | +++ |
| 24 | +++ | + | ++ | ++ |
| 25 | ++++ | +++ | +++ | ++++ |
| 26 | ++++ | + | + | ++ |
| 27 | +++ | ++ | ND | ++ |
| 28 | +++ | +++ | ND | ND |
| 29 | +++ | + | + | ++ |
| 30 | ++++ | + | ++ | +++ |
| 31 | +++ | ++ | ND | ND |
| 32 | ++++ | + | ++ | +++ |
| 33 | +++ | ++ | + | ++ |
| 34 | ++++ | +++ | +++ | ++++ |
| 35 | + | NA | ND | ND |
| 36 | + | NA | ND | ND |
| 37 | NA | NA | ND | ND |
| 38 | +++ | ++ | ND | ND |
| 39 | ++ | NA | ND | ND |
| 40 | +++ | ++ | ND | ++ |
| 41 | ++++ | +++ | +++ | ++++ |
| 42 | ++++ | ++ | ++ | ++ |
| 43 | +++ | ++ | ND | ++ |
| 44 | + | NA | ND | ND |
| 45 | ++++ | +++ | +++ | ++++ |
| 46 | ++++ | ++ | ++ | +++ |
| 47 | ++++ | + | ++ | +++ |
| 48 | +++ | + | + | ++ |
| 49 | +++ | + | ND | ++ |
| 50 | + | NA | ND | ND |
| 51 | +++ | ++ | ND | ND |
| 52 | ++++ | +++ | ++ | ++++ |
| 53 | ++ | NA | ND | ND |
| 54 | ++ | +++ | ND | ND |
| 55 | ++ | + | ND | ND |
| 56 | ++++ | +++ | ND | ND |
| 57 | + | + | ND | ND |
| 58 | ++++ | ++ | ND | ND |
| 59 | ++ | + | ND | ND |
| 60 | ++++ | ++ | ND | ND |
| 61 | +++ | +++ | ND | ND |
| 62 | ++++ | + | +++ | +++ |

| | | | | |
|---|---|---|---|---|
| 63 | +++ | + | ND | ND |
| 64 | ++++ | ++ | ND | ND |
| 65 | + | + | ND | ND |
| 66 | ++ | + | ND | ND |
| 67 | ++ | + | ND | ND |
| 68 | ++++ | ++ | ND | ND |
| 69 | ++++ | +++ | +++ | ++++ |
| 70 | ++++ | +++ | +++ | +++ |
| 71 | ++++ | ++ | ND | ++ |
| 72 | ++++ | +++ | ND | ND |
| 73 | ++++ | +++ | ND | ++++ |
| 74 | +++ | + | ND | + |
| 74.1 | ++++ | ++++ | ++++ | ++++ |
| 74.2 | +++ | + | ND | + |
| 75 | ++++ | +++ | ND | +++ |
| 76 | ++++ | +++ | ND | +++ |
| 77 | ++++ | + | ND | ND |
| 78 | +++ | NA | ND | ND |
| 79 | ++++ | +++ | +++ | +++ |
| 80 | ++++ | +++ | +++ | ++++ |
| 81 | ++++ | ++ | ++ | +++ |
| 82 | ++ | + | ND | ND |
| 83 | ++++ | +++ | ND | ND |
| 84 | ++++ | +++ | ND | ND |
| 85 | ++++ | + | ++ | +++ |
| 86 | ++++ | ++++ | +++ | ++++ |
| 87 | ++++ | ++ | +++ | ++++ |
| 88 | +++ | + | + | + |
| 89 | ++++ | +++ | +++ | +++ |
| 90 | +++ | + | ND | ND |
| 91 | ++++ | +++ | +++ | +++ |
| 92 | +++ | + | ND | + |
| 93 | ++++ | +++ | ND | ++++ |
| 94 | ++++ | ++++ | ND | ++++ |
| 95 | ++++ | ++ | ND | ND |
| 96 | ++++ | ++ | ND | +++ |
| 97 | ++++ | + | ND | ++ |
| 98 | ++++ | ++ | ND | + |
| 99 | ++++ | +++ | ND | ++++ |
| 100 | ++++ | ++++ | ND | ++++ |
| 101 | ++++ | +++ | ND | ++++ |
| 102 | ++++ | + | ND | ND |
| 103 | +++ | + | ND | ND |
| 104 | ++++ | + | ND | ND |
| 105 | ++++ | + | ND | ND |

| | | | | |
|---|---|---|---|---|
| 106 | +++ | + | ND | ND |
| 107 | +++ | + | ND | ND |
| 108 | +++ | + | ND | + |
| 109 | +++ | ND | ND | ND |
| 110 | +++ | ND | ND | ND |
| 111 | +++ | ND | ND | ND |

**[00903] Example 14: Synergistic effect using Compounds and Inhibitors in various KRAS cell lines**

**[00904]** GP2D cells were purchased from Sigma Aldrich. All other cell lines were purchased from ATCC. All cells were cultured in appropriate culture medium supplemented with 10% FBS in a humidified $CO_2$ incubator at 37 °C.

**[00905]** For in vitro assay studies, cells grown at exponential phase were trypsinized, fully resuspended in complete medium, and cell density/viability were determined using a Bio-Rad T20 automated cell counter. Cells were diluted to 25,000 cells/mL and 40 mL of culture (total of 1,000 cells/well) was dispensed into 384-well white plates (Greiner 781080) using an electronic multi-channel pipette (Rainin) and let grow overnight in a 37 °C $CO_2$ incubator. The next day, a compound herein and combination partners were dispensed as a 6-point, ½ log serial dilution to achieve a 7x7 matrix using a Tecan digital dispenser (D300e) and incubated with cells in a $CO_2$ incubator for 7 days. For cetuximab combination, series dilutions of working stocks were made and added to plates manually using a multiple channel pipette. A row of wells without treatment was used as a minimal inhibition control. At the end of the incubation, plates and CTG reagent (Promega # G9243) were equilibrated at RT for 30 minutes following manufacturer's recommendation and 40 mL of CTG reagent was added to all wells. Plates were incubated on an orbital shaker for 30 min, spun at 1,000 rpm for 1 min, and luminescent signals were acquired using a ClarioStar Plus plates reader (BMG).

**[00906]** Synergy was calculated by the following method: the raw luminescent signal from each well was normalized to the average luminescent signal from blank wells (no treatment) to obtain % viable cells signal relative to blank control. Viability matrix for each combination was analyzed by SynergyFinder 3.0 (https://synergyfinder.fimm.fi/) and the ZIP synergy score was used to evaluate potency synergy.

**[00907]** **Table 5** demonstrates the observed synergy response of combinations between selected compounds and the inhibitors. Combinations having a ZIP score of greater than 8 were considered to have synergy. Combinations have a score of 8 or less, and greater than negative 10 were considered to be additive.

**[00908]** **Table 5:** Zip Synergy scores

| Cpd# | HPAC (PDAC, G12D) | | | GP2D (CRC, G12D) | | |
|---|---|---|---|---|---|---|
| | EGFRi | | SHP2i | EGFRi | | SHP2i |
| | Afatinib | Erlotinib | RMC4550 | Erlotinib | RMC4550 | RMC4550 |
| **2** | 15.7 | 15.2 | 20.5 | 12.7 | 8.5 | 9.8 |
| **3** | 13.3 | 13.6 | 20.8 | 8.9 | 3.9 | 5.7 |
| **4** | 15.1 | 5.0 | 11.1 | 12.1 | 4.2 | 14.4 |
| **14** | 17.5 | 15.5 | 20.1 | 13.3 | 8.8 | 10.9 |
| **25** | 16.5 | 10.9 | 24.4 | 10.2 | 0.6 | 8.9 |
| **74** | 16.2 | 12.7 | 23.4 | 13.0 | 5.8 | 12.1 |

**[00909]** **Example 15: In vivo combination studies**

**[00910]** The KRASG12D mutant cell line HPAC was maintained in DMEM/Ham's F12(1:1) medium supplemented with 5% fetal bovine serum, 1xITS, 40 ng/ml Hydrocortisone and 10 ng/ml EGF, and LS513 cells were maintained in vitro in RPMI 1640 medium supplemented with 10% fetal bovine serum and 1% AA. Cells were grown in 37°C incubator with 5% $CO_2$.

**[00911]** Cells in exponential growth phase were harvested and quantitated by cell counter. Cells were resuspended in PBS and 0.2 mL of cells (1e7 cells for HPAC and 5e6 cells for LS513) were mixed with Matrigel (1:1) and inoculated subcutaneously to the right flank of each mouse (NOD/SCID mice for HPAC model and BALB/c nude mice for LS513 model, all female). Animals were randomized into different groups (N=5 per group) when the mean tumor size reached 150 -200 $mm^3$ and treated with test article or cetuximab or in combination. Test article was dosed orally, twice daily, and cetuximab was dosed intraperitoneally, twice weekly. Tumor volume and animal body weight were measured twice or three times a week. TGI is calculated for each group using the formula: TGI (%) = [1-(Ti-T0)/ (Vi-V0)] ×100; Ti is the average tumor volume of a treatment group on a given day, T0 is the average tumor volume of the treatment group on the first day of treatment, Vi is the average tumor volume of the vehicle control group on the same day with Ti, and V0 is the average tumor volume of the vehicle group on the first day of treatment.

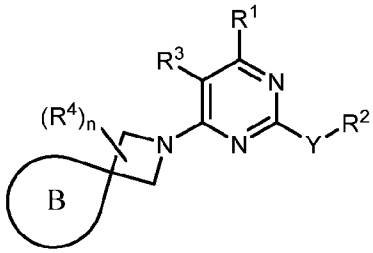
**[00912]** As shown in **FIGS. 1A-1B**, the combination treatment of compound 4 and cetuximab displays enhanced tumor growth inhibition and tumor regression, compared to single agent treatment with either cetuximab alone or compound 4 alone in both LS513, KRASG12D colorectal cancer (**FIG. 1A**), and HPAC, KRASG12D pancreatic cancer (**FIG. 1B**), xenograft models. These data support clinical combination treatment of such a compound and an EGFR inhibitor such as cetuximab in patients with various cancer types harboring KRAS G12D (e.g., tumors harboring KRAS G12D).

**[00913]** While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

## CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of an RTK-MAPK pathway inhibitor and a compound of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt thereof wherein:

B is selected from a 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle, wherein the 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle are each optionally substituted with one or more substituents independently selected from halogen, -CN, -$NO_2$, =O, -$N(R^{21})_2$, -$B(OR^{21})_2$, -$OR^{21}$, -$SR^{21}$, -$S(O)_2(R^{21})$, -$S(O)_2N(R^{21})_2$, -$NR^{21}S(O)_2R^{21}$, -$C(O)N(R^{21})_2$, -$C(O)NR^{21}OR^{21}$, -$N(R^{21})C(O)R^{21}$, -$N(R^{21})C(O)N(R^{21})_2$, -$N(R^{21})C(O)OR^{21}$, -$C(O)R^{21}$, $C(O)OR^{21}$, -$OC(O)R^{21}$, -$OC(O)N(R^{21})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

$R^1$ is selected from hydrogen and 5- to 15-membered heterocycle, wherein the 5- to 15-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -$B(OR^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$C(=NR^{20})N(R^{20})_2$, -$C_{1-6}$ alkyl$(=NOR^{20})$, -$C(O)NR^{20}OR^{20}$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$N(R^{20})_2$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, -$NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl-$SO_2R^{20}$, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle, wherein the $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, -$B(OR^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$C(O)NR^{20}OR^{20}$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$N(R^{20})_2$, -

$C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, and $C_3$-$C_{12}$ carbocycle;

Y is selected from a bond, -O-, -S-, and $-N(R^5)-$;

$R^2$ is selected from heterocycle, aryl, $C_1$-$C_6$ alkyl, -L-heterocycle, -L-$N(R^{23})_2$, -L-$OR^{23}$, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-$NHC(=NH)NH_2$, -L-$C(O)N(R^{23})_2$, -L-$C_1$-$C_6$ haloalkyl, -L-$OR^{23}$, -L-$NR^{23}C(O)$-aryl, -L-COOH, -L-$NR^{23}S(O)_2(R^{23})$, -L-$S(O)_2N(R^{23})_2$, -L-$N(R^{23})C(O)(OR^{23})$, -L-$OC(O)N(R^{23})_2$, and -L-$C(=O)OC_1$-$C_6$ alkyl, wherein the heterocycle, the heterocycle portion of -L-heterocycle, and the cycloalkyl portion of the -L-cycloalkyl are each optionally substituted with one or more $R^6$, and wherein the aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$;

$R^3$ is selected from hydrogen, halogen, -CN, $-NO_2$, $-N(R^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

each $R^4$ is independently selected from halogen, $-NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

n is selected from 0, 1, 2, 3, and 4;

each $R^5$ is independently selected from hydrogen and $C_1$-$C_6$ alkyl;

each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, $=CH_2$, =NO-$C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, $-N(R^5)S(O)_2(R^5)$, -Q-phenyl, -Q-phenyl$SO_2F$, -NHC(O)phenyl, -NHC(O)phenyl$SO_2F$, $C_1$-$C_3$ alkyl substituted pyrazolyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, $-C(O)N(R^5)_2$, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, $-C(O)N(R^5)_2$, tert-butyldimethylsilyloxy$CH_2$-, $-N(R^5)_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$ alkyl)C(=O), oxo, ($C_1$-$C_3$ haloalkyl)C(=O)-, $-SO_2F$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, $-CH_2OC(O)N(R^5)_2$, $-CH_2NHC(O)OC_1$-$C_6$ alkyl, $-CH_2NHC(O)N(R^5)_2$, $-CH_2NHC(O)C_1$-$C_6$ alkyl, $-CH_2$(pyrazolyl), $-CH_2NHSO_2C_1$-$C_6$ alkyl, $-CH_2OC(O)$heterocycle, $-OC(O)N(R^5)_2$, $-OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl), $-OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl($C_1$-$C_3$ alkyl)$N(CH_3)_2$, $-OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl, -OC(O)heterocycle, -O-$C_1$-$C_3$ alkyl, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, and -$CH_2$heterocycle, wherein the phenyl of -NHC(O)phenyl and $-OC(O)NH(C_1$-$C_3$ alkyl)($C_1$-$C_3$

alkyl)phenyl are optionally substituted with one or more substituents selected from -C(O)H and OH, and wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo and hydroxy; and wherein the heterocycle of -$CH_2$heterocyclyl is optionally substituted with oxo;

each Q is selected from a bond, S, and O;

each $R^7$ is independently selected from halogen, hydroxy, HC(=O)-, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, -$C_1$-$C_3$ alkyl-N($R^5$)$_2$, -C(O)N($R^5$)$_2$, and -N($R^5$)$_2$;

each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, hydroxy, $C_{1-6}$ alkoxy, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle, and 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-N($R^{20}$)$_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-N($R^{20}$)$_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle.

2. The method of claim 1, wherein the combination exhibits synergy.

3. The method of claims 1 or 2, wherein the therapeutically effective amount of the combination of the RTK-MAPK pathway inhibitor and the compound or salt of Formula (I) results in an increased duration of overall survival, an increased duration of progression free survival, an increase in tumor growth regression, an increase in tumor growth inhibition, an increased duration of stable disease in the subjects relative to treatment with only the compound or salt of Formula (I), or any combination thereof.

4. The method of any one of claims 1 to 3, wherein the therapeutically effective amount of the compound or salt of Formula (I) of the combination is between about 0.01 to 100 mg/kg per day.

5. The method of any one of claims 1 to 4, wherein the therapeutically effective amount of the compound or salt of Formula (I) in the combination is between about 0.1 to 50 mg/kg per day.

6. The method of any one of claims 1 to 5, wherein the therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination is between about 0.01 to 100 mg/kg per day.

7. The method of any one of claims 1 to 6, wherein the therapeutically effective amount of the RTK-MAPK pathway inhibitor of the combination is between about 0.1 to 50 mg/kg per day.

8. The method of any one of claims 1 to 7, wherein the RTK-MAPK pathway inhibitor and the compound or salt of Formula (I) are administered on different days.

9. The method of any one of claims 1 to 8, wherein the compound or salt of Formula (I) is administered at a maximum tolerated dose.

10. The method of any one of claims 1 to 9, wherein the RTK-MAPK pathway inhibitor is administered at a maximum tolerated dose.

11. The method of any one of claims 1 to 10, wherein the RTK-MAPK pathway inhibitor and the compound or salt of Formula (II) are each administered at a maximum tolerated dose.

12. The method of any one of claims 1 to 11, wherein the RTK-MAPK pathway inhibitor is a RAF-MEK-ERK pathway inhibitor.

13. The method of any one of claims 1 to 11, wherein the RTK-MAPK pathway inhibitor is a ERBB family inhibitor.

14. The method of any one of claims 1 to 13, wherein the inhibitor is selected from the group consisting of afatinib, dacomitinib, poziotinib, erlotinib, gefitinib, sapitinib, tarloxotinib, and cetuximab.

15. The method of any one of claims 1 to 14, wherein the inhibitor is cetuximab.

16. The method of any one of claims 1 to 15, wherein the RTK-MAPK pathway inhibitor is an epidermal growth factor receptor (EGFR) inhibitor.

17. The method of any one of claims 1 to 11, wherein the RTK-MAPK pathway inhibitor is a SHP-2 inhibitor.

18. The method of claim 17, wherein the SHP-2 inhibitor is SHP-099 (6-(4-Amino-4-methylpiperidin-l-yl)-3-(2,3-dichlorophenyl)pyrazin-2-amine dihydrochloride); RMC-4550 (3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazin-2-yl)methanol), RMC-4360 or TNO155 (Novartis).

19. The method of claim 17, wherein the SHP-2 inhibitor is RMC-4550.

20. The method of claim 17, wherein the SHP-2 inhibitor is RMC-4360.

21. The method of claim 17, wherein the SHP-2 inhibitor is TNO155.

22. The method of claim 17, wherein the SHP-2 inhibitor is SHP-099.

23. The method of any one of claims 1 to 11, wherein the RTK-MAPK pathway inhibitor is a SOS1 inhibitor.

24. The method of claim 23, wherein the SOS1 inhibitor is BI-3406.

25. The method of any one of claims 1 to 24, wherein the RTK-MAPK pathway inhibitor is administered orally.

26. The method of any one of claims 1 to 25, wherein the cancer is selected from:

Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma;

Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma;

Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma);

Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma);

Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma;

Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma;

Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors;

Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma);

Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma);

Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma);

Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and

Adrenal glands: neuroblastoma.

27. The method of any one of claims 1 to 26, wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer.

28. The method of any one of claims 1 to26, wherein the cancer is non-small cell lung cancer.

29. The method of any one of claims 1 to 26, wherein the cancer is small cell lung cancer.

30. The method of any one of claims 1 to 26, wherein the cancer is colorectal cancer.

31. The method of any one of claims 1 to 26, wherein the cancer is rectal cancer.

32. The method of any one of claims 1 to 26, wherein the cancer is pancreatic cancer.

33. The method of any one of claims 1 to 26, wherein the cancer is a solid tumor cancer.

34. The method of any one of claims 1 to 26, wherein the cancer is selected from a KRas mutant-associated cancer.

35. The method of any one of claims 1 to 26, wherein the cancer is selected from a KRas wildtype-associated cancer.

36. The method of any one of claims 1 to 26, wherein the cancer is selected from a KRas G12D-associated cancer, a KRas G12V-associated cancer, and a KRas wildtype-associated cancer.

37. The method of any one of claims 1 to 26, wherein the cancer is a KRas G12D-associated cancer.

38. The method of any one of claims 1 to 26, wherein the cancer is a KRas G12V-associated cancer.

39. The method of any one of claims 1 to 26, wherein the cancer is a KRas wildtype-associated cancer.

40. The method of any one of claims 1 to 38, wherein the RTK-MAPK pathway inhibitor synergistically increases the sensitivity of cancer cells to the compound or salt of Formula (I).

41. The method of any one of claims 1 to 40, wherein the compound is selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutical acceptable salt thereof.

42. The method of any one of claims 1 to 40, wherein the compound is compound 2, or a pharmaceutical acceptable salt thereof.

43. The method of any one of claims 1 to 40, wherein the compound is compound 3, or a pharmaceutical acceptable salt thereof.

44. The method of any one of claims 1 to 40, wherein the compound is compound 4, or a pharmaceutical acceptable salt thereof.

45. The method of any one of claims 1 to 40, wherein the compound is compound 14, or a pharmaceutical acceptable salt thereof.

46. The method of any one of claims 1 to 40, wherein the compound is compound 25, or a pharmaceutical acceptable salt thereof.

47. The method of any one of claims 1 to 40, wherein the compound is compound 74, or a pharmaceutical acceptable salt thereof.

48. The compound or salt of any one of claim 1 to 40, wherein B is selected from an optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle.

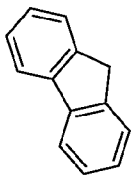
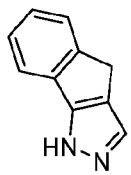
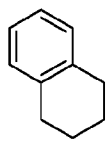
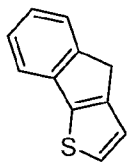
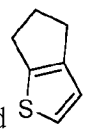
49. The compound or salt of any one of claim 1 to 40, or 48, wherein B is an optionally substituted 8- to 15-membered fused heterocycle.

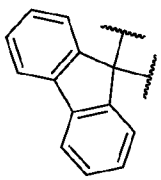
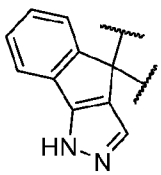
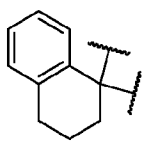
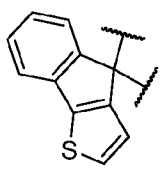
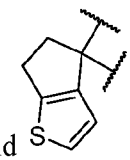
50. The compound or salt of any one of claim 1 to 40, or 48, wherein B is an optionally substituted $C_8$-$C_{15}$ fused carbocycle.

51. The compound or salt of any one of claims 1 to 40, or 48 to 50, wherein for B, the optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle are each independently bicyclic or tricyclic.

52. The compound or salt of any one of claims 1 to 40, or 48 to 51, wherein the heterocycle or carbocycle of B is bicyclic.

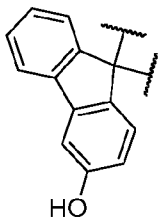
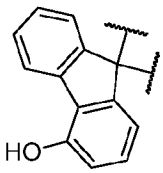
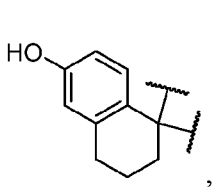
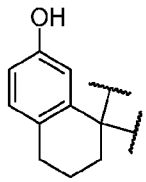
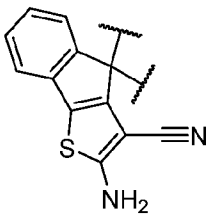
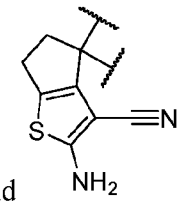
53. The compound or salt of any one of claims 1 to 40, or 48 to 51, wherein the heterocycle or carbocycle of B is tricyclic.

54. The compound or salt of any one of claims 1 to 40, or 48 to 53, wherein for B, the optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle are selected from  ,  ,  ,  , and  , each of which is optionally substituted with one or more substituents.

55. The compound or salt of claim 54, wherein for B, the optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle are selected from  ,  ,  ,  , and  each of which is optionally substituted with one or more substituents.

56. The compound or salt of any one of claim 1 to 40, or 48 to 55, wherein for B, the one or more optional substituents of the heterocycle and carbocycle are each independently selected from oxo, $-NH_2$, halogen, and $C_1$-$C_3$ alkyl.

57. The compound or salt of any one of claim 1 to 40, or 48 to 56, wherein for B, the optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$

fused carbocycle are selected from  ,  ,  ,  ,  , and  .

58. The compound or salt of any one of claims 1 to 40, or 48 to 53, wherein B is selected from an optionally substituted 5- to 15-membered heterocycle and optionally substituted $C_3$-$C_{15}$ carbocycle.

59. The compound or salt of claim 58, wherein B is selected from an optionally substituted 8- to 15-membered fused heterocycle and optionally substituted $C_8$-$C_{15}$ fused carbocycle.

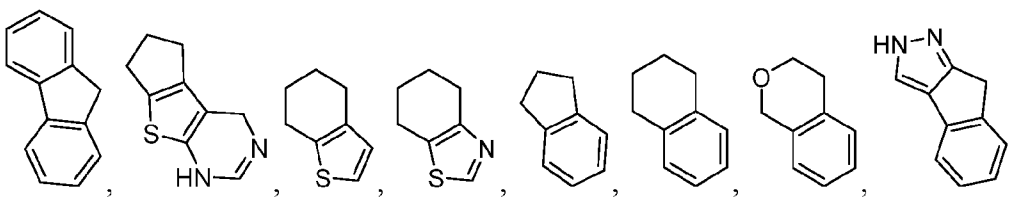
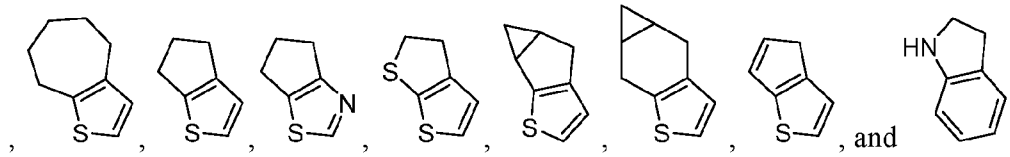
60. The compound or salt of claim 59, wherein B is an optionally substituted 8- to 15-membered fused heterocycle.

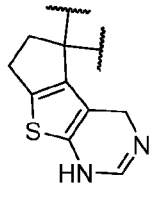
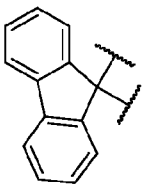
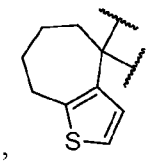
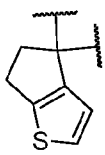
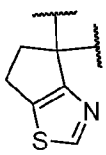
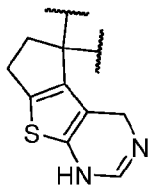
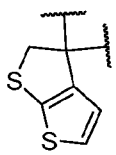
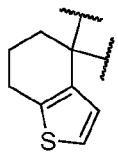
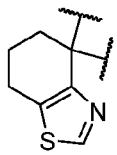
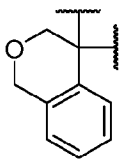
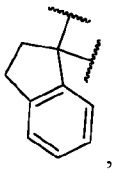
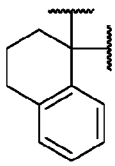
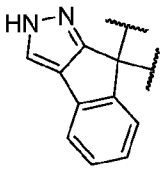
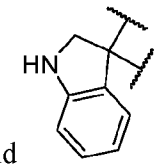
61. The compound or salt of claim 59, wherein B is an optionally substituted unsaturated $C_8$-$C_{15}$ fused carbocycle.

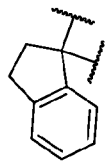
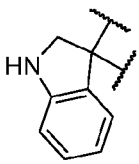
62. The compound or salt of any one of claims 1 to 40, or 58 to 61, wherein for B, the heterocycle and carbocycle are each independently bicyclic or tricyclic.

63. The compound or salt of claim 62, wherein for B, the heterocycle and carbocycle are each independently bicyclic.

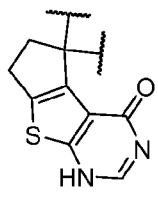
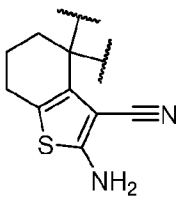
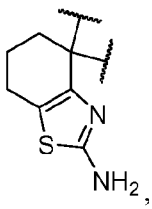
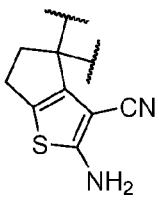
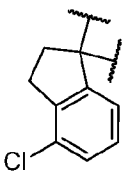
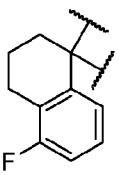
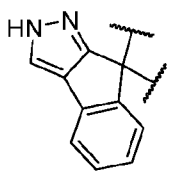
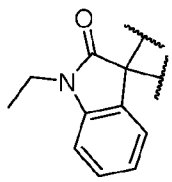
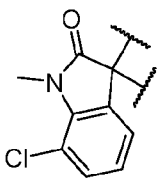
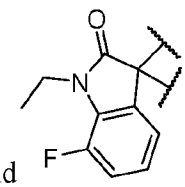
64. The compound or salt of claim 62, wherein for B, the heterocycle and carbocycle are each independently tricyclic.

65. The compound or salt of any one of claims 1 to 40, or 58 to 64, wherein B is selected from  ,  , and , each of which is optionally substituted with one or more substituents.

66. The compound or salt of claim 65, wherein B is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted with one or more substituents.

67. The compound or salt of claim 66, wherein B is selected from  , and  , each of which is optionally substituted with one or more substituents.

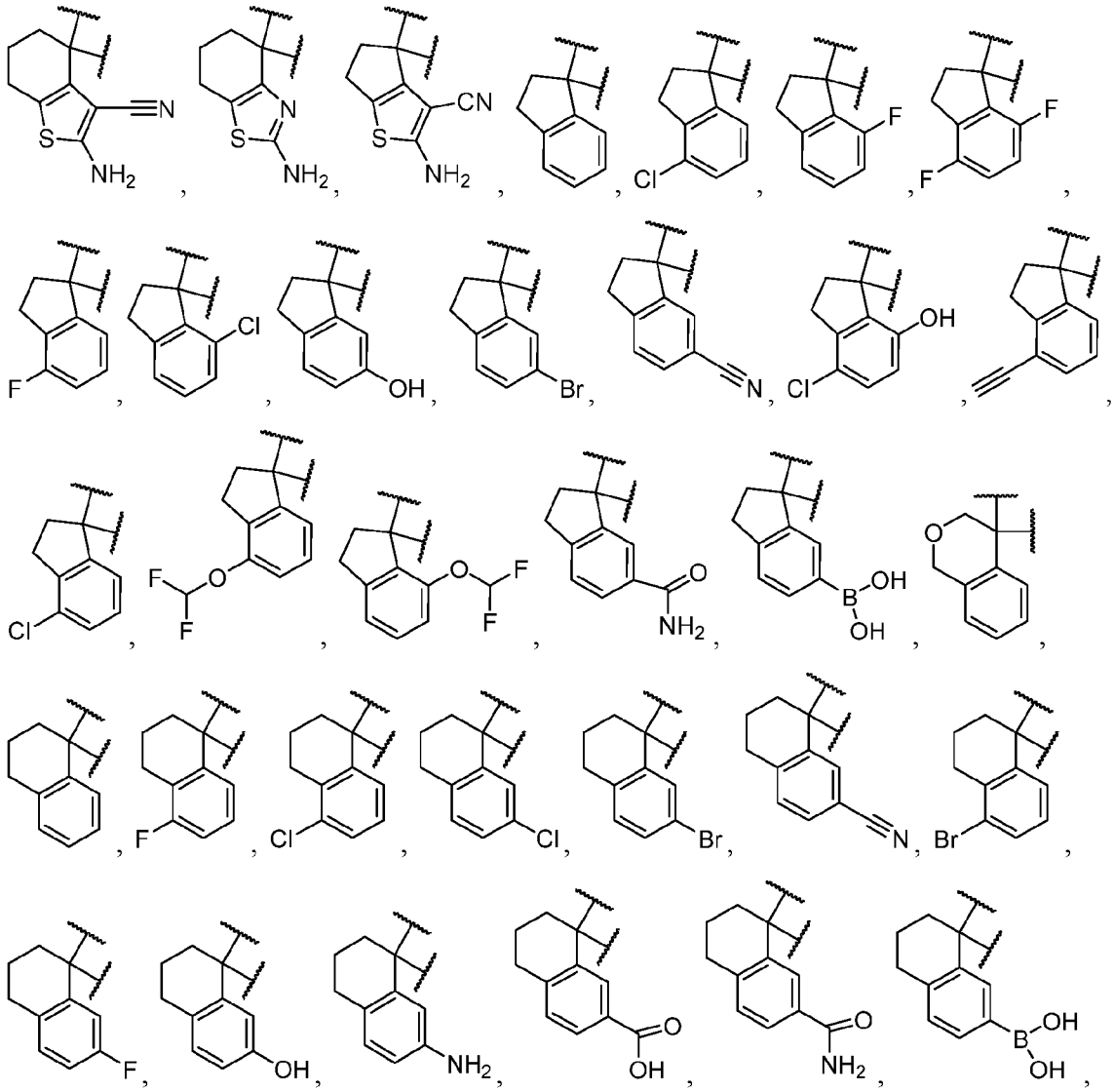
68. The compound or salt of any of claims 1 to 40, 58 to 67, wherein for B, the one or more optional substituents are independently selected from oxo, $-NH_2$, halogen, $C_1$-$C_3$ alkyl.

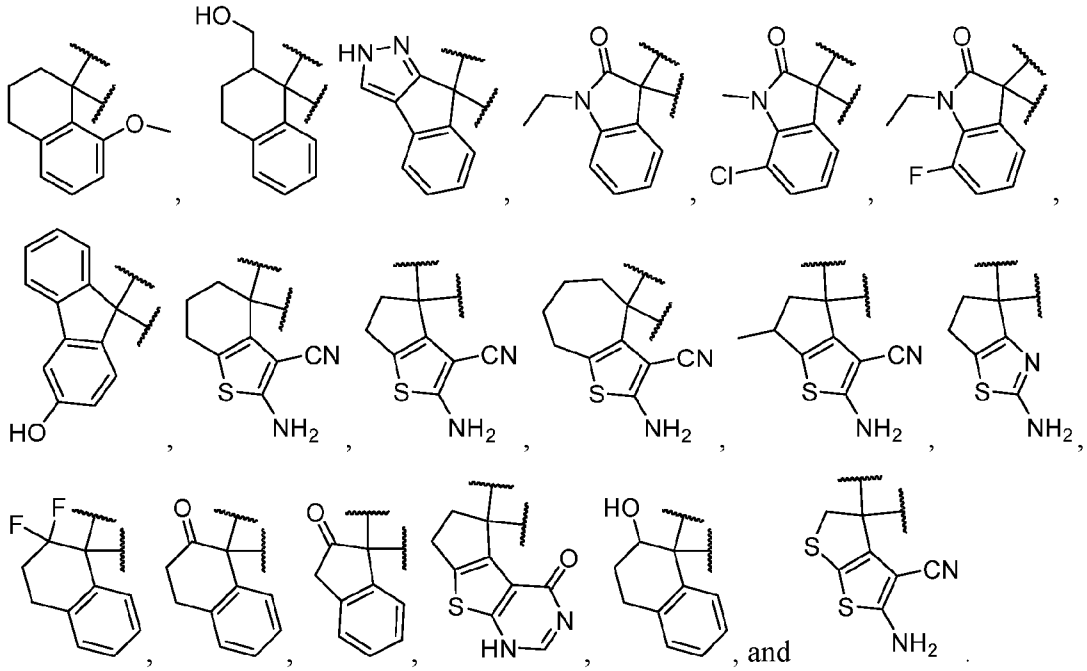
69. The compound or salt of claim 68, wherein B is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

70. The compound or salt of any of claims 1 to 40, 48 to 67, wherein for B, the one or more optional substituents of the heterocycle and carbocycle are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, -B($OR^{20}$)$_2$, -$OR^{20}$, -C(O)N($R^{20}$)$_2$, -N($R^{20}$)$_2$, =O, -CN, -NHCN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl.

71. The compound or salt of claim 70, wherein for B, the one or more optional substituents of the heterocycle and carbocycle are independently selected at each occurrence from halogen, oxo, -$NH_2$, $C_1$-$C_3$ alkyl, -B(OH)$_2$, -OH, -O-$C_1$-$C_3$ haloalkyl, -C(O)$NH_2$, -$NH_2$, =O, -CN, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{2-6}$ alkynyl.

72. The compound or salt of claims 70 or 71, wherein B is selected from





73. The compound or salt of any one of claims 1 to 40, or 48 to 53, wherein B is an optionally substituted 7- to 12-membered fused heterocycle.

74. The compound or salt of any one of claims 1 to 40, or 48 to 53, wherein B is an optionally substituted 7- to 11-membered fused heterocycle.

75. The compound or salt of claims 73 or 74, wherein B is an optionally substituted 8- to 10-membered fused heterocycle.

76. The compound or salt of claim 75, wherein B is an optionally substituted 8- to 9-membered fused heterocycle.

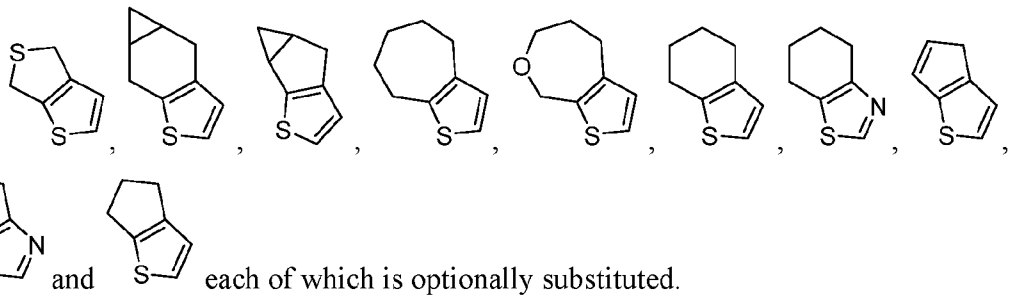
77. The compound or salt of claims 73 or 74, wherein the heterocycle is an unsaturated heterocycle.

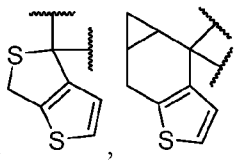
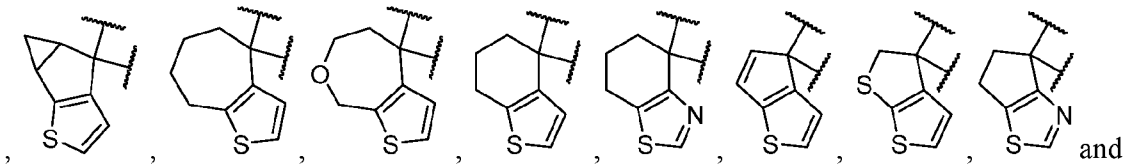
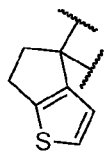
78. The compound or salt of any one of claims 1 to 40, 73 to 77, wherein B has at least one sulfur atom.

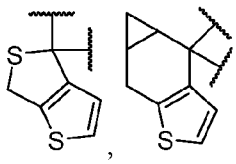
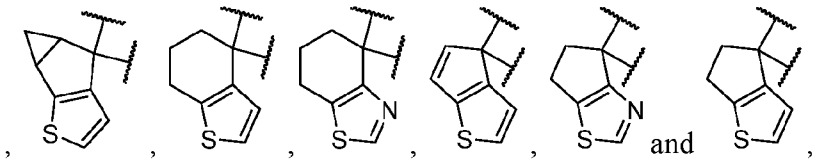
79. The compound or salt of any one of claims 1 to 40, 73 to 78, wherein B has at least one sulfur atom and at least one nitrogen atom.

80. The compound or salt of any one of claims 1 to 40, 73 to 78, wherein B has at least one sulfur atom and at least one oxygen atom.

81. The compound or salt of any one of claims 1 to 40, or 73 to 78, wherein B has at two sulfur atoms.

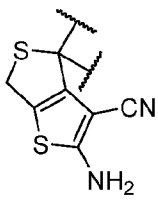
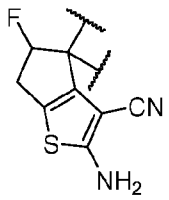
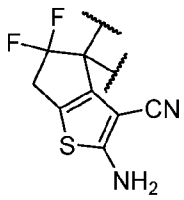
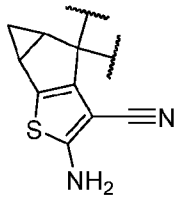
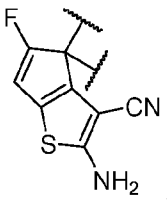
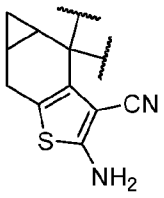
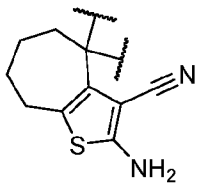
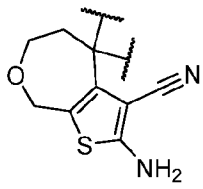
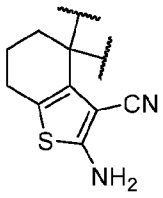
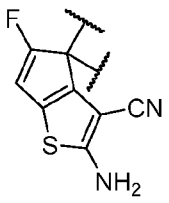
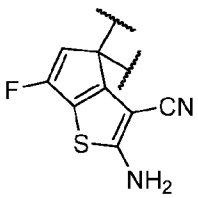
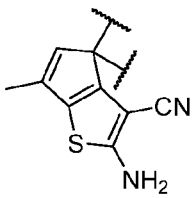
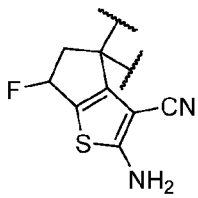
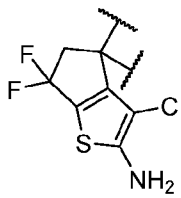
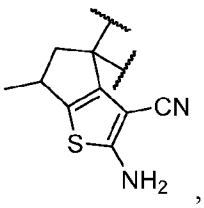
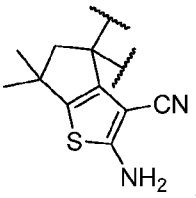
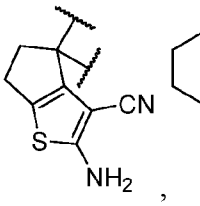
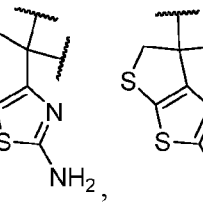
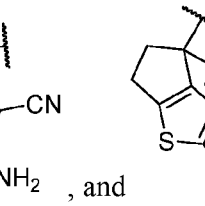
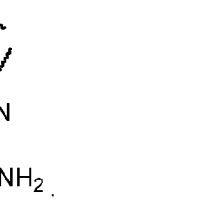
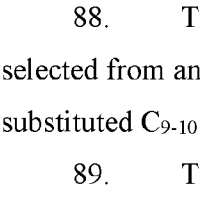
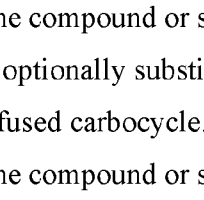
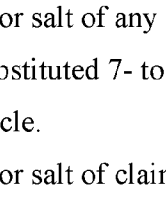
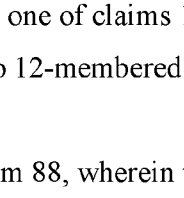
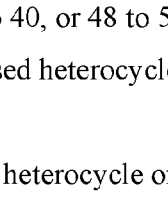
82. The compound or salt of any one of claims 1 to 40, or 73 to 81, wherein B is selected from  , each of which is optionally substituted.

83. The compound or salt of claim 82, wherein B is selected from  ,  , and  , each of which is optionally substituted.

84. The compound or salt of claim 83, wherein B is selected from  ,  , and , each of which is optionally substituted.

85. The compound or salt of any one of claims 1 to 40, or 73 to 84, wherein the one or more optional substituents of B, are independently selected at each occurrence from halogen, oxo, $-NH_2$, $C_1$-$C_3$ alkyl, $-B(OH)_2$, -OH, -O-$C_1$-$C_3$ haloalkyl, $-C(O)NH_2$, $-NH_2$, =O, -CN, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{2-6}$ alkynyl.

86. The compound or salt of claim 85, wherein the one or more optional substituents of B, are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, $-NH_2$, and -CN.

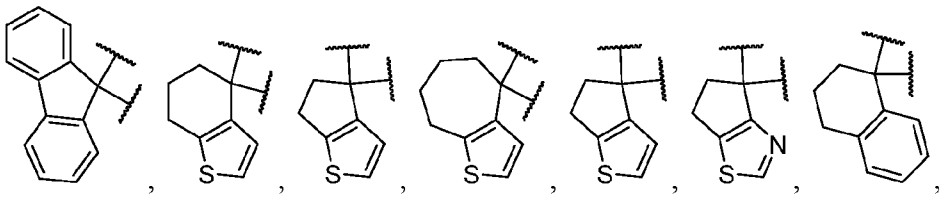
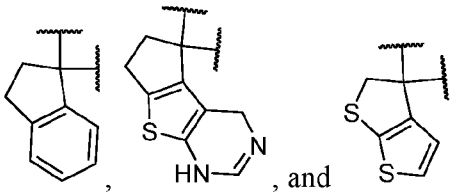
87. The compound or salt of any one of claims 1 to 40, or 73 to 83, wherein B is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

88. The compound or salt of any one of claims 1 to 40, or 48 to 53, wherein B is selected from an optionally substituted 7- to 12-membered fused heterocycle and optionally substituted $C_{9-10}$ fused carbocycle.

89. The compound or salt of claim 88, wherein the heterocycle of B has at least one sulfur atom.

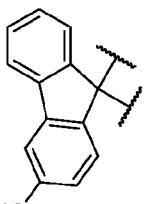
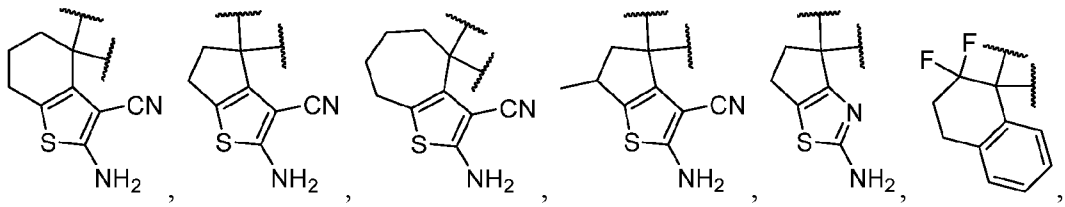
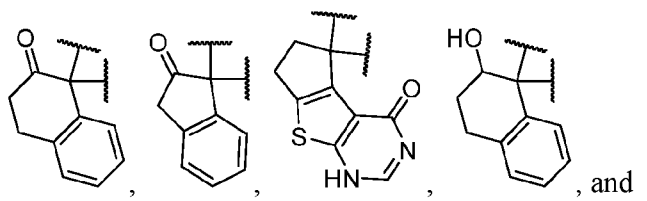
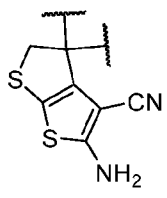
90. The compound or salt of claim 88 or 89, wherein the heterocycle of B has one or sulfur atoms.

91. The compound or salt of claim 90, wherein the heterocycle of B has at least one nitrogen atom.

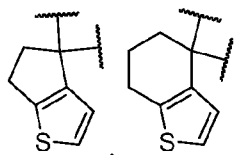
92. The compound or salt of any one of claims 1 to 40, or 88 to 91, wherein B is selected from  ,  , and , each of which is optionally substituted.

93. The compound or salt of any one of claims 1 to 40, or 88 to 92, wherein the one or more optional substituents of B are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, $-B(OR^{20})_2$, $-OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})_2$, =O, -CN, -NHCN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl.

94. The compound or salt of any one of claims 1 to 40, or 88 to 92, wherein the one or more optional substituents of B are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, -OH, $-NH_2$, =O, and -CN.

95. The compound or salt of claim 93, wherein B is selected from  ,  ,  , and  .

96. The compound or salt of any one of claims 1 to 40, or 48 to 53, wherein B is selected from an optionally substituted 8- to 10-membered fused heterocycle having at least one sulfur atom.

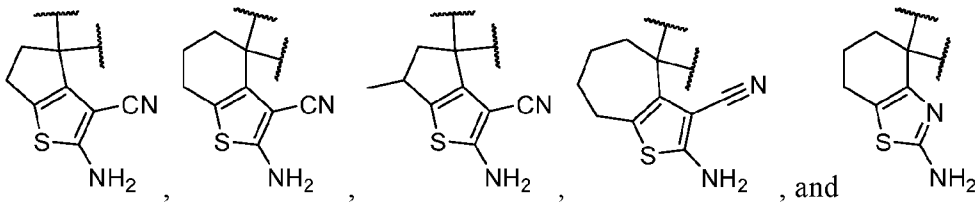
97. The compound or salt of claim 96, wherein B is selected from  , each of which is optionally substituted.

98. The compound or salt of claims 96 or 97, wherein the one or more optional substituents of B are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, -$OR^{20}$, -$C(O)N(R^{20})_2$, -$N(R^{20})_2$, =O, -CN, -NHCN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl.

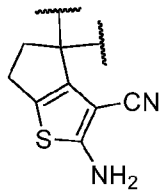
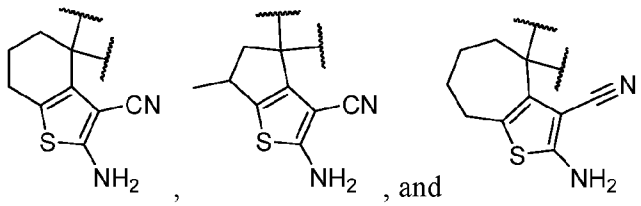
99. The compound or salt of claim 98, wherein the one or more optional substituents of B are independently selected at each occurrence from halogen, $C_1$-$C_3$ alkyl, -$NH_2$, and -CN.

100. The compound or salt of any one of claims 1 to 40, or 96 to 99, wherein B is substituted.

101. The compound or salt of any one of claims 1 to 40, or 96 to 99, wherein B is substituted with at least one -$NH_2$.

102. The compound or salt of any one of claims 1 to 40, or 96 to 101, wherein B is selected from  .

103. The compound or salt of any one of claims 1 to 40, or 96 to 101, wherein B is substituted with at least one -$NH_2$ at least one -CN.

104. The compound or salt of claim 103, wherein B is selected from  ,  .

105. The compound or salt of any one of claims 1 to 40, or 48 to 104, wherein $R^3$ is selected from hydrogen, halogen, -CN, -$C(O)R^{22}$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

106. The compound or salt of claim 105, wherein $R^3$ is selected from hydrogen, fluorine, -CN, -C(O)H, $C_1$ hydroxyalkyl, and $C_{1-6}$ alkyl.

107. The compound or salt of claims 105 or 106, wherein $R^3$ is selected from hydrogen, fluorine, and -CN.

108. The compound or salt of claim 107, wherein $R^3$ is selected from fluorine.

109. The compound or salt of claim 107, wherein $R^3$ is selected from hydrogen.

110. The compound or salt of claim 107, wherein $R^3$ is selected from -CN.

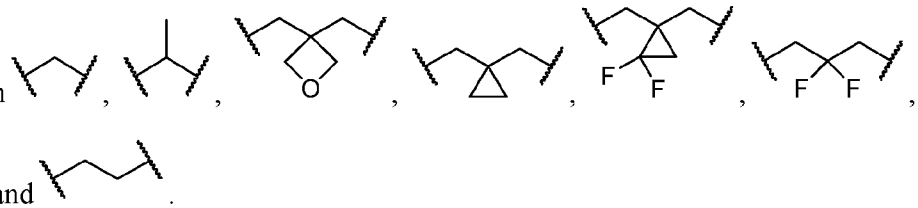
111. The compound or salt of any one of claims 1 to 40, or 48 to 110, wherein Y is -O-.

112. The compound or salt of any one of claims 1 to 40, or 48 to 111, wherein L is selected from $C_1$-$C_4$ alkylene.

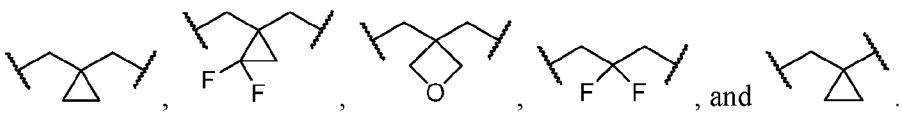
113. The compound or salt of claim 112, wherein L is selected from unsubstituted $C_1$-$C_4$ alkylene.

114. The compound or salt of claim 112, wherein each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl.

115. The compound or salt of claim 114, wherein the optional substituents of L are selected from $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are optionally substituted with one or more substituents selected from halogen and $C_{1-6}$ haloalkyl.

116. The compound or salt of any one of claims 1 to 40, or 111 to 115, wherein L is selected from 

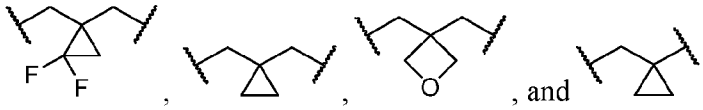
, and .

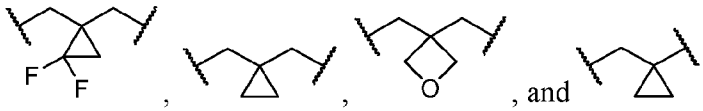
117. The compound or salt of claim 116, wherein L is selected from  , 

, and .

118. The compound or salt of claim 114 or 115, wherein each L is independently selected from a substituted $C_1$-$C_4$ alkylene, and wherein two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle 3- to 5-membered heterocycle.

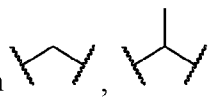
119. The compound or salt of claim 118, wherein each L is independently selected from a substituted $C_{2-3}$ alkylene, and wherein two substituents on the same carbon atom of L come together to form a $C_3$ carbocycle or 4-membered heterocycle, wherein the $C_3$ carbocycle is optionally substituted with one or more substituents selected from halogen.

120. The compound or salt of claim 119, wherein each L is independently selected from  .

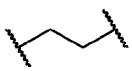
121. The compound or salt of claim 120, wherein each L is independently selected from  .

122. The compound or salt of claim 121, wherein each L is independently selected from  .

123. The compound or salt of claim 112, wherein each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen and $C_1$-$C_4$ alkyl.

124. The compound or salt of claim 123, wherein L is selected from  .

125. The compound or salt of claim 112, wherein each L is independently selected from an unsubstituted $C_1$-$C_4$ alkylene.

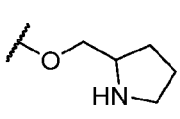
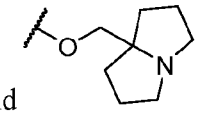
126. The compound or salt of claim 125, wherein L is selected from  and  .

127. The compound or salt of claim 126, wherein L is selected from  .

128. The compound or salt of any one of claims 1 to 40, or 48 to 127, wherein $R^2$ is selected from heterocycle, -L-heterocycle, -L-aryl, -L-heteroaryl, and -L-N($R^{23}$)$_2$, wherein the heterocycle, the heterocycle portion of -L-heterocycle, are each optionally substituted with one or more $R^6$, and wherein the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$.

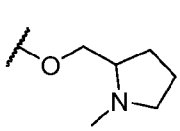
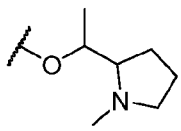
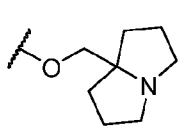
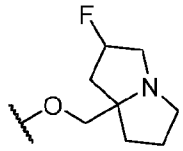
129. The compound or salt of claim 128, wherein $R^2$ is -L-heterocycle, wherein the heterocycle portion of $R^2$ is an optionally substituted heterocycle.

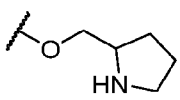
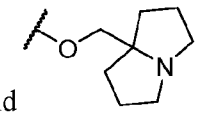
130. The compound or salt of claim 128 or 129, wherein $R^2$ is -L-heterocycle, optionally substituted with one or more $R^6$.

131. The compound or salt of any one of claims 1 to 40, or 48 to 130, wherein Y-$R^2$ is selected from  and  , wherein the heterocycle portion is optionally substituted with one or more $R^6$.

132. The compound or salt of any one of claims 1 to 40, or 128 to 131, wherein the heterocycle portion of $R^2$ is a heterocycle optionally substituted with one or more substituents selected from halogen, hydroxy, -CN, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, and $C_1$-$C_3$ aminoalkyl.

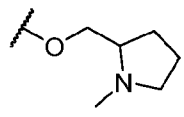
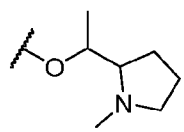
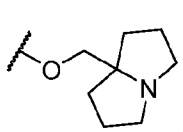
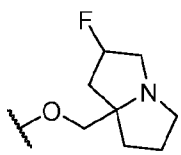
133. The compound or salt of claim 132, wherein the heterocycle portion of $R^2$ is a heterocycle optionally substituted with one or more substituents selected from $C_1$-$C_3$ alkyl and halogen.

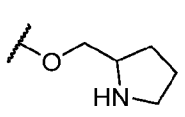
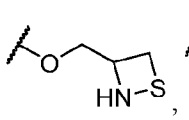
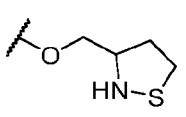
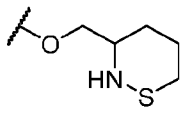
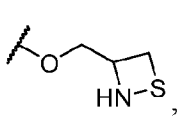
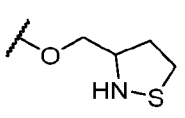
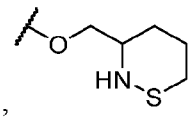
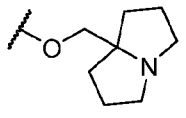
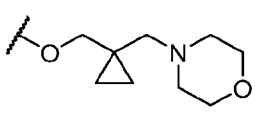
134. The compound or salt of any one of claims 1 to 40, or 48 to 133, wherein Y-$R^2$ is selected from  ,  ,  , and  .

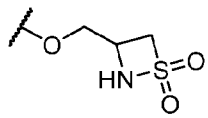
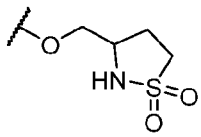
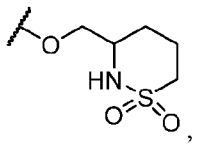
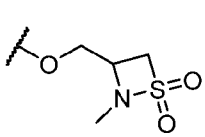
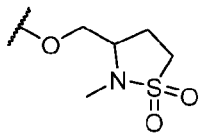
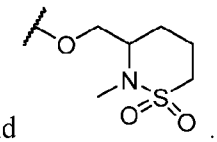
135. The compound or salt of any one of claims 1 to 40, or 48 to 131, wherein Y-$R^2$ is selected from  and  , wherein the heterocycle portion is optionally substituted with one or more $R^6$.

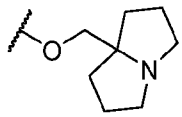
136. The compound or salt of claim 135, wherein $R^6$ of $R^2$ is independently selected at each occurrence from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, and $C_1$-$C_3$ aminoalkyl.

137. The compound or salt of claim 136, wherein $R^6$ of $R^2$ is independently selected at each occurrence from $C_1$-$C_3$ alkyl and halogen.

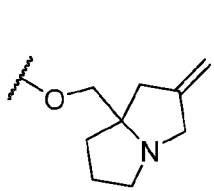
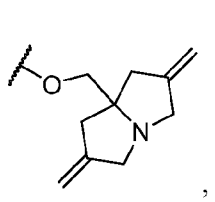
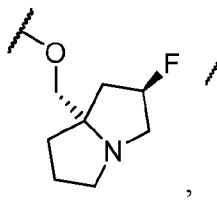
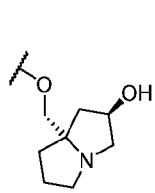
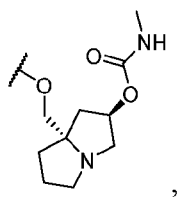
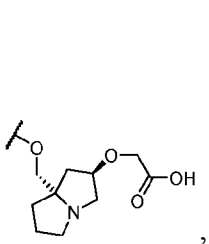
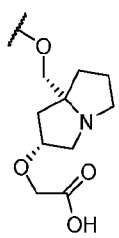
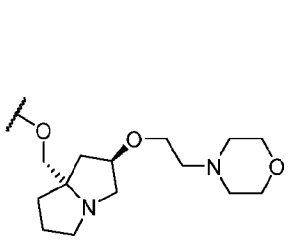
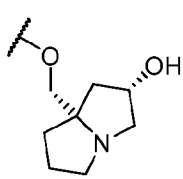
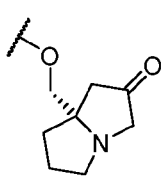
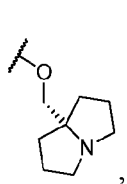
138. The compound or salt of claim 137, wherein Y-$R^2$ is selected from  ,  ,  , and  .

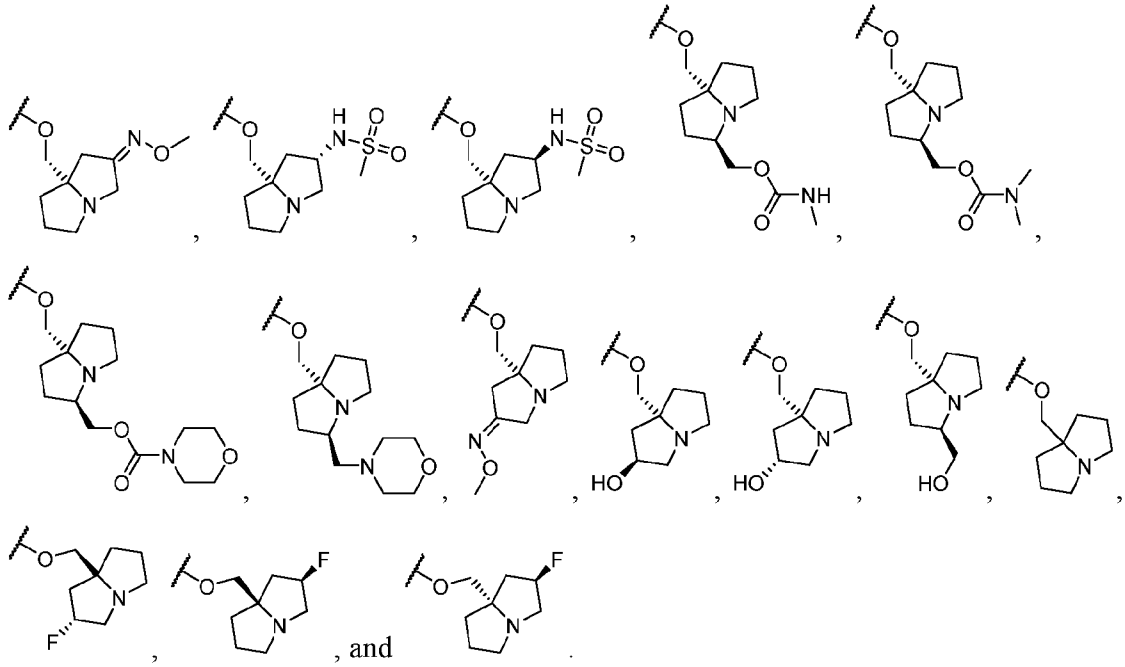
139. The compound or salt of any one of claims 1 to 40, or 48 to 128, wherein Y-$R^2$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , wherein the heterocycle portion is optionally substituted with one or more $R^6$.

140. The compound or salt of claim 139, wherein Y-$R^2$ selected from  ,  ,  ,  ,  , and  .

141. The compound or salt of claim 140, wherein Y-$R^2$ is selected from  , wherein the heterocycle is optionally substituted.

142. The compound or salt of claim 141, wherein the heterocycle is optionally substituted with one or more substituents selected from halogen, hydroxy, $C_1$-$C_3$ alkyl, -$N(R^5)S(O)_2(R^5)$, -$OC(O)N(R^5)_2$, =$CH_2$, oxo, =NO-$C_1$-$C_3$ alkyl, -$CH_2OC(O)$heterocycle, -$CH_2$heterocycle, -$CH_2OC(O)N(R^5)_2$, and -O-$C_1$-$C_3$ alkyl, wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo, and hydroxy.

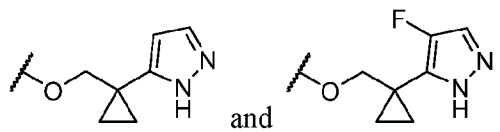
143. The compound or salt of claims 1 to 40, or 48, or 141-142, wherein Y-$R^2$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,



144. The compound or salt of claim 128, wherein $R^2$ is -L-heteroaryl, wherein the heteroaryl portion is optionally substituted with one or more $R^7$.

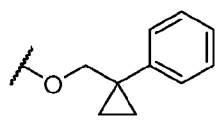
145. The compound or salt of claim 144, wherein each $R^7$ is independently selected from halogen, and $C_1$-$C_4$ haloalkyl;

146. The compound or salt of claim 145, wherein Y-$R^2$ is selected from



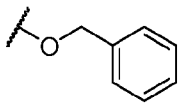
147. The compound or salt of claim 128, wherein $R^2$ is -L-aryl, optionally substituted with one or more $R^7$.

148. The compound or salt of claim 147, wherein Y-$R^2$ is selected from

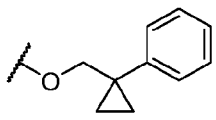


, wherein the heterocycle portion is optionally substituted with one or more $R^7$.

149. The compound or salt of claim 148, wherein Y-$R^2$ is selected from

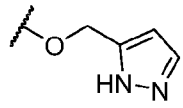
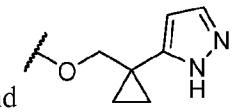


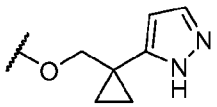
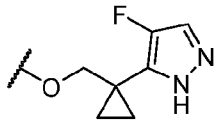
and



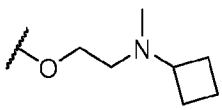
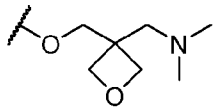
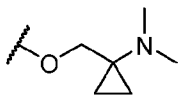
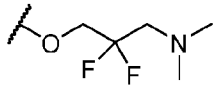
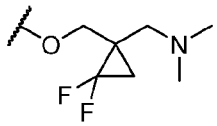
.

150. The compound or salt of claim 128, wherein $R^2$ is -L-heteroaryl, optionally substituted with one or more $R^7$.

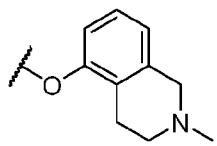
151. The compound or salt of claim 150, wherein Y-$R^2$ is selected from  and  , wherein the heteroaryl portion is optionally substituted with one or more $R^7$.

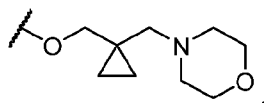
152. The compound or salt of claims 150 or 151, wherein Y-$R^2$ is selected from  and  .

153. The compound or salt of claim 128, wherein $R^2$ is -L-N($R^{23}$)$_2$.

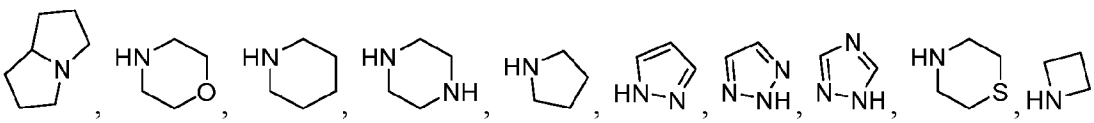
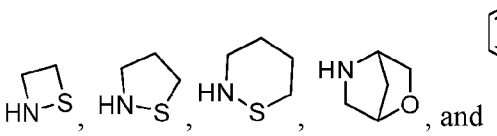
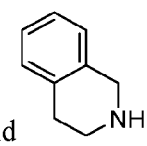
154. The compound or salt of claim 153, wherein Y-$R^2$ is selected from  ,  ,  ,  , and  .

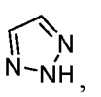
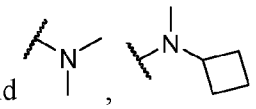
155. The compound or salt of claim 154, wherein $R^2$ is heterocycle, optionally substituted with one or more $R^6$.

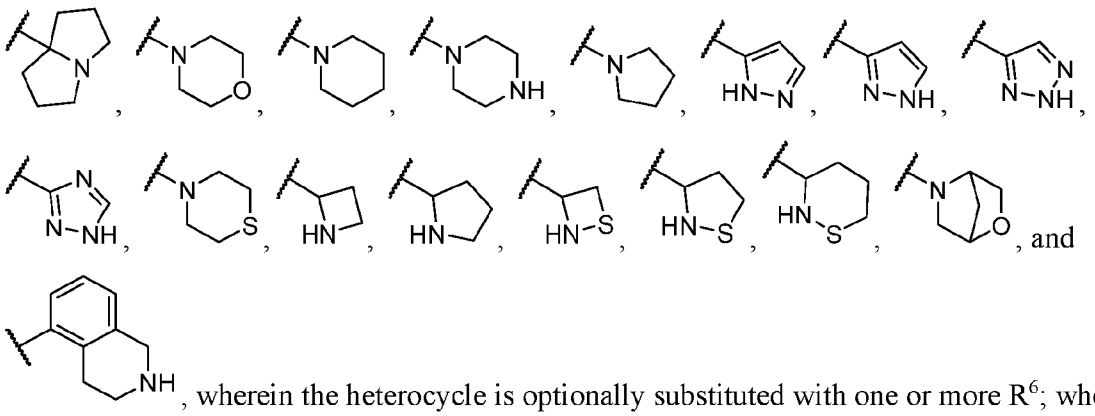
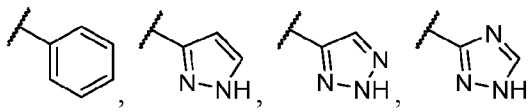
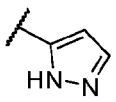
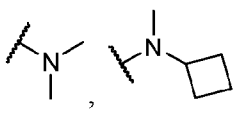
156. The compound or salt of claim 155, wherein Y-$R^2$ is  .

157. The compound or salt of claim 128, wherein Y-$R^2$ is  .

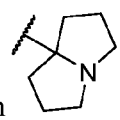
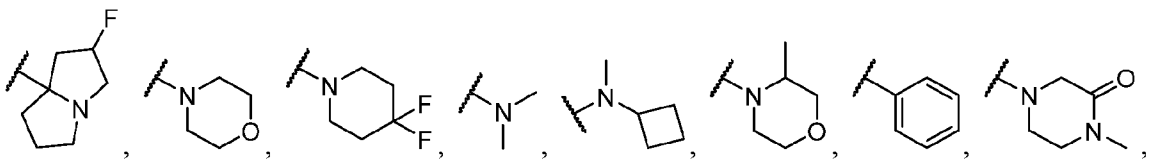
158. The compound or salt of any one of claims 1 to 40, or 48 to 127, wherein $R^2$ is selected from heterocycle, -L-heterocycle, wherein the heterocycle, and the heterocycle portion of -L-heterocycle, are each optionally substituted with one or more $R^6$; -L-aryl, and -L-heteroaryl, wherein the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$; and -L-N($R^{23}$)$_2$.

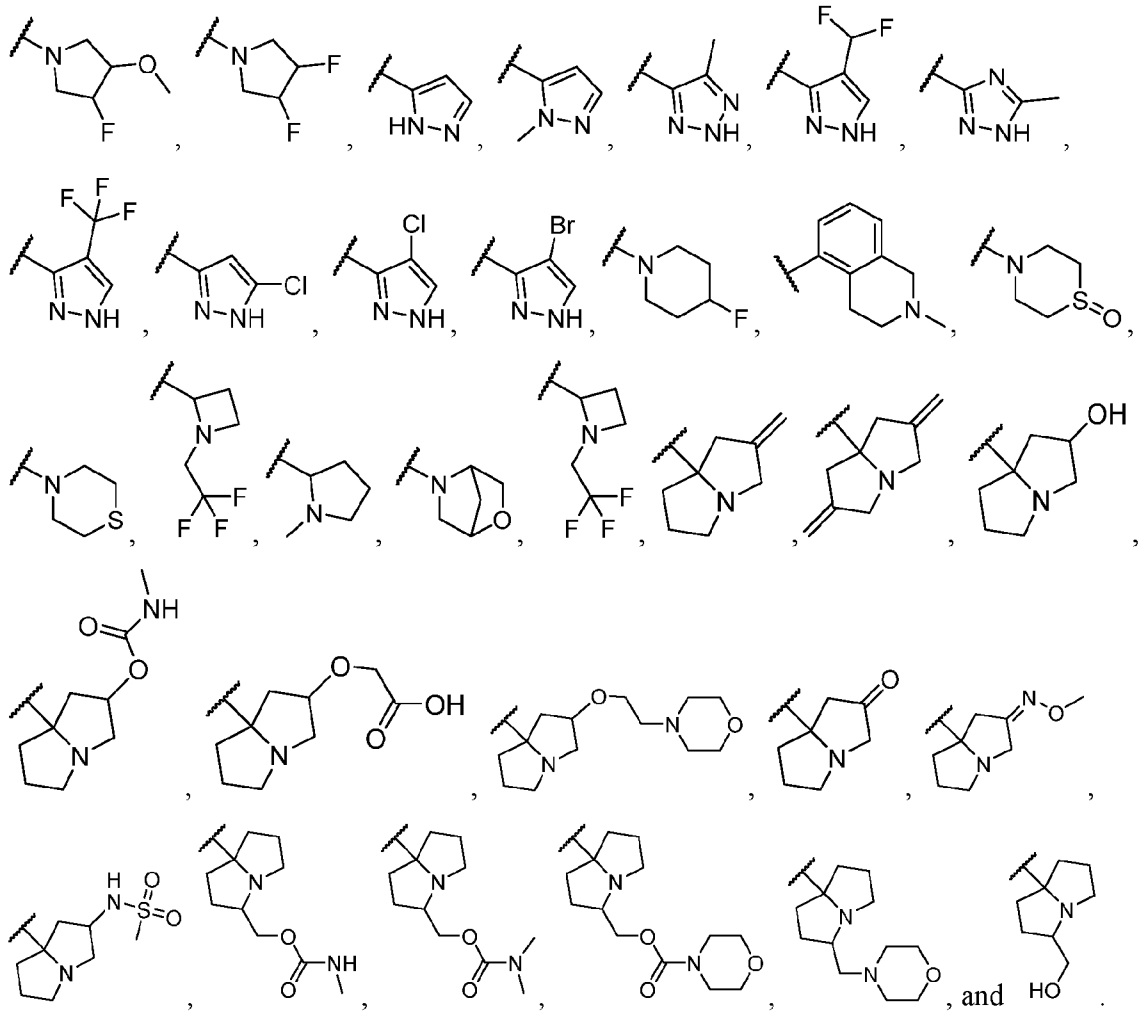
159. The compound or salt of claim 158, wherein the heterocycle of $R^2$ is selected from  ,  , and  , wherein the heterocycle of $R^2$ is optionally

substituted with one or more $R^6$; wherein the aryl and heteroaryl of $R^2$ is selected from  ,  , and  , wherein the aryl and the heteroaryl are each optionally substituted with one or more $R^7$; and  .

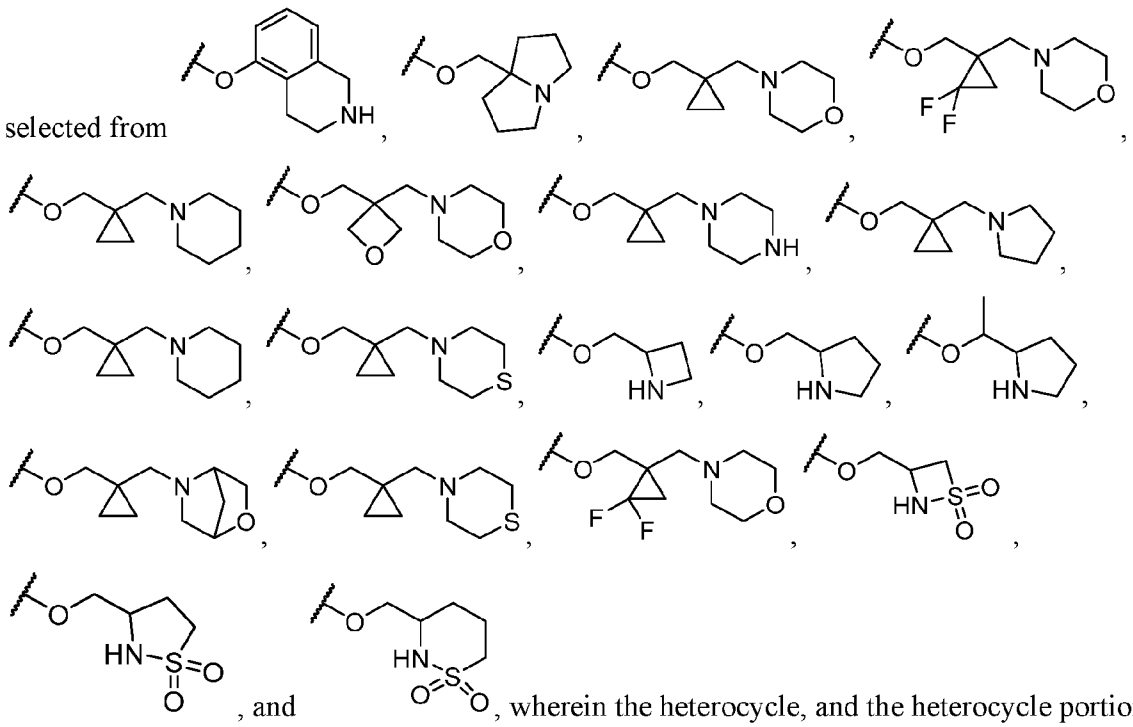
160. The compound or salt of claim 159, wherein the heterocycle of $R^2$ is selected from  , and , wherein the heterocycle is optionally substituted with one or more $R^6$; wherein the aryl and heteroaryl of $R^2$ is selected from  , and  , wherein the aryl and the heteroaryl are each optionally substituted with one or more $R^7$; and  .

161. The compound or salt of any one of claims 158 to 160, wherein each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ haloalkyl, $-N(R^5)S(O)_2(R^5)$, $-OC(O)N(R^5)_2$, $=CH_2$, oxo, $=NO$-$C_1$-$C_3$ alkyl, $-CH_2OC(O)$heterocycle, $-CH_2$heterocycle, $-CH_2OC(O)N(R^5)_2$, and $-O$-$C_1$-$C_3$ alkyl, wherein the alkyl of $-O$-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo, and hydroxy; and wherein each $R^7$ is selected from $C_1$-$C_3$ alkyl, halogen and $C_1$-$C_3$ haloalkyl.

162. The compound or salt of any one of claims 158-161, wherein the heterocycle of $R^2$, the aryl and heteroaryl of $R^2$, and $-N(R^{20})_2$ of $R^2$ is selected from is selected from  ,  .



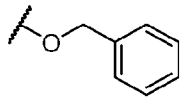
163. The compound or salt of any one of claims 1 to 40, or 48 to 162, wherein Y-$R^2$ is selected from

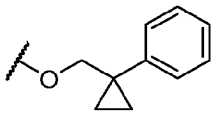
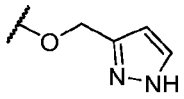
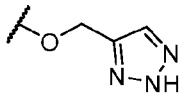
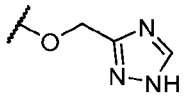
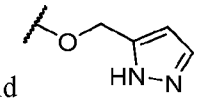
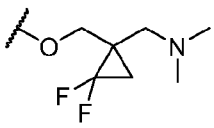
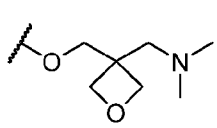
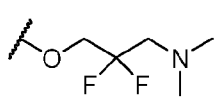
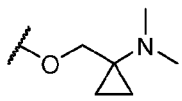
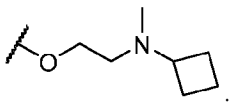


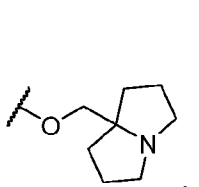
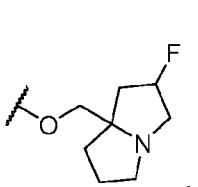
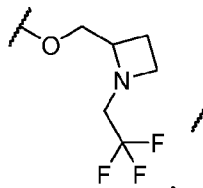
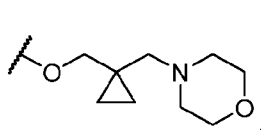
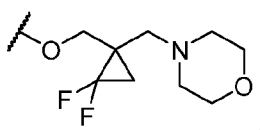
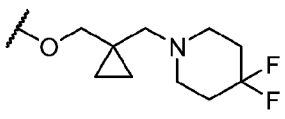
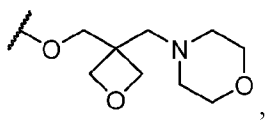
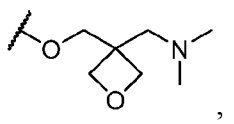
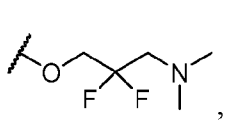
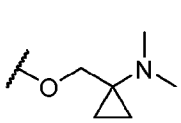
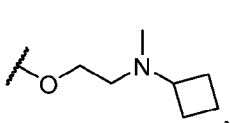
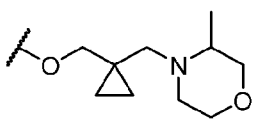
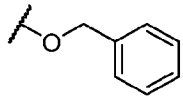
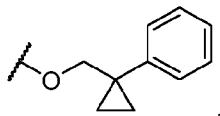
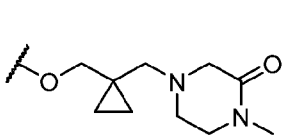
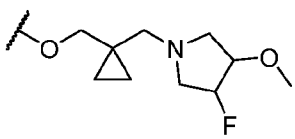
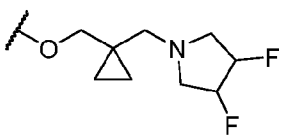
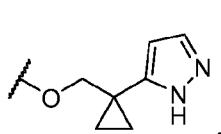
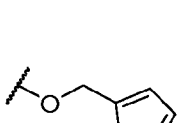
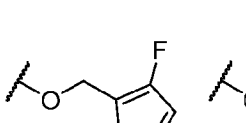
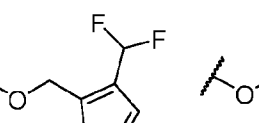
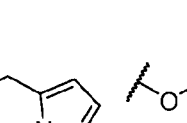
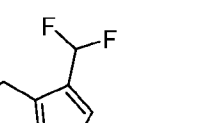
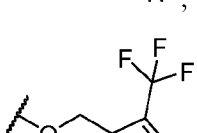
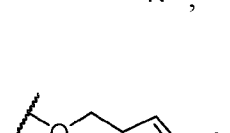
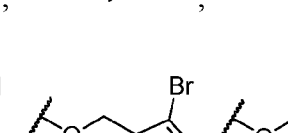
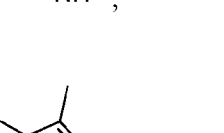
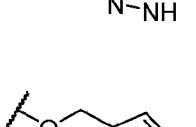
, and

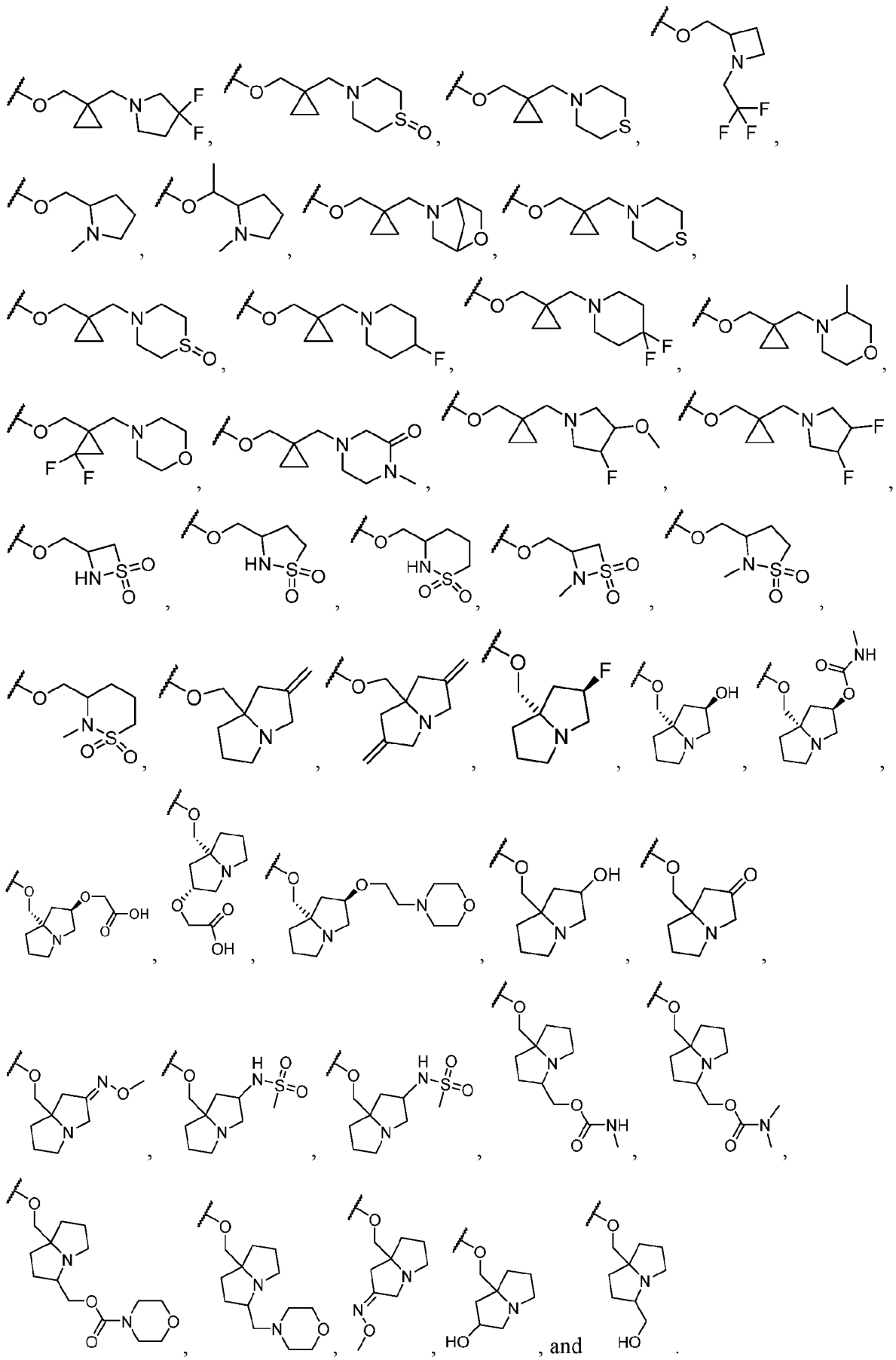


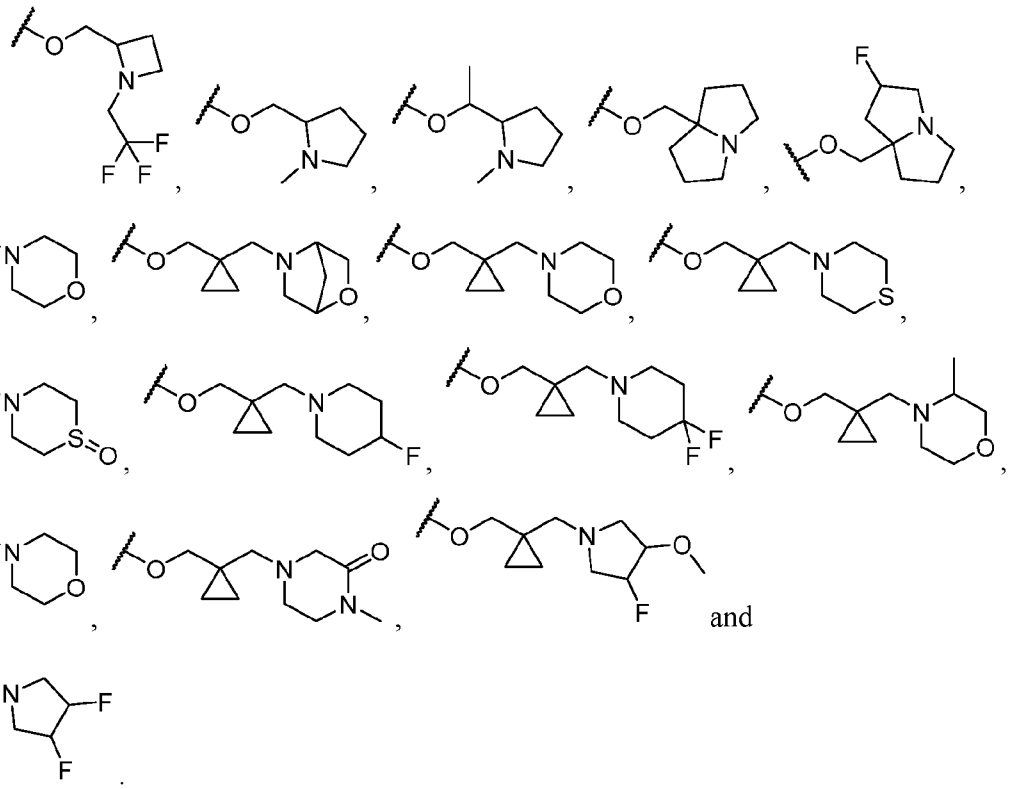
, wherein the heterocycle, and the heterocycle portion of

-L-heterocycle, are each optionally substituted with one or more $R^6$;  ,

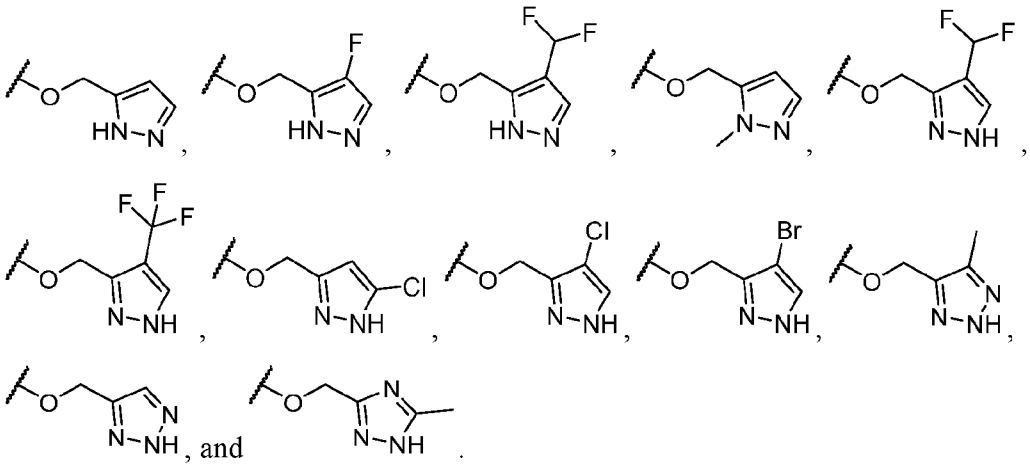
 ,  ,  ,  , and  , wherein the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$; and  ,  ,  ,  ,  .

164. The compound or salt of any one of claims 158-163, wherein Y-$R^2$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  , , , , , , , , , , , , , , .



165. The compound or salt of any one of claims 1 to 40, or 48 to 164, wherein Y-$R^2$ is selected from  .

166. The compound or salt of any one of claims 1 to 40, or 48, wherein Y is -O- and $R^2$ is selected from L-5-membered heteroaryl, wherein L is selected from an optionally substituted $C_1$-$C_4$ alkylene, and wherein the heteroaryl is optionally substituted with one or more $R^7$, wherein each $R^7$ is preferably selected from halogen, $C_1$-$C_4$ alkyl, and $C_1$-$C_4$ haloalkyl.

167. The compound or salt of any one of claims 166, wherein Y-$R^2$ is selected from  .

168. The compound or salt of any one of claims 1 to 40, or 48 to 165, wherein $R^1$ is selected from 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -OH, -$N(R^{20})_2$, -$NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl.

169. The compound or salt of claim 166, wherein $R^1$ is selected from 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -OH, $-N(R^{20})_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl.

170. The compound or salt of any one of claims 1 to 40, or 48 to 168, wherein $R^1$ is an optionally substituted 5- to 12-membered heterocycle.

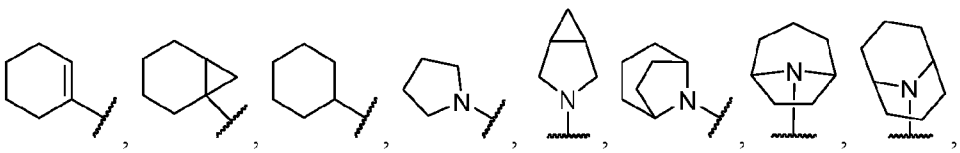
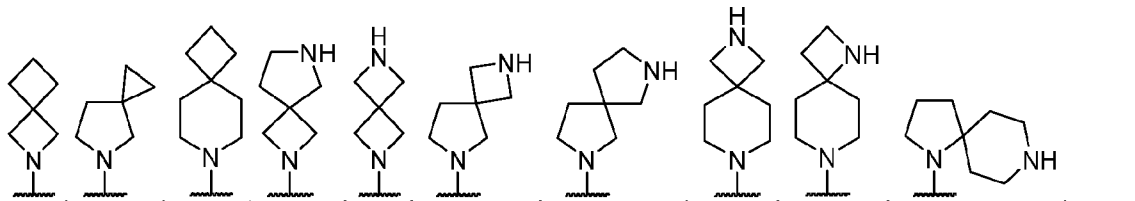
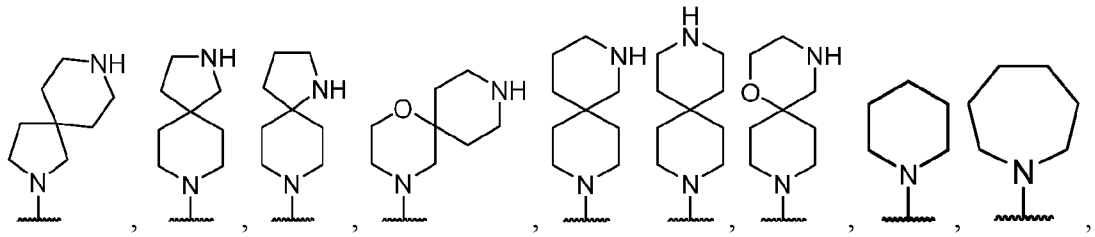
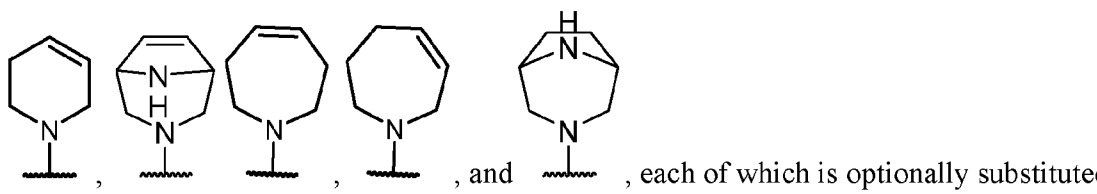
171. The compound or salt of claim 170, wherein the 5- to 12-membered heterocycle of $R^1$ is unsaturated.

172. The compound or salt of claim 170, wherein the 5- to 12-membered heterocycle of $R^1$ is saturated.

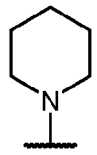
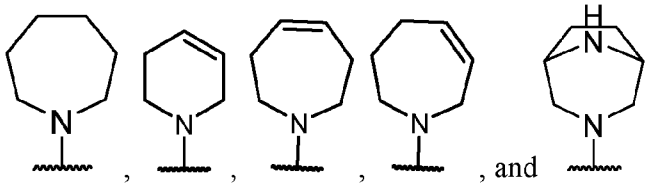
173. The compound or salt of claim 170, wherein the 5- to 12-membered heterocycle of $R^1$ is bridged.

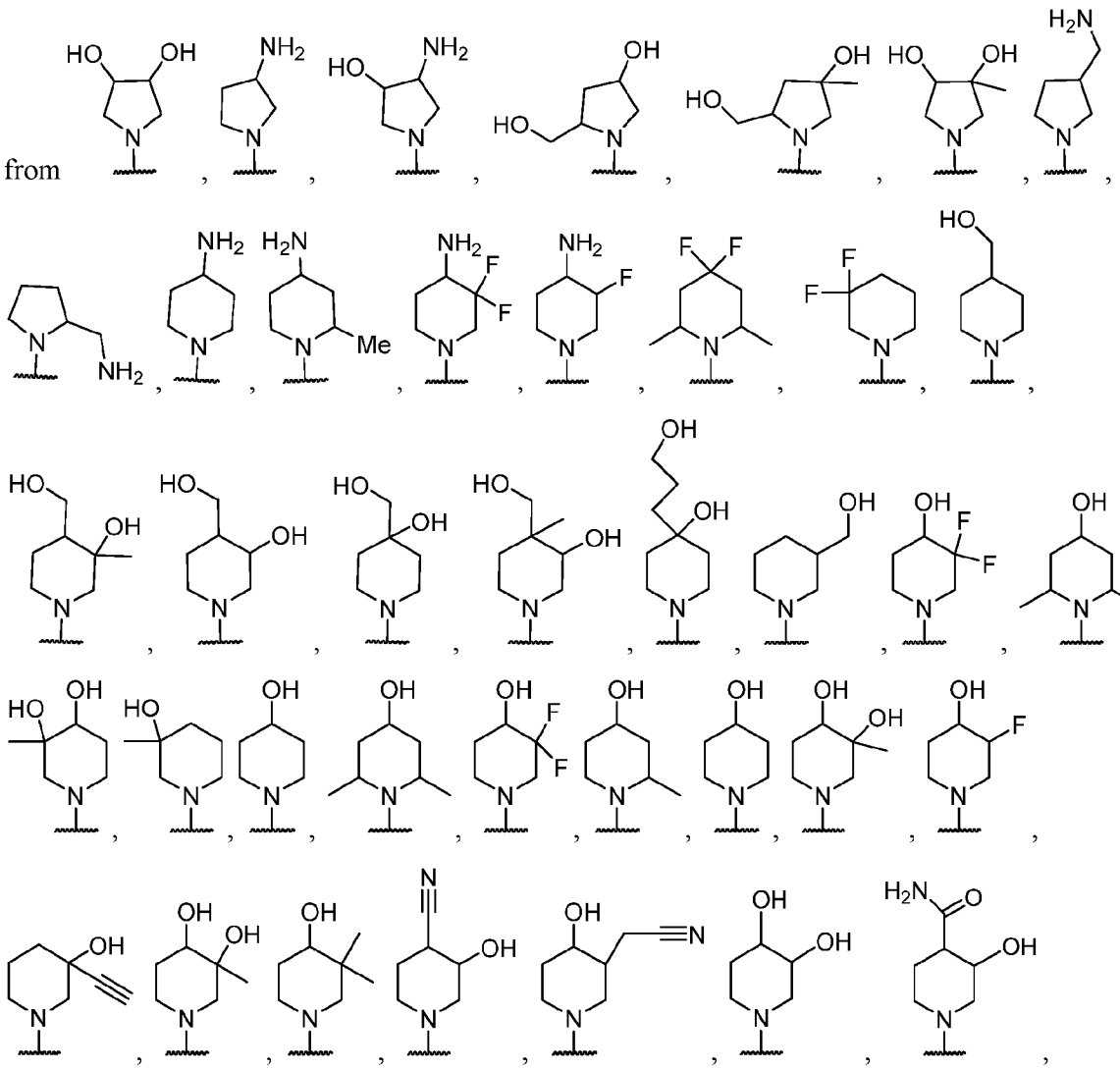
174. The compound or salt of claim 170, wherein the 5- to 12-membered heterocycle of $R^1$ is a spiro heterocycle.

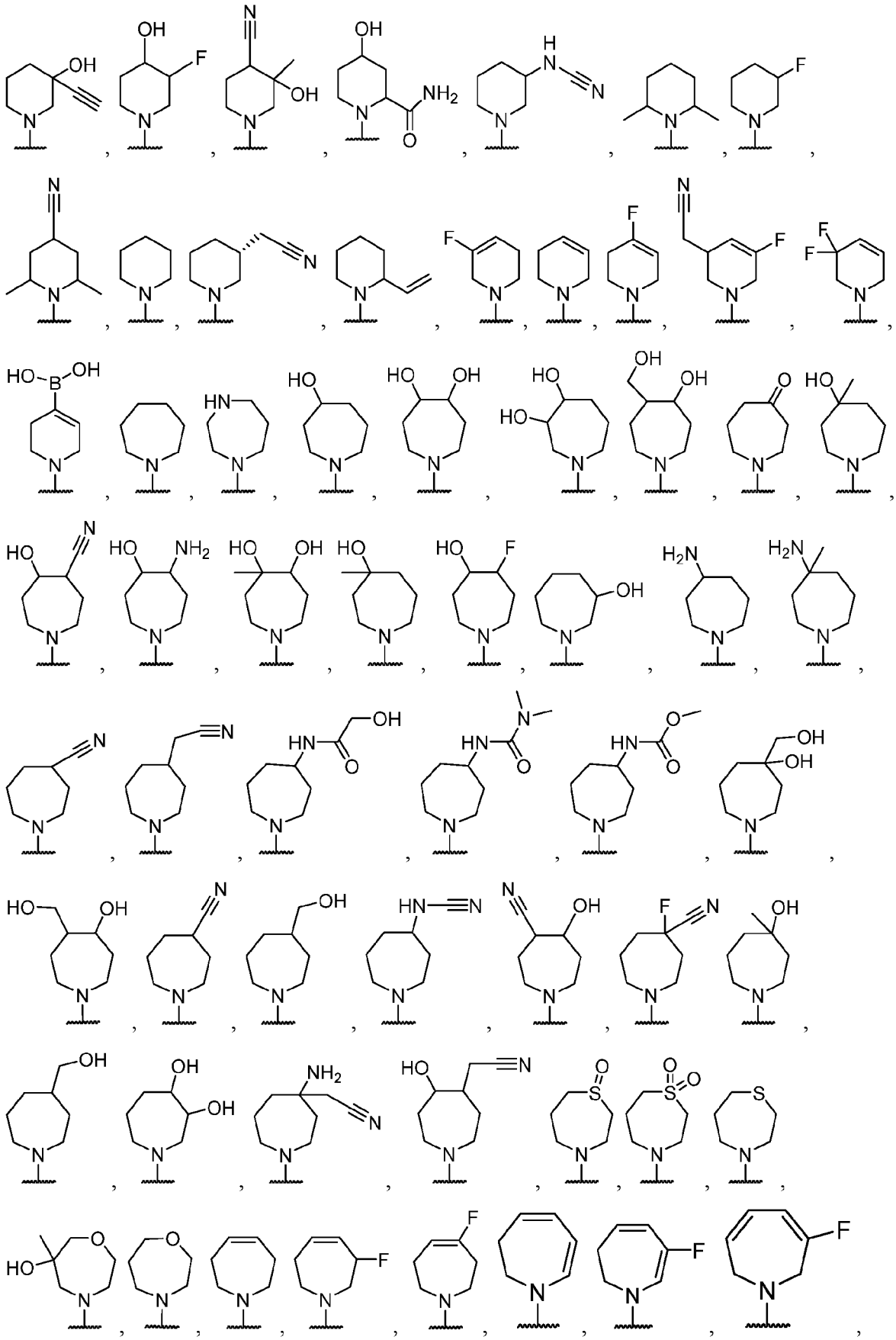
175. The compound or salt of claim 170, wherein the 5- to 12-membered heterocycle of $R^1$ is non-aromatic.

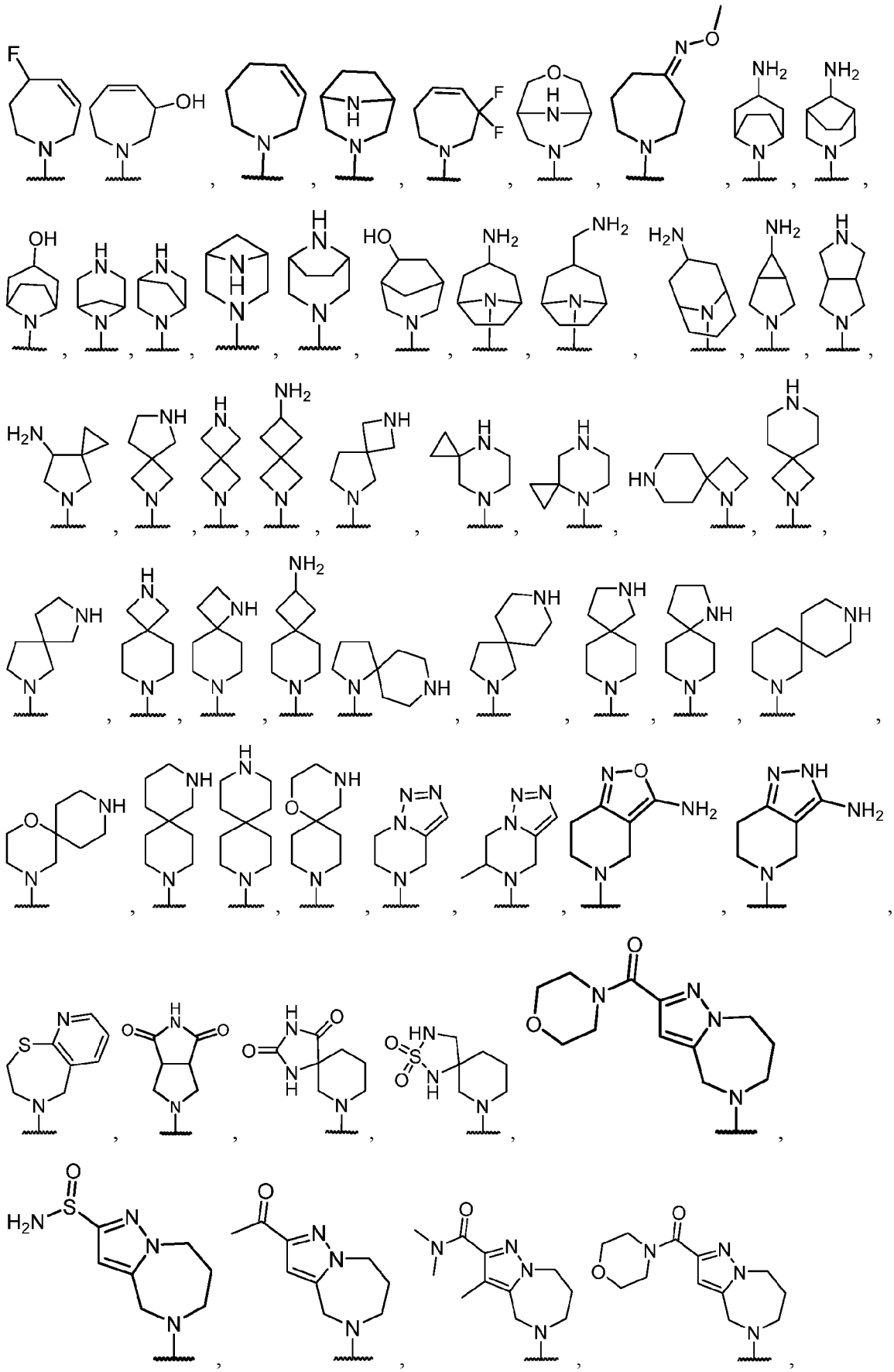
176. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from  ,  ,  ,  , and , each of which is optionally substituted.

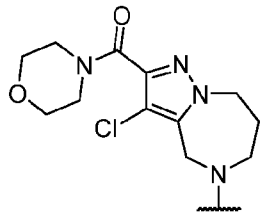
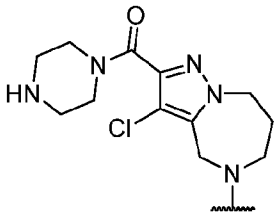
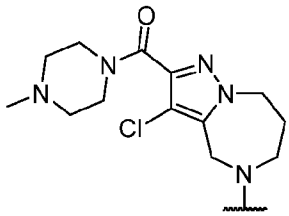
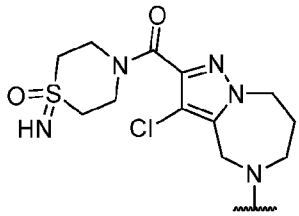
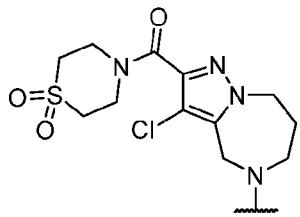
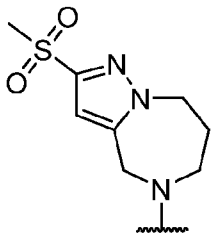
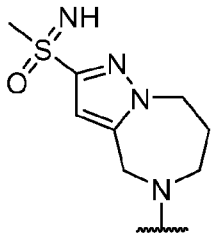
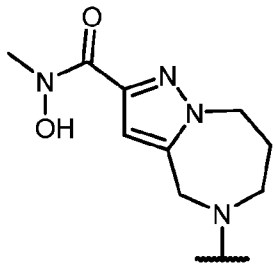
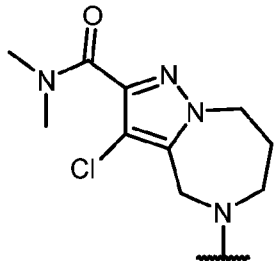
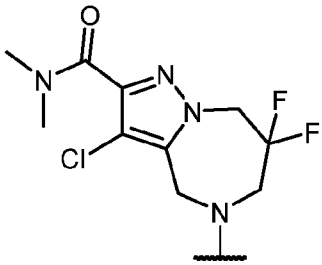
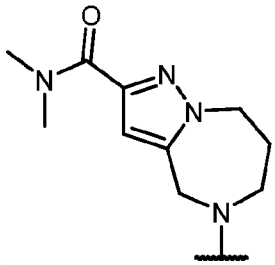
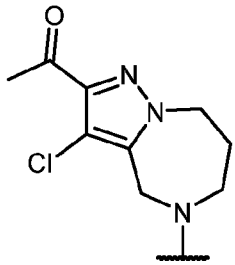
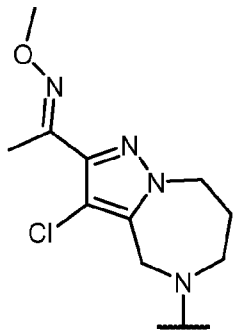
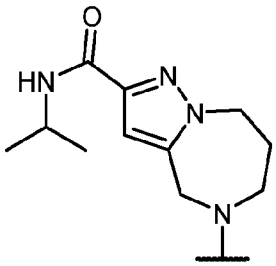
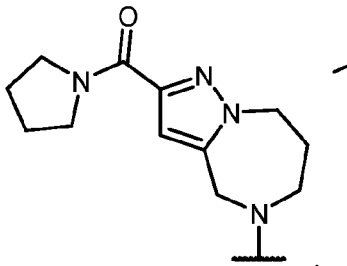
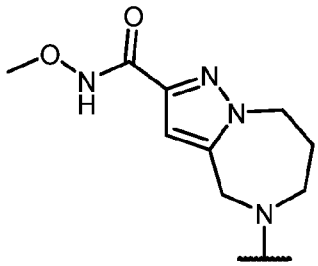
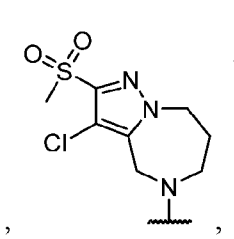
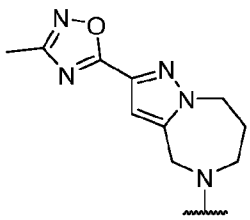
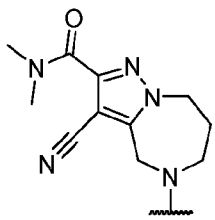
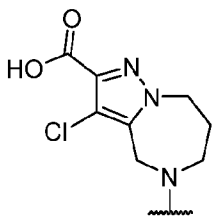
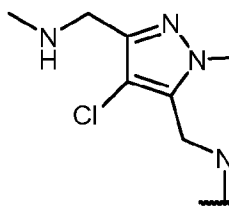
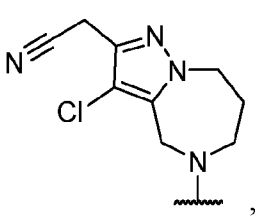
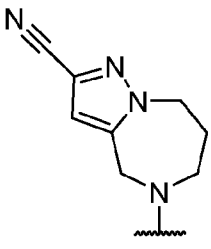
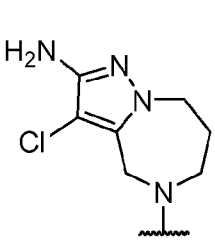
177. The compound or salt of claim 176, wherein the optional one or more substituents are each independently selected from halogen, -OH, -N($R^{20}$)$_2$, -$NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, =O, -CN, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl.

178. The compound or salt of claim 177, wherein $R^1$ is selected from  ,  , and , each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -N($R^{20}$)$_2$, -$NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, =O, -CN, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl.

179. The compound or salt of any one of claims 1 to 40, or 48, wherein $R^1$ is selected from 





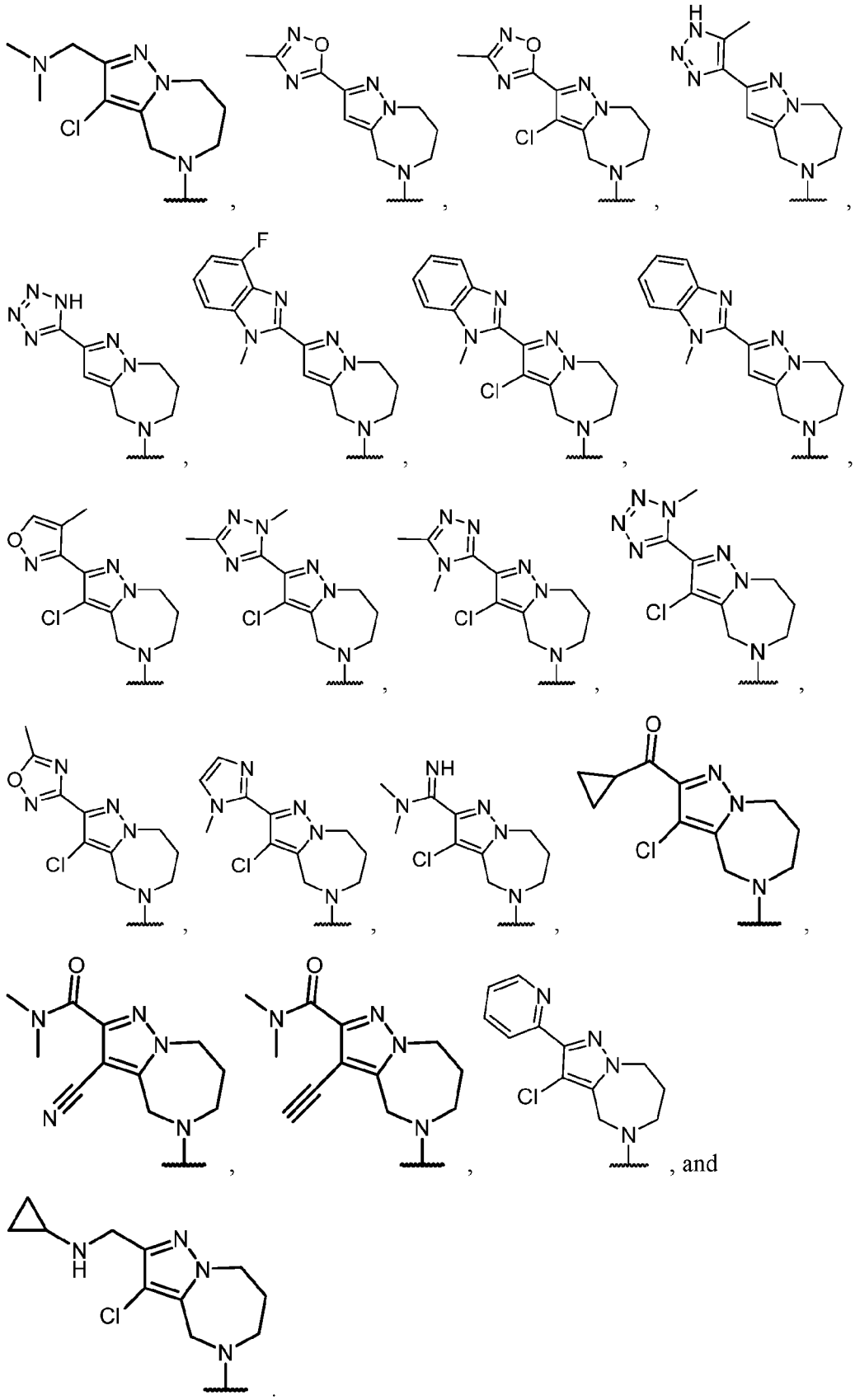

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

.

,

,

,

,

,

,

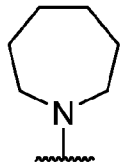
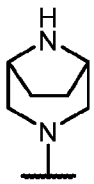
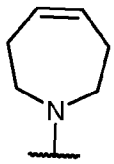
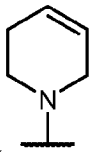
,

,

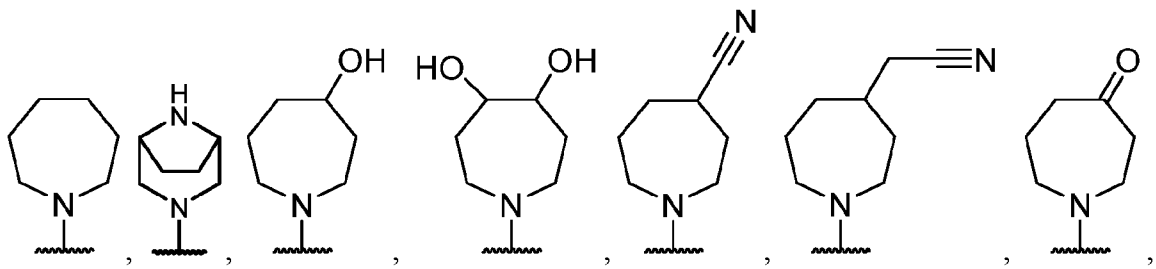
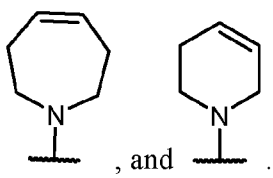


180. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from 6- to 8-membered heterocycle, which is optionally substituted.

181. The compound or salt of claim 180, wherein $R^1$ is selected from 7-membered saturated heterocycle, 8-membered bridged heterocycle, and 6- to 7-membered unsaturated heterocycle, each of which is optionally substituted.

182. The compound or salt of claim 181, wherein $R^1$ is selected from  ,  ,  , and  , each of which is optionally substituted.

183. The compound or salt of claim 182, wherein the one or more optional substituents are independently selected from -OH, -CN, oxo, $C_{1-6}$ cyanoalkyl.

184. The compound or salt of claims 182 or 183, wherein $R^1$ is selected from  ,  , and .

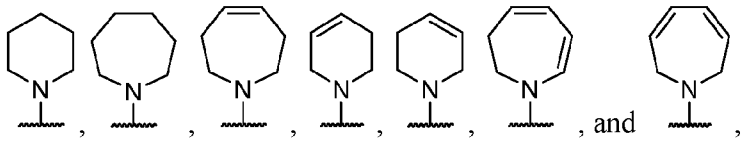
185. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from an optionally substituted 6- to 7-membered heterocycle.

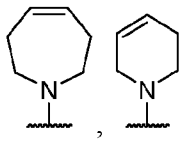
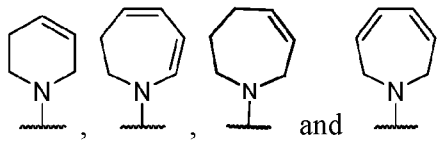
186. The compound or salt of claim 185, wherein the 6- to 7-membered heterocycle contains only 1 nitrogen atom, and wherein the 6- to 7-membered heterocycle is optionally substituted.

187. The compound or salt of 186, wherein the 6- to 7-membered heterocycle of $R^1$ is bound to Formula (I) via the only 1 nitrogen atom.

188. The compound or salt of any one of claims 185 to 187, wherein $R^1$ is selected from an optionally substituted unsaturated 6-membered heterocycle.

189. The compound or salt of any one of claims 185 to 187, wherein $R^1$ is selected from an optionally substituted unsaturated 7-membered heterocycle.

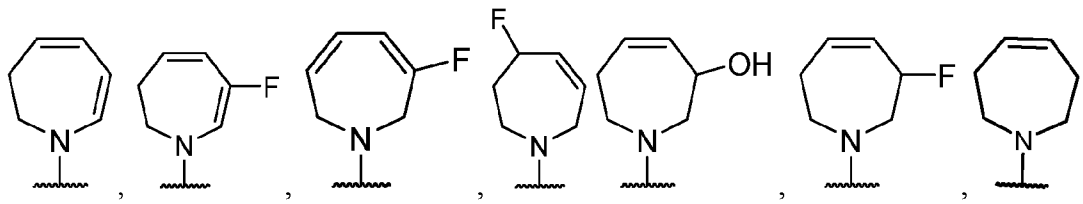
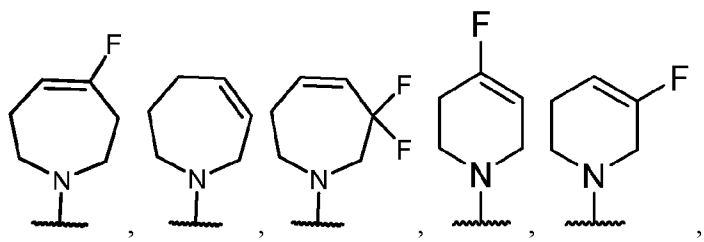
190. The compound or salt of any one of claims 185 to 188, wherein $R^1$ is selected from  , any of which is optionally substituted.

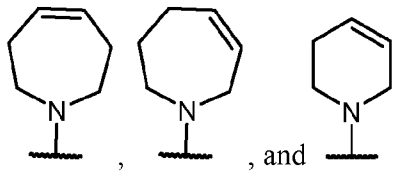
191. The compound or salt of claim 185, wherein $R^1$ is selected from  ,  , any of which is optionally substituted.

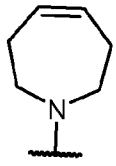
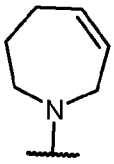
192. The compound or salt of claim 185 to 191, wherein the one or more optional substituents of $R^1$ are each independently selected from halogen, $-OR^{20}$, $-N(R^{20})_2$, =O, -CN, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl, -NHCN, and $C_{2-6}$ alkynyl.

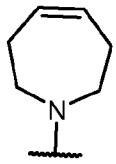
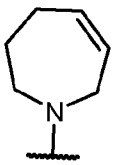
193. The compound or salt of any one of claims 185 to 192, each is optionally substituted with one or more substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

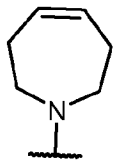
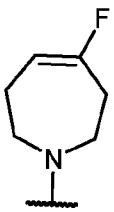
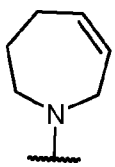
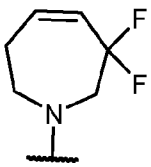
194. The compound or salt of any one of claims 185 to 193, wherein the one or more optional substituents of $R^1$ are each independently selected from halogen.

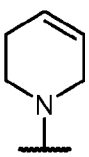
195. The compound or salt of any one of claims 185 to 194, wherein $R^1$ is selected from  ,  .

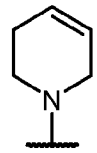
196. The compound or salt of any one of claims 185 to 191, wherein $R^1$ is selected from  , wherein each is optionally substituted with one or more substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

197. The compound or salt of claim 196, wherein $R^1$ is selected from  , and  , wherein each is optionally substituted with one or more substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

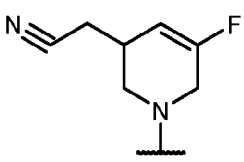
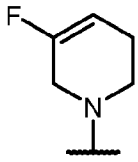
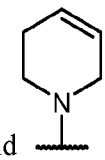
198. The compound or salt of claim 197, wherein $R^1$ is selected from  , and  , wherein each is optionally substituted with one or more substituents independently selected from halogen, and $C_{1-6}$ haloalkyl.

199. The compound or salt of claim 198, wherein $R^1$ is selected from  ,  ,  , and  .

200. The compound or salt of any one of claims 182, wherein $R^1$ is selected from  , which is optionally substituted with one or more substituents independently selected from halogen, -OH, $-NH_2$, $-NO_2$, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

201. The compound or salt of claim 200, wherein $R^1$ is selected from  , which is optionally substituted with one or more substituents independently selected from halogen.

202. The compound or salt of claim 201, wherein $R^1$ is selected from

 ,  , and  .

203. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from an optionally substituted 6- to 7-membered heterocycle.

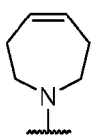
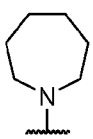
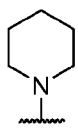
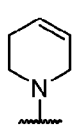
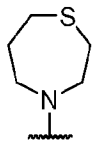
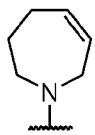
204. The compound or salt of claim 203, wherein the 6- to 7-membered heterocycle contains only 1 nitrogen atom and optionally one or more additional heteroatoms selected from oxygen, and sulfur.

205. The compound or salt of claim 204, wherein the optionally one or more additional heteroatoms are selected from sulfur.

206. The compound or salt of any one of claims 203 to 205, wherein the 6- to 7-membered heterocycle contains only 1 nitrogen atom and no further additional heteroatoms.

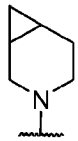
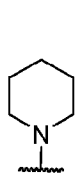
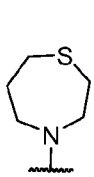
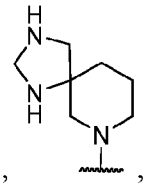
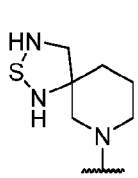
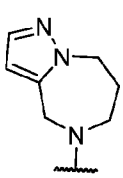
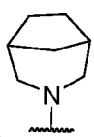
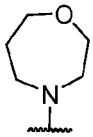
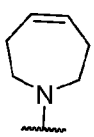
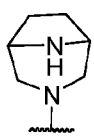
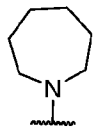
207. The compound or salt of any one of claims 203 to 206, wherein the 6- to 7-membered heterocycle is a non-aromatic 6- to 7-membered heterocycle.

208. The compound or salt of any one of claims 203 to 207, wherein the 6- to 7-membered heterocycle of $R^1$ is bound to Formula (I) via the only 1 nitrogen atom.

209. The compound or salt of any one of claims 203 to 208, wherein $R^1$ is selected from  ,  ,  ,  ,  , and  , each of which is optionally substituted.

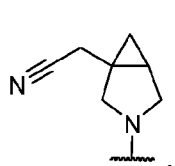
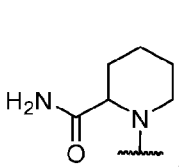
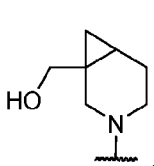
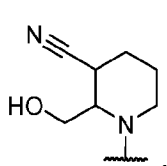
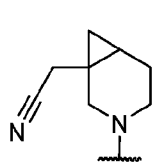
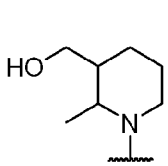
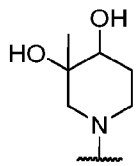
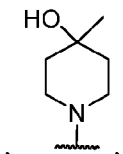
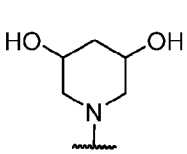
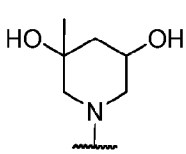
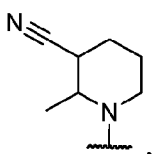
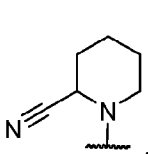
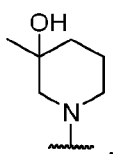
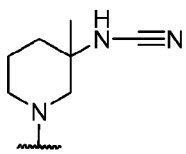
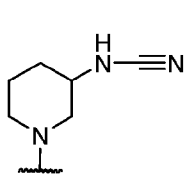
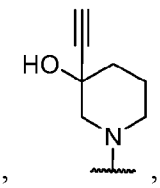
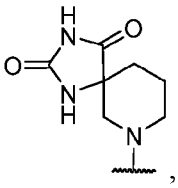
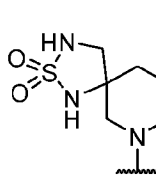
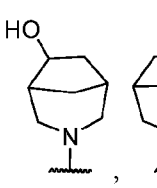
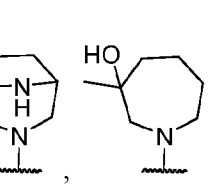
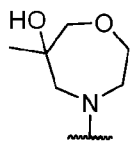
210. The compound or salt of any one of claims 203 to 209, wherein the one or more optional substituents of $R^1$ are each independently selected from halogen, -OH, -CN, $C_{1-6}$ cyanoalkyl, -NHCN, $C_{1-6}$ alkyl, oxo, and $C_{2-6}$ alkynyl.

211. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from an optionally substituted 6- to 10-membered heterocycle.

212. The compound or salt of claim 211, wherein $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted.

213. The compound or salt of claim 212, wherein the one or more optional substituents are independently selected from halogen, =O, -OH, $-C(O)N(R^{20})_2$, $C_{2-6}$ alkynyl, -NHCN, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, and $C_{1-6}$ alkyl.

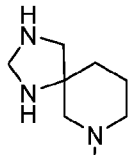
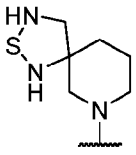
214. The compound or salt of claims 212 or 213, wherein $R^1$ is selected from

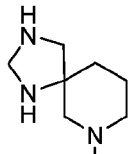
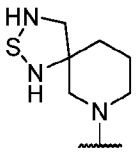
 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

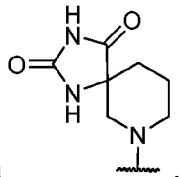
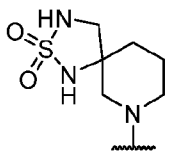
215. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from a 7- to 11-membered spiro heterocycle.

216. The compound or salt of claim 215, wherein $R^1$ is selected from a 10-membered spiro heterocycle.

217. The compound or salt of claims 215 or 216, wherein the spiro heterocycle has at least 3 nitrogen atoms.

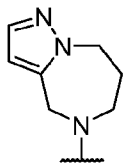
218. The compound or salt of claim 217, wherein $R^1$ is selected from  , and  , each of which is optionally substituted.

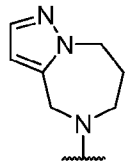
219. The compound or salt of claim 218, wherein $R^1$ is selected from  , and  , each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, $-N(R^{20})_2$, $-NO_2$, =O, -CN, -NHCN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, and $C_{2-6}$ alkynyl.

220. The compound or salt of claim 219, wherein $R^1$ is selected from  , 
and .

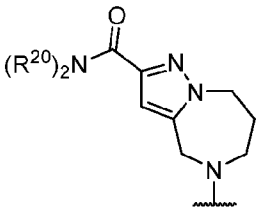
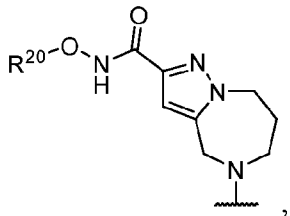
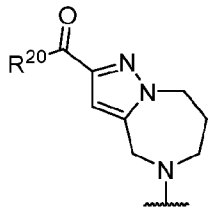
221. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from an optionally substituted unsaturated 9- to 11-membered heterocycle.

222. The compound or salt of claim 221, wherein $R^1$ is selected from an optionally substituted unsaturated 10-membered heterocycle.

223. The compound or salt of claims 221 or 222, wherein $R^1$ is  , which is optionally substituted.

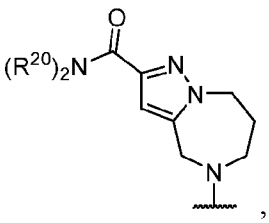
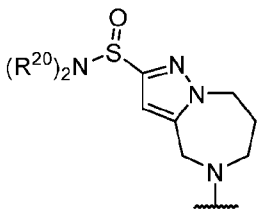
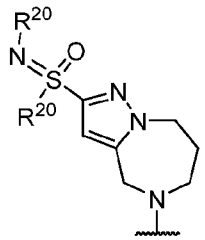
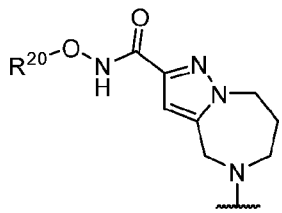
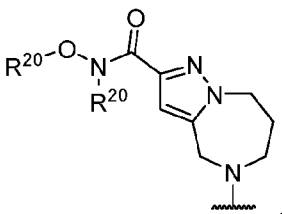
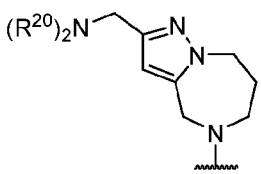
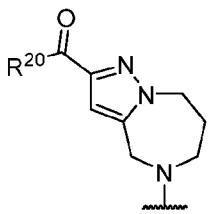
224. The compound or salt of claim 223, wherein $R^1$ is  , which is optionally substituted with one or more substituents selected from halogen, -OH, -C(O)N($R^{20}$)$_2$, -C(O)NHOR$^{20}$, -N($R^{20}$)$_2$, -C(O)$R^{20}$, -$NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl.

225. The compound or salt of claim 224, wherein $R^1$ is selected from

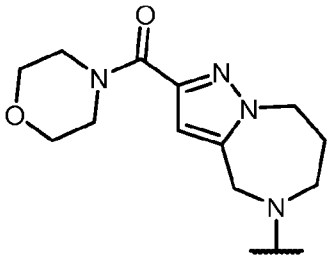
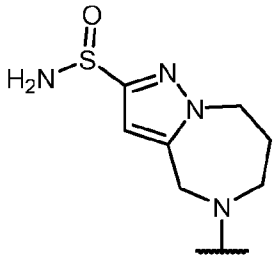
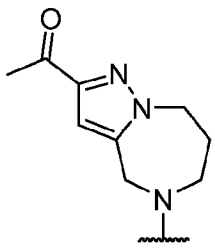
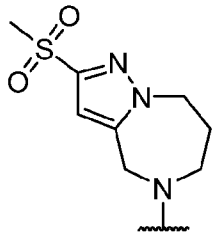
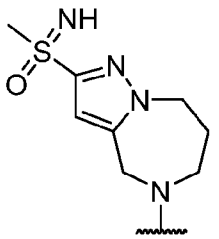
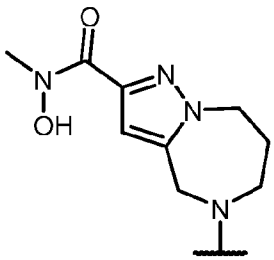
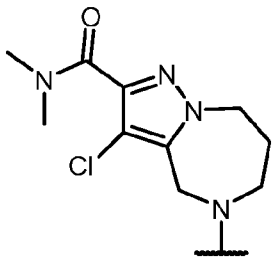
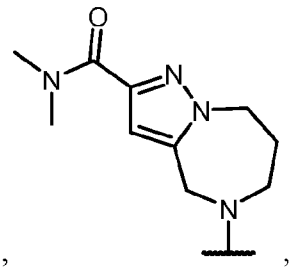
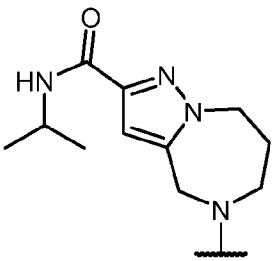
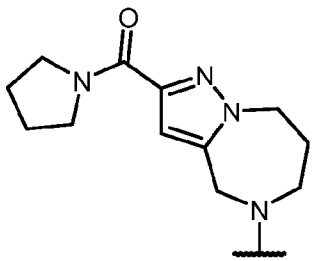
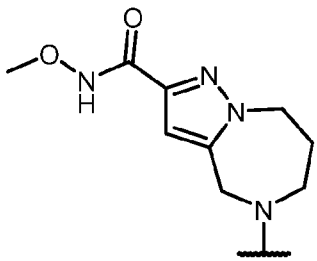
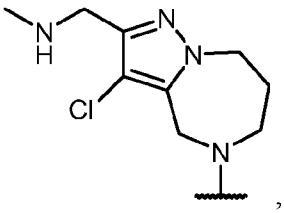
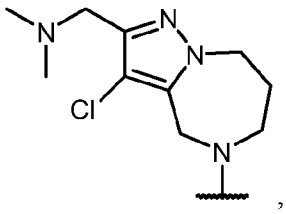
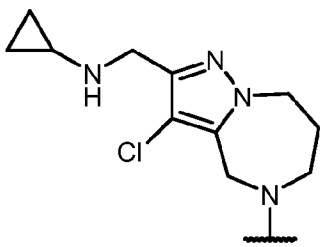
 and  , and  , each of which is further optionally substituted with one or more substituents selected from halogen, -OH, -N($R^{20}$)$_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl.

226. The compound or salt of any one of claims 221 to 223, wherein the one or more optional substituents of $R^1$ are independently selected from halogen, -OH, -S(O)$_2$($R^{20}$), -S(O)$_2$N($R^{20}$)$_2$, -S(O)N($R^{20}$)$_2$, -S(O)$R^{20}$(=N$R^{20}$), -C(O)N($R^{20}$)$_2$, -C(O)NHOR$^{20}$, -N($R^{20}$)$_2$, -C(O)$R^{20}$, -$NO_2$, =O, -CN, $C_{1-6}$ alkyl-N($R^{20}$)$_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl.

227. The compound or salt of claims 223 or 226, wherein $R^1$ is selected from

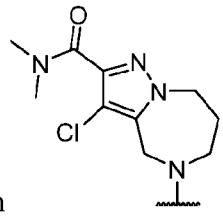
 ,  ,  ,  ,  ,  , and  , each of which is optionally substituted.

228. The compound or salt of claim 227, wherein $R^1$ is selected from

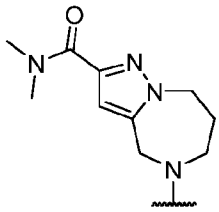

,

,

,

,

,

,

,

,

,

,

,

,

,

, and
.

229. The compound or salt of claim 223, wherein the one or more optional substituents of $R^1$ are independently selected from halogen, -OH, $-N(R^{20})_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $-C(O)N(R^{20})_2$, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl.

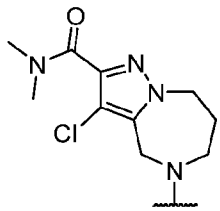
230. The compound or salt of claim 229, wherein the one or more optional substituents of $R^1$ are independently selected from halogen, and $-C(O)N(R^{20})_2$.

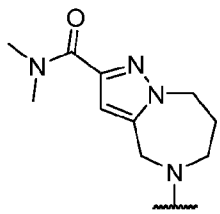


231. The compound or salt of claim 230, wherein $R^1$ is selected from

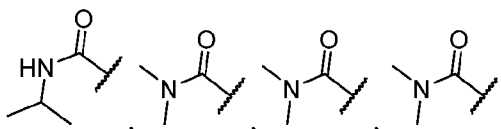
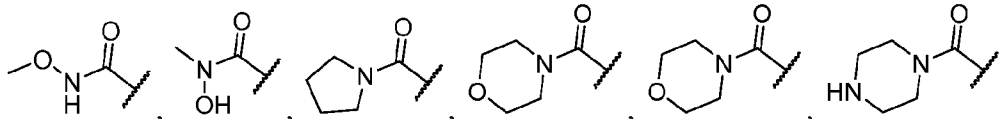
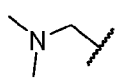


and .

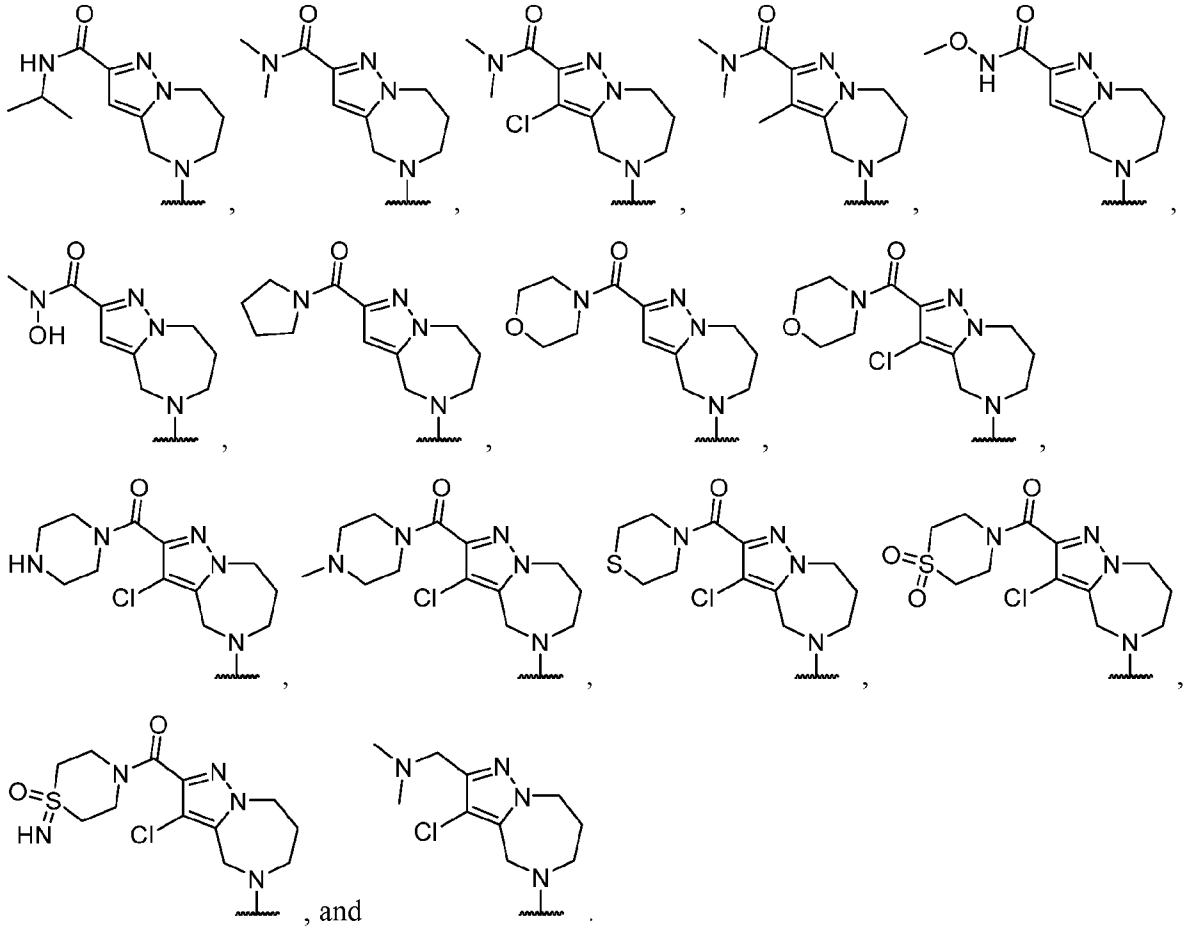
232. The compound or salt of claim 231, wherein $R^1$ is  .

233. The compound or salt of claim 231, wherein $R^1$ is  .

234. The compound or salt of claim 223, wherein the one or more optional substituents of $R^1$ are independently selected from halogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, -$C(O)NR^{20}OR^{20}$, -$C(O)N(R^{20})_2$, and -$C(O)R^{20}$.

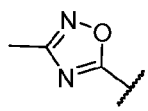
235. The compound or salt of claims 234, wherein the one or more optional substituents of $R^1$ are selected from chlorine,  ,  , and  .

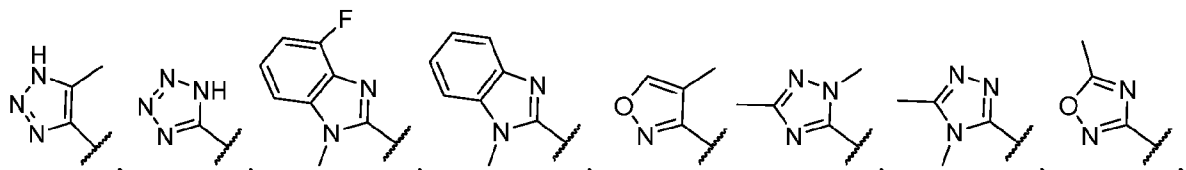
236. The compound or salt of claim 235, wherein $R^1$ is selected from

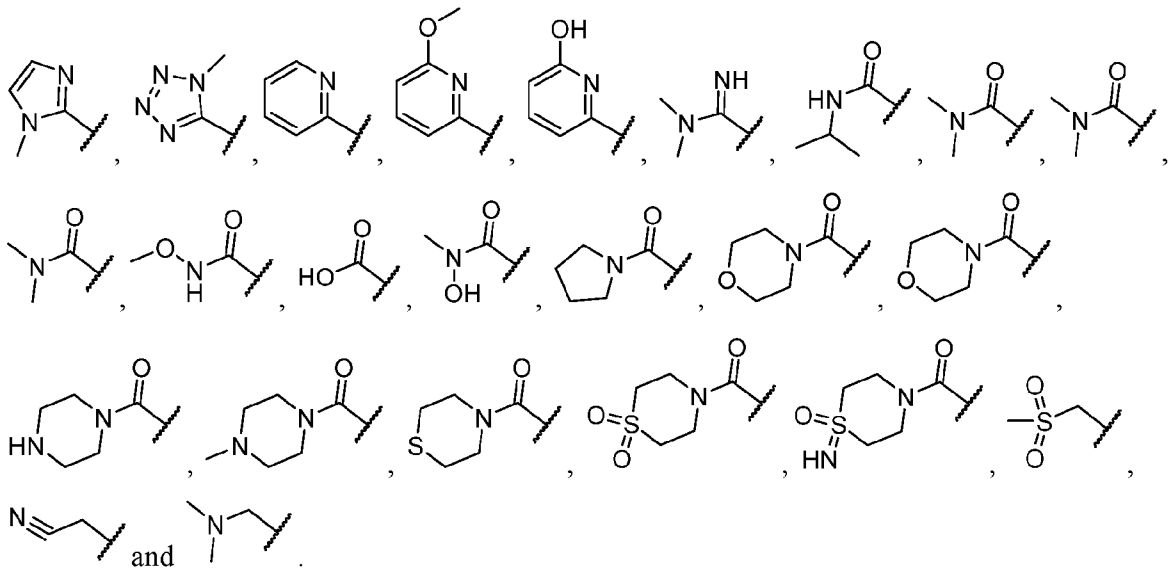


, and .

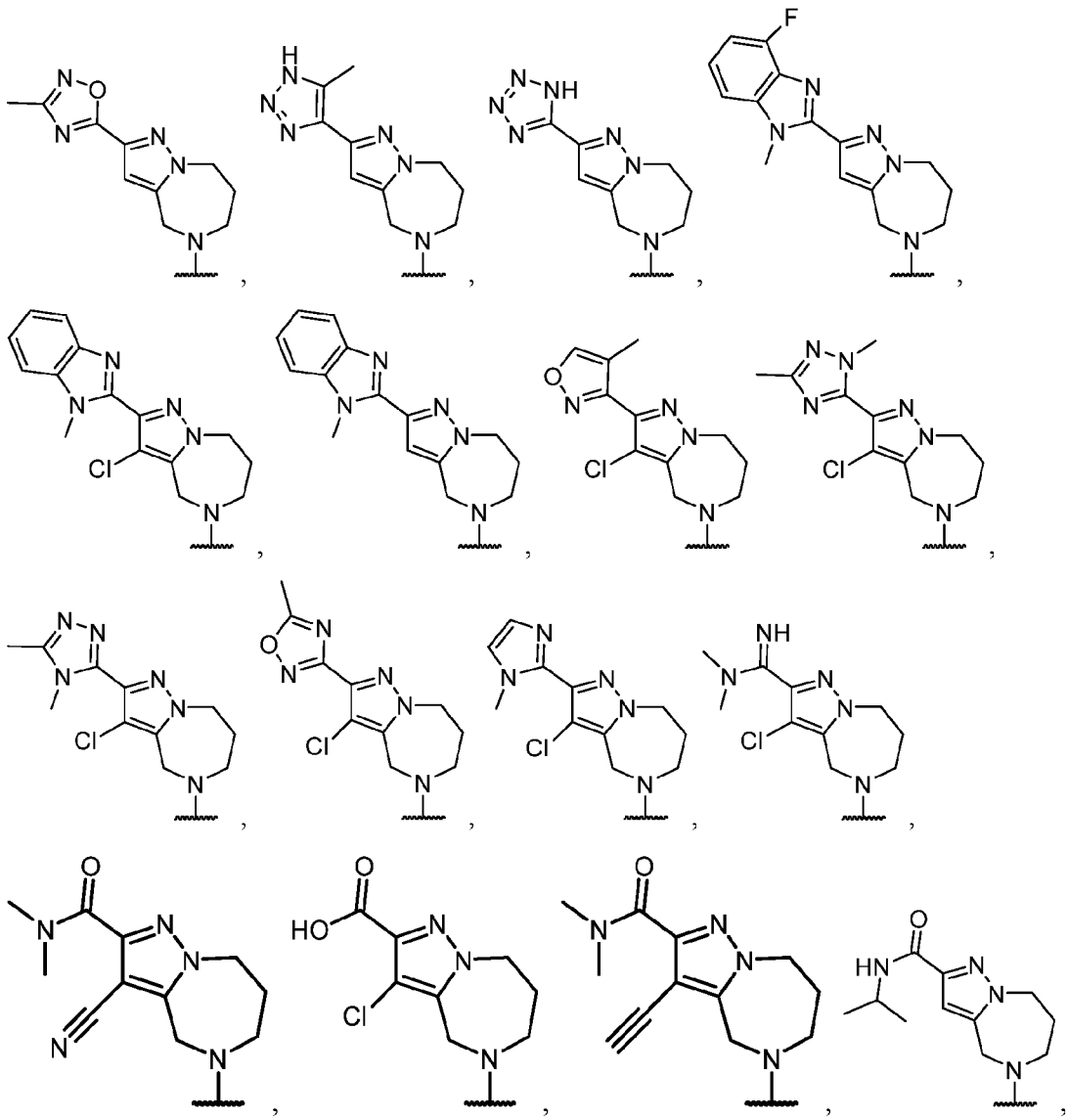
237. The compound or salt of any one of claims 221 to 223, wherein the one or more optional substituents of $R^1$ are independently selected from halogen, $-N(R^{20})_2$, -CN, $C_{1-6}$ alkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ alkyl-$SO_2$-$C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $-C(O)NR^{20}OR^{20}$, $-C(O)N(R^{20})_2$, $-C(O)R^{20}$, and 5- to 10-membered heterocycle, wherein the 5- to 10-membered heterocycle is optionally substituted independently with one or more $R^{1*}$, wherein each $R^{1*}$ is independently selected from halogen, $-OR^{20}$, and $C_{1-6}$ alkyl.

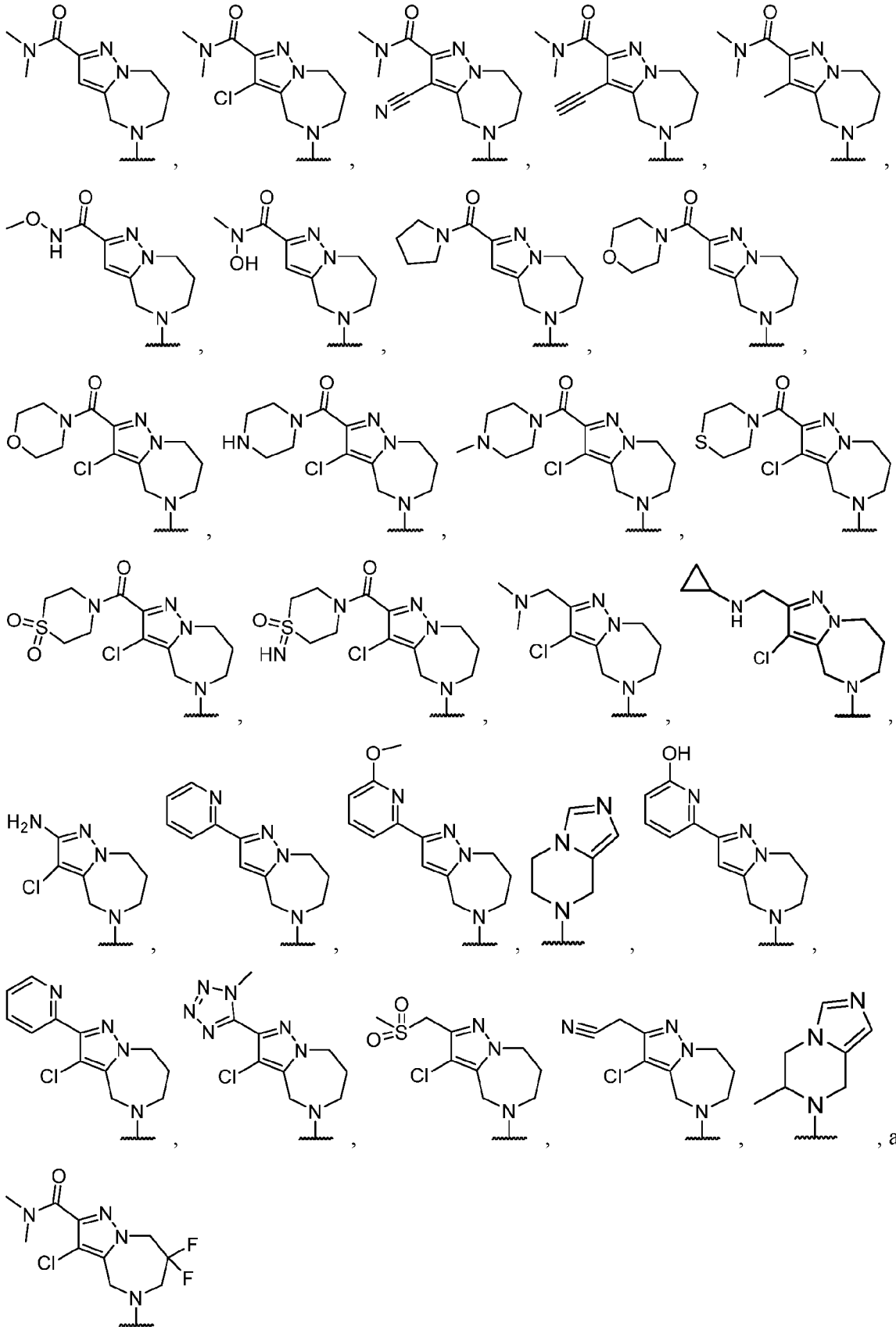
238. The compound or salt of claims 223 or 237, wherein the one or more optional substituents of $R^1$ are selected from chlorine, $-NH_2$, -CN, $C_1$ alkyl, $C_2$ alkenyl,  ,





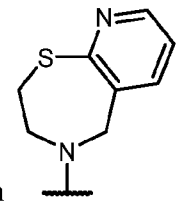
239. The compound or salt of claim 238, wherein $R^1$ is selected from

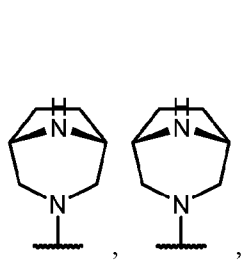
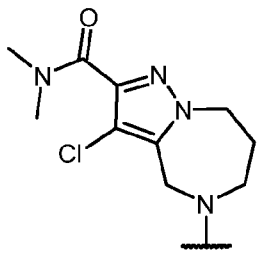
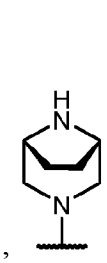
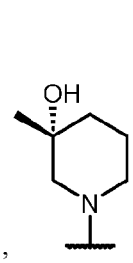
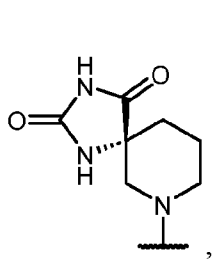
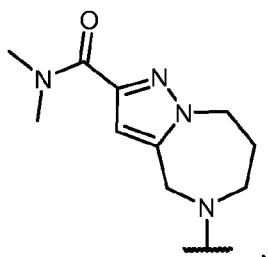
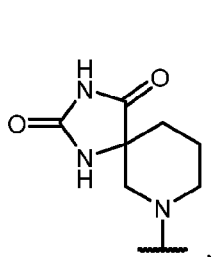
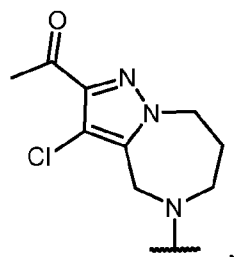
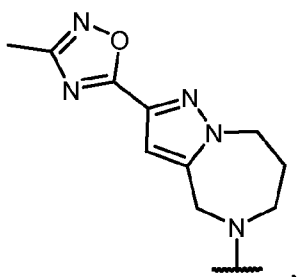
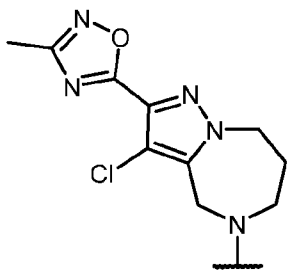
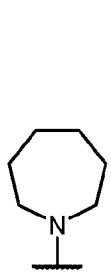
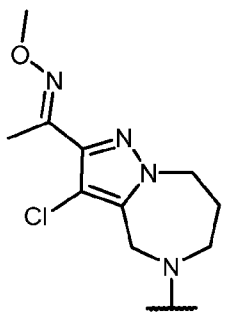
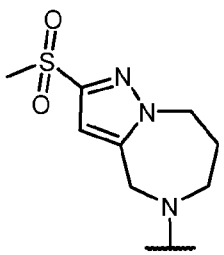
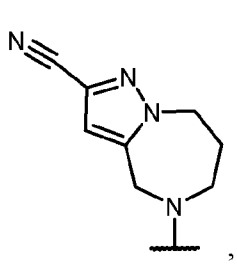


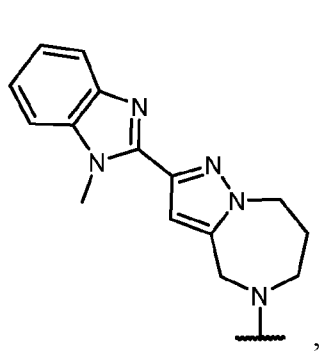
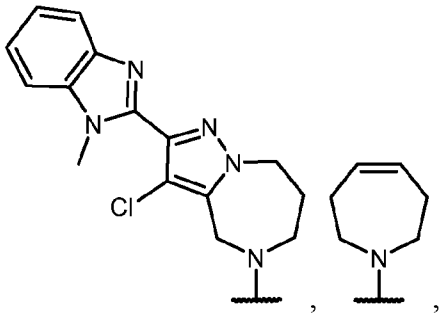
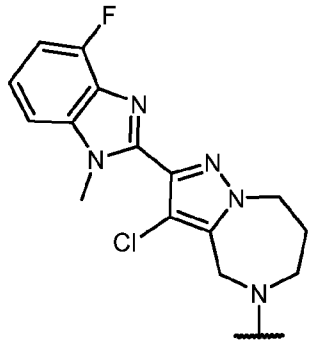
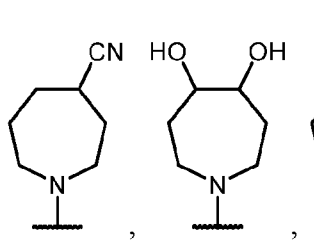


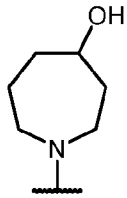
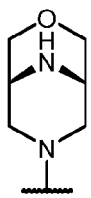
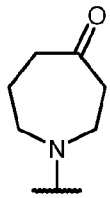
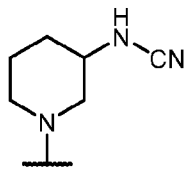
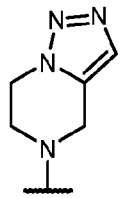
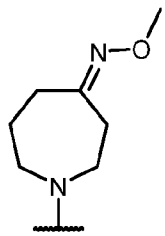
240. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from an optionally substituted 6- to 11-membered heterocycle, wherein the 6- to 11-membered heterocycle has at least one nitrogen atom.

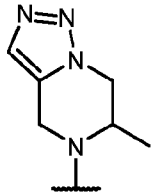
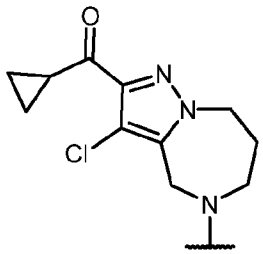
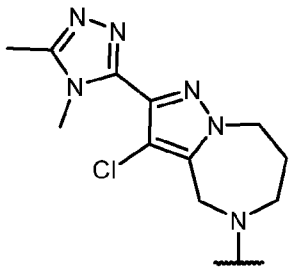
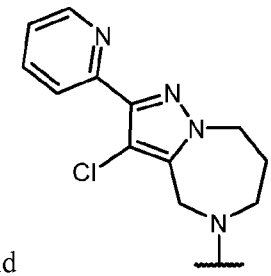
241. The compound or salt of claim 240, wherein the one or more optional substituents of $R^1$ is selected from halogen, $-OR^{20}$, $-C(O)N(R^{20})_2$, $-C(O)R^{20}$, $-S(O)_2R^{20}$, =O, $-C_{1-6}$ alkyl(=$NOR^{20}$), =$NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted independently with one or more $R^{1*}$; and wherein each $R^{1*}$ is independently selected from halogen, and $C_{1-6}$ alkyl.

242. The compound or salt of claim 240, wherein $R^1$ is selected from  ,

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 .

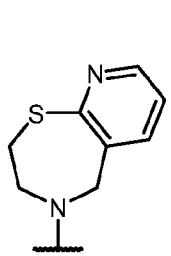
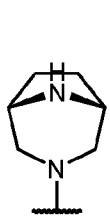
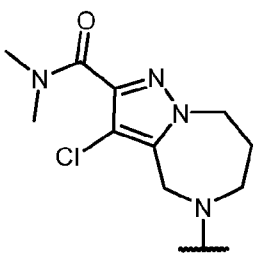





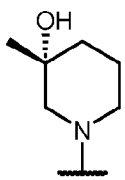
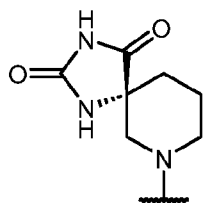
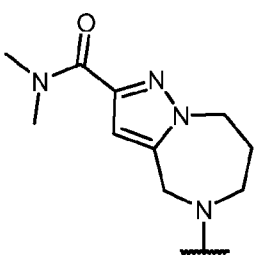
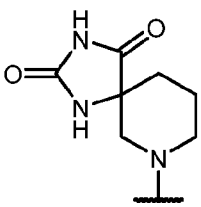
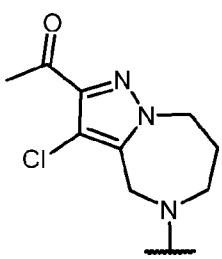
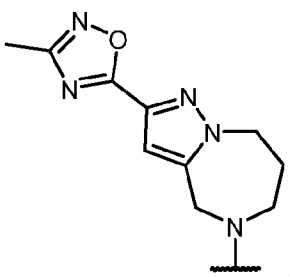
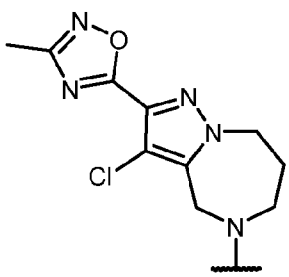
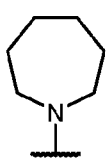
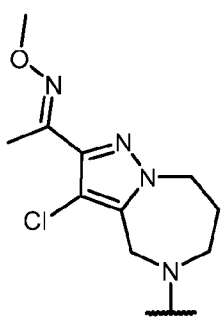







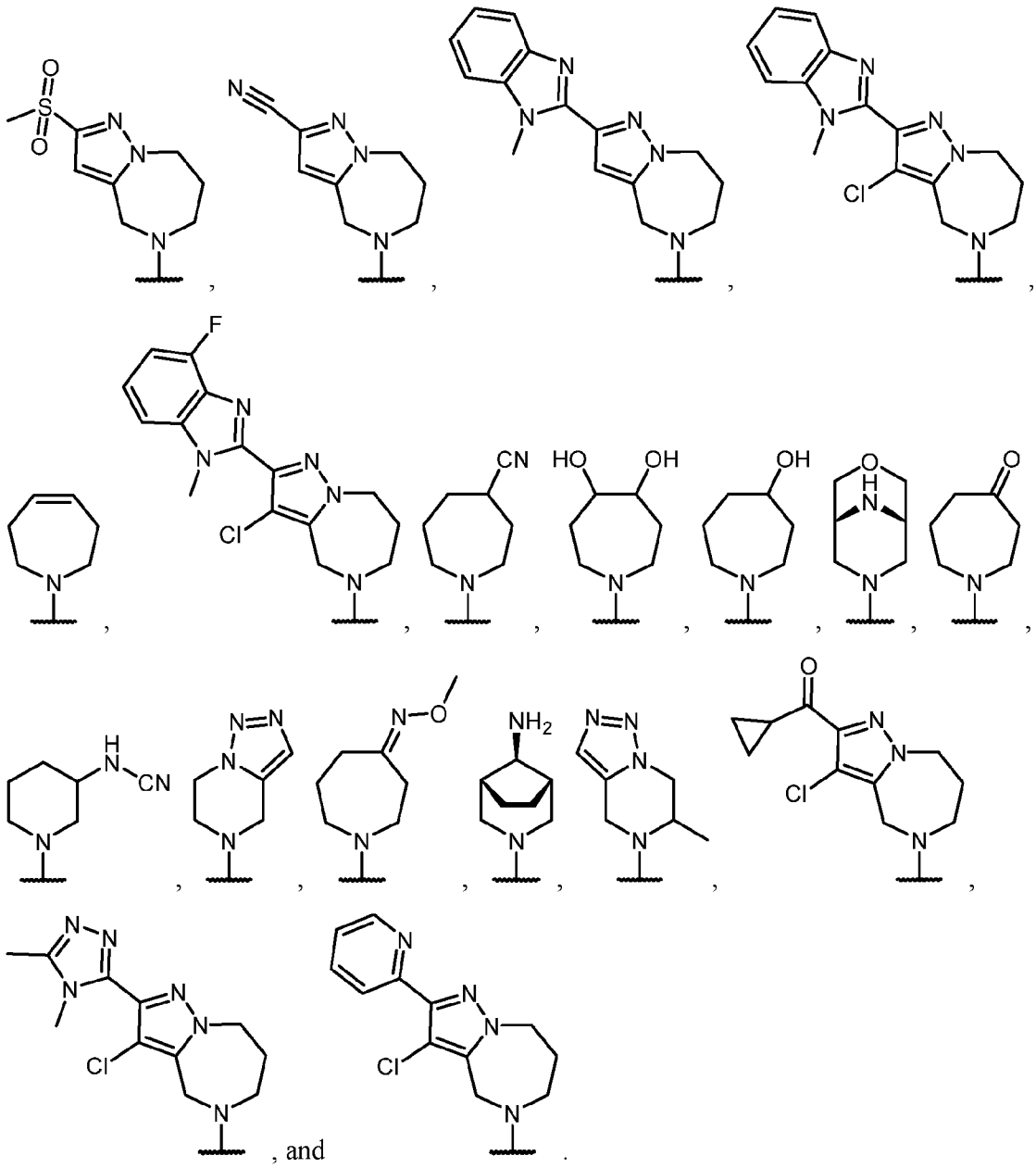





, and .

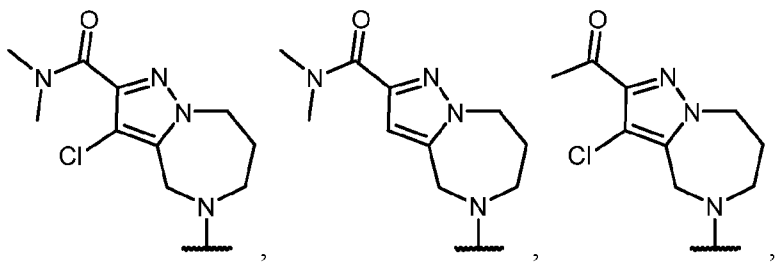
243. The compound or salt of any one of claims 1 to 40, or 48, wherein $R^1$ is selected from hydrogen,

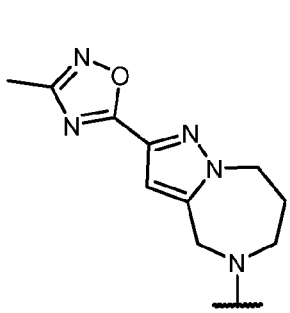
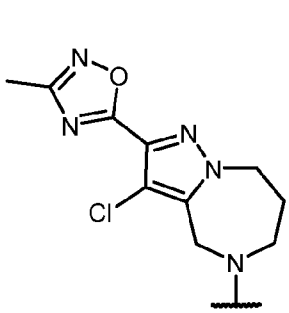
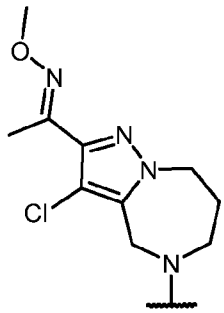
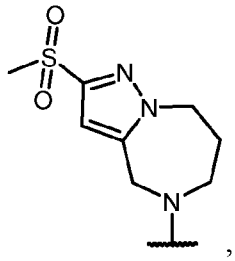
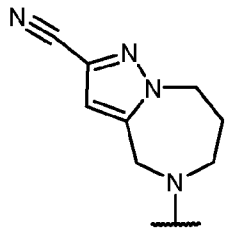
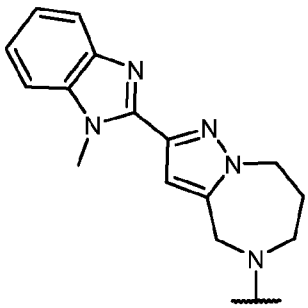
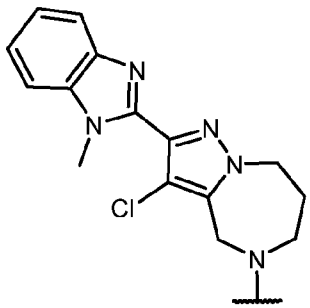
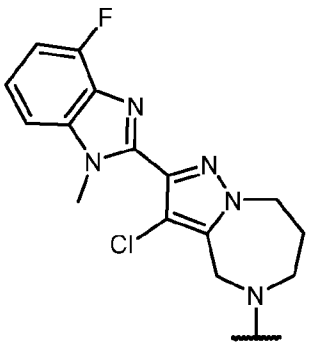
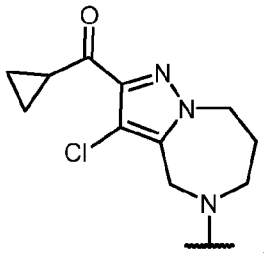
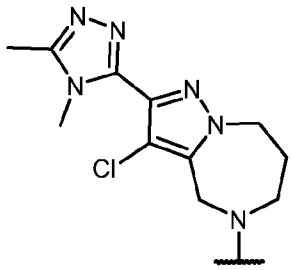
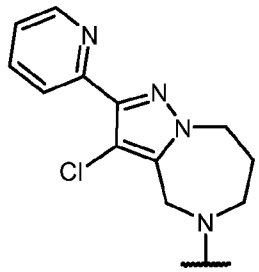




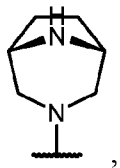
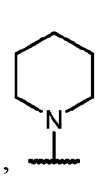
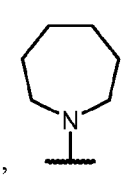
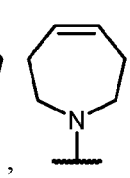
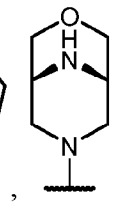
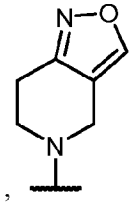
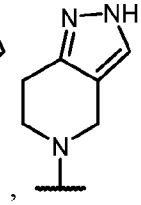
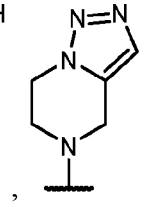
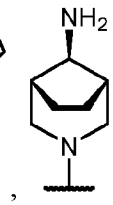
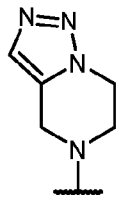


244. The compound or salt of any one of claim 1 to 40, or 48, wherein $R^1$ is selected from hydrogen,

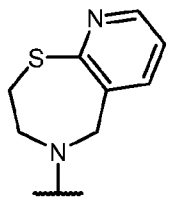
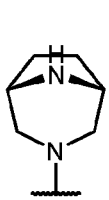
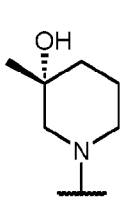
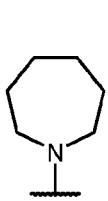
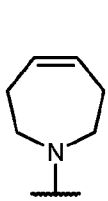
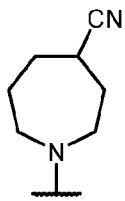
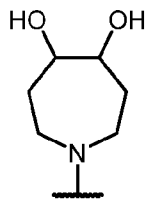
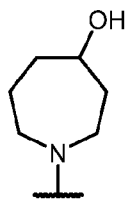
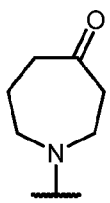
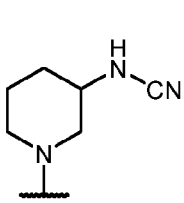
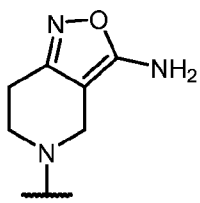
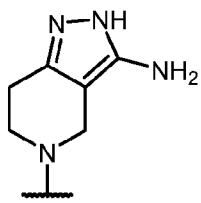
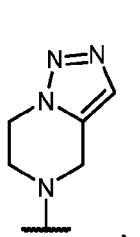
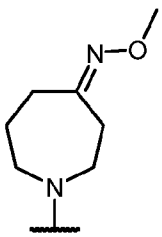
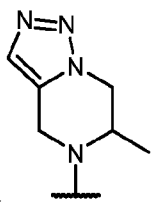



,

,

,

,

,

,

,

,

,

, and

.

245. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from hydrogen and optionally substituted 5- to 15-membered heterocycle.

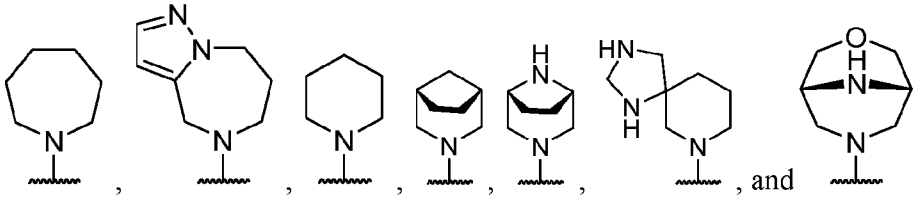
246. The compound or salt of claims 245, wherein $R^1$ is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  , each of which is optionally substituted.

247. The compound or salt of claim 246, wherein the optional one or more substituents of $R^1$ is selected from -OH, =NO($R^{20}$), -NHCN, and $C_{1-6}$ alkyl.

248. The compound or salt of any one of claims 245 to 247, wherein $R^1$ is selected from hydrogen,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

249. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from hydrogen and optionally substituted 7- to 10-membered heterocycle.

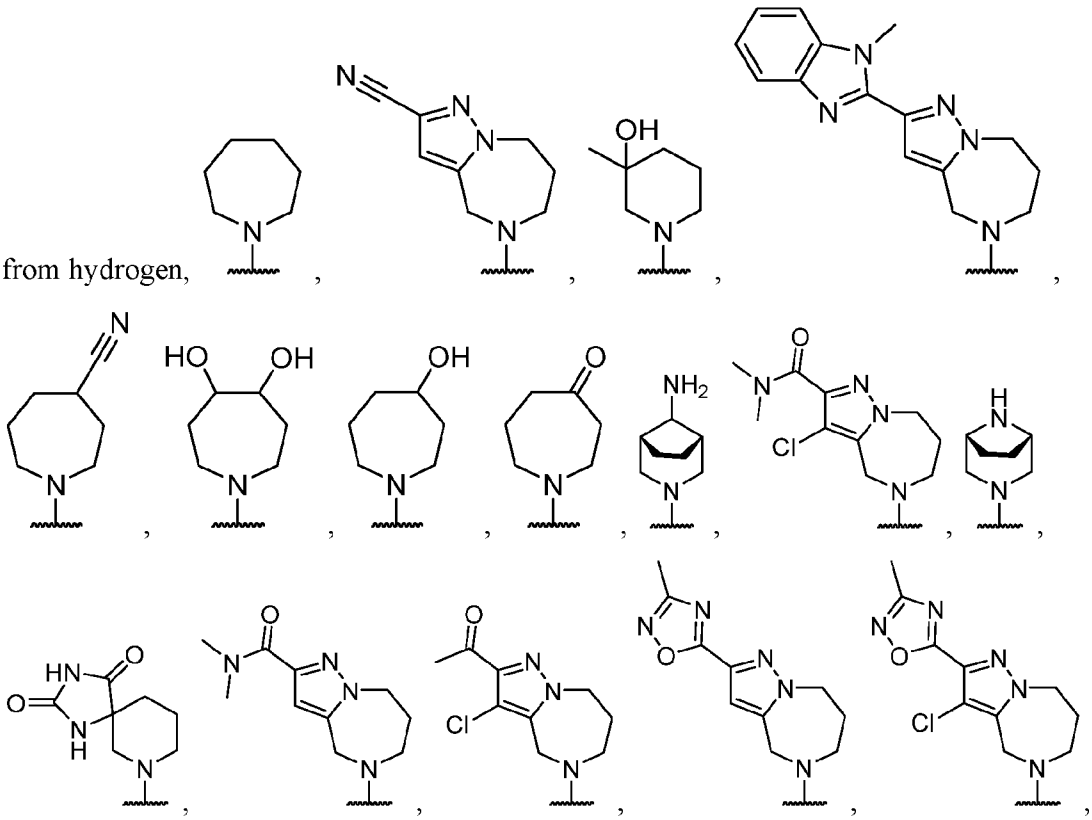
250. The compound or salt of claim 249, wherein $R^1$ is selected from hydrogen

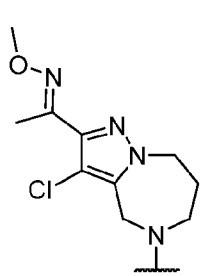
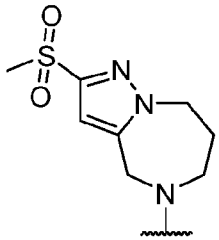
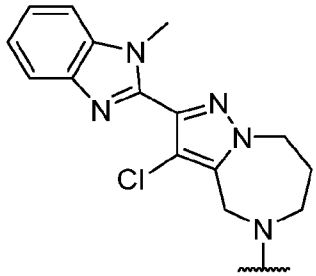
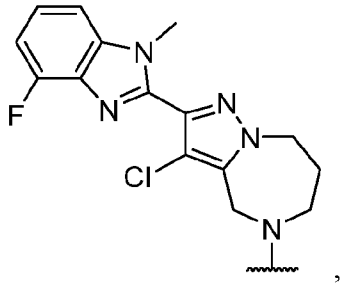
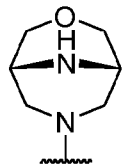
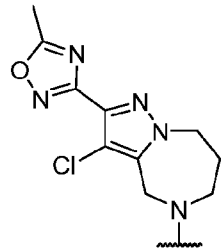
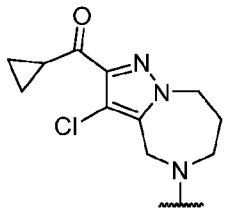


, each of which is optionally substituted.

251. The compound or salt of claims 249 or 250, wherein the optional one or more substituents of $R^1$ are independently selected from halogen, $-NH_2$, $-S(O)_2(R^{20})$, $-C(O)R^{20}$, $-C(O)N(R^{20})_2$, =O,=NO($R^{20}$), -CN, -NHCN, $C_{1-6}$ alkyl, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle is optionally substituted independently with one or more $R^{1*}$; and wherein each $R^{1*}$ is independently selected from halogen, and $C_{1-6}$ alkyl.

252. The compound or salt of any one of claims 249 to 251, wherein $R^1$ is selected from hydrogen,



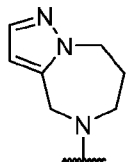








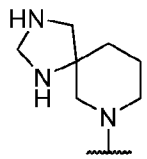
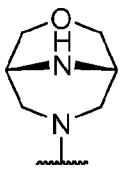
253. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from an optionally substituted 8- to 10-membered heterocycle.

254. The compound or salt of claim 253, wherein the heterocycle is bicyclic.

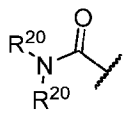
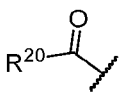
255. The compound or salt of claims 253 or 254, wherein the heterocycle has at least one nitrogen atom.

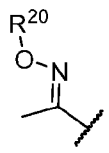
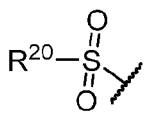
256. The compound or salt of claims 253 or 254, wherein the heterocycle has at least two nitrogen atoms.

257. The compound or salt of any one of claims 253 to 256,  

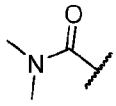
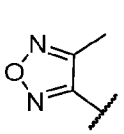
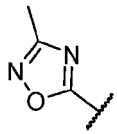
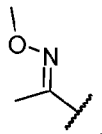
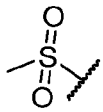
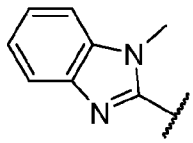
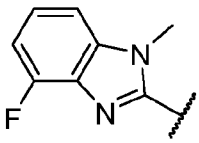
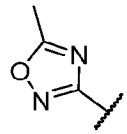
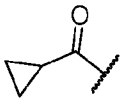
 

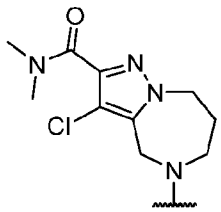
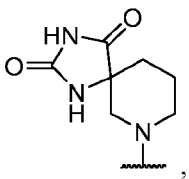
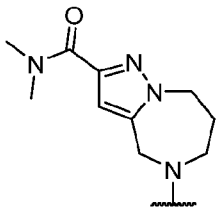
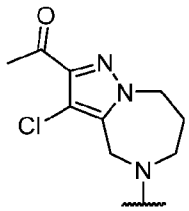
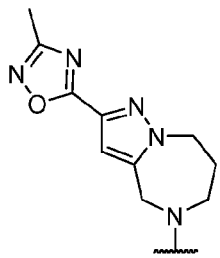
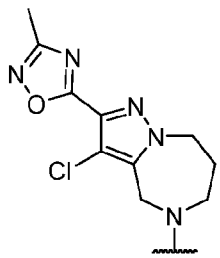
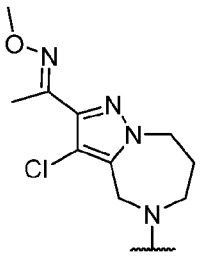
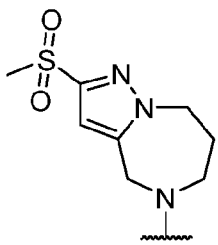
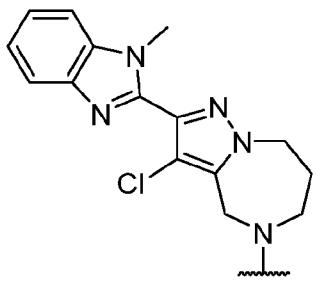
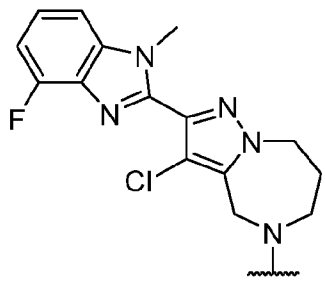
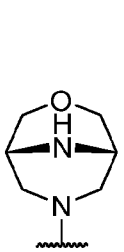
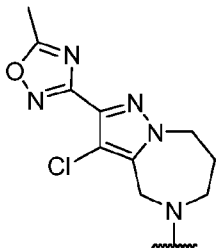
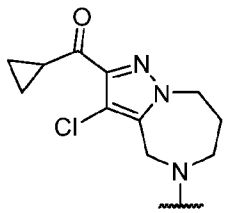
, each of which is optionally substituted.

258. The compound or salt of any one of claims 253 or 257, wherein the optional one or more substituents of $R^1$ are independently selected from halogen,  , oxo,  ,

, and 5- to 9-membered heteroaryl, wherein the 5- to 9-membered heteroaryl is substituted with at least one $R^{1*}$, wherein the $R^{1*}$ is selected from halogen, and $C_{1-6}$ alkyl.

259. The compound or salt of any one of claims 253 or 258, wherein the optional one or more substituents of $R^1$ are independently selected from chlorine,  , oxo,  ,  ,  ,  ,  ,  ,  ,  , and  .

260. The compound or salt of any one of claims 253 or 259,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

261. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is an optionally substituted 12- to 15-membered heterocycle.

262. The compound or salt of claim 261, wherein $R^1$ is an optionally substituted 12-membered heterocycle.

263. The compound or salt of claim 262, wherein $R^1$ is an optionally substituted 13-membered heterocycle.

264. The compound or salt of claim 263, wherein $R^1$ is an optionally substituted 14-membered heterocycle.

265. The compound or salt of claim 264, wherein $R^1$ is an optionally substituted 15-membered heterocycle.

266. The compound or salt of any one of claims 261 to 265, wherein the heterocycle of $R^1$ is tricyclic.

267. The compound or salt of any one of claims 261 to 266, wherein the heterocycle of $R^1$ contains a fused heterocycle.

268. The compound or salt of any one of claims 261 to 267, wherein the heterocycle of $R^1$ contains a spiro heterocycle.

269. The compound or salt of any one of claims 261 to 268, wherein the heterocycle of $R^1$ contains a fused and spiro-heterocycle.

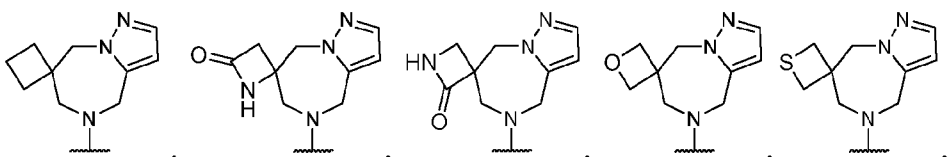
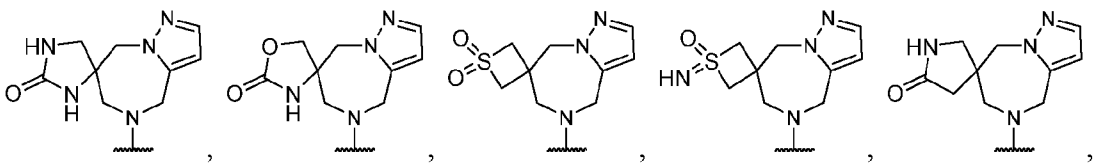
270. The compound or salt of any one of claims 261 to 269, wherein the heterocycle of $R^1$ is an unsaturated heterocycle.

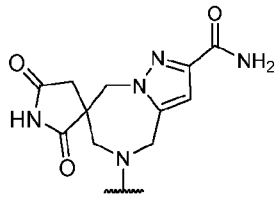
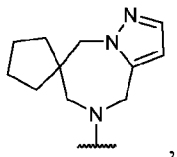
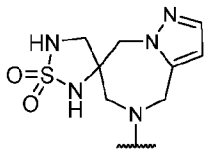
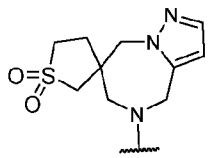
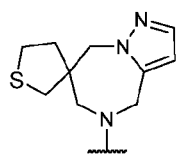
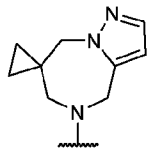
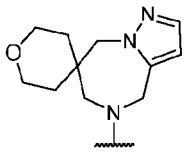
271. The compound or salt of any one of claims 261 to 269, wherein the heterocycle of $R^1$ is a non-aromatic heterocycle.

272. The compound or salt of any one of claims 261 to 271, wherein the heterocycle of $R^1$ has at least one double bond.

273. The compound or salt of any one of claims 261 to 272, wherein the heterocycle of $R^1$ has at least two double bonds.

274. The compound or salt of any one of claims 261 to 272, wherein the heterocycle of $R^1$ has two double bonds.

275. The compound or salt of any one of claims 261 to 273, wherein $R^1$ is selected from  ,  .

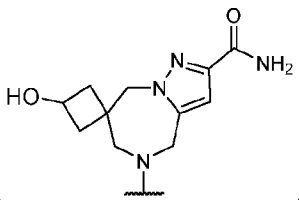
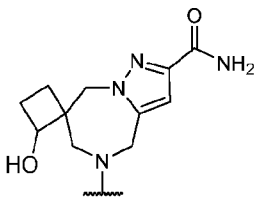
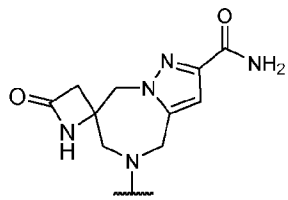
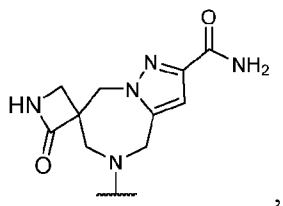
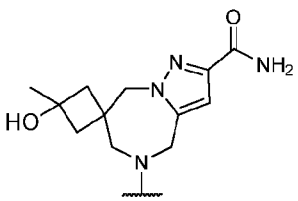
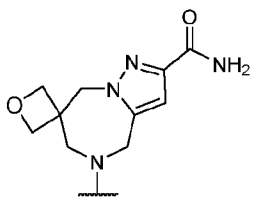
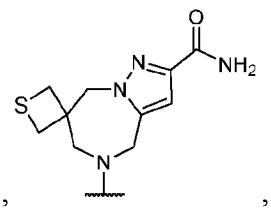
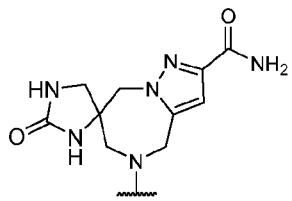
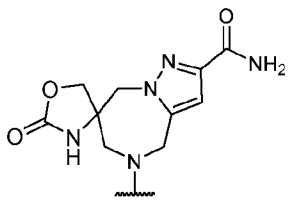
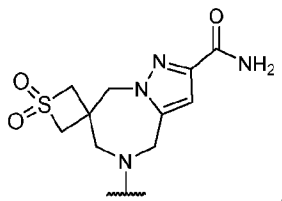
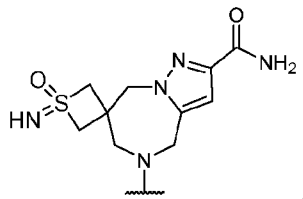
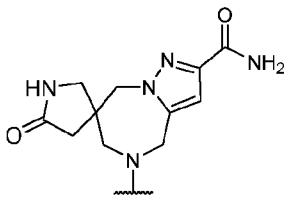
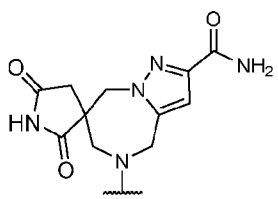








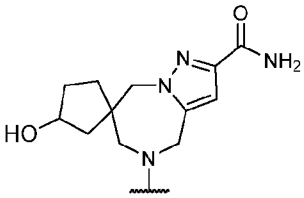
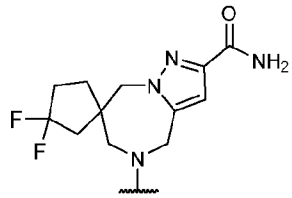
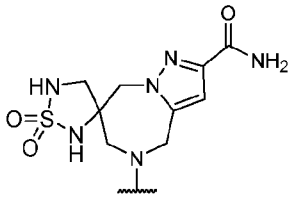
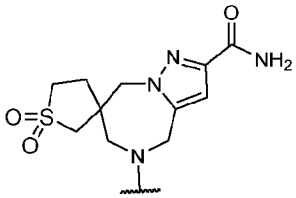
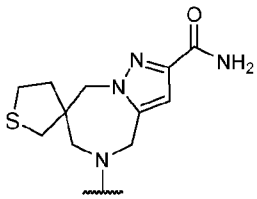
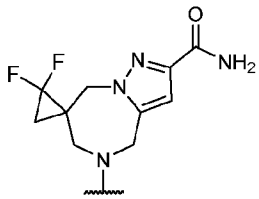
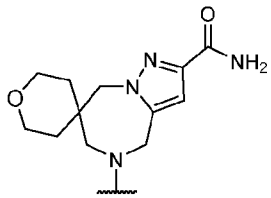
, and , each of which is optionally substituted with one or more substituents.

276. The compound or salt of claim 275, wherein the optional one or more substituents are selected from halogen, -OH, -NHCN, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-C(O)N(R^{20})_2$, $-C(O)NHOR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-NO_2$, =O, -CN, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl.

277. The compound or salt of claim 276, wherein the optional one or more substituents are selected from halogen, -OH, $C_{1-6}$ alkyl, and $-C(O)N(R^{20})_2$.

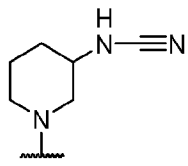
278. The compound or salt of any one of claims 261 to 277, wherein $R^1$ is selected from

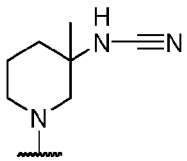




















, and 

.

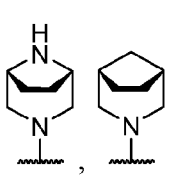
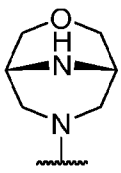
279. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from substituted 6- to 7-membered heterocycle, wherein the 6- to 7-membered heterocycle is substituted with at least one -NHCN, and further optionally substituted with one or more $C_{1-6}$ alkyl.

280. The compound or salt of claim 279, wherein $R^1$ is selected from 

and  .

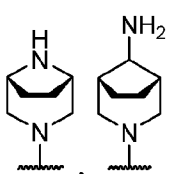
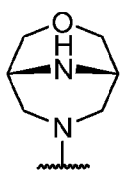
281. The compound or salt of any one of claims 1 to 40, or 48 to 175, wherein $R^1$ is selected from an optionally substituted bridged 8- to 9-membered heterocycle.

282. The compound or salt of claim 281, wherein the heterocycle of $R^1$ is selected from


, 
, and 
, each of which is optionally substituted.

283. The compound or salt of claims 281 or 282, wherein the one or more substituents of $R^1$ are selected from halogen, $C_{1-6}$ alkyl, $-N(R^{20})_2$, and $C_{1-6}$ aminoalkyl.

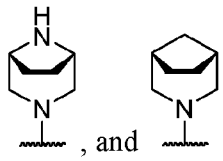
284. The compound or salt of any one of claims 281 to 283, wherein $R^1$ is selected


, 
, and 
.

285. The compound or salt of claim 281, wherein $R^1$ is selected from an optionally substituted bridged 8-membered heterocycle, wherein the heterocycle contains heteroatoms selected from nitrogen.

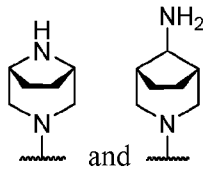
286. The compound or salt of claim 285, wherein the one or more substituents of $R^1$ are selected from $C_{1-6}$ alkyl, $-N(R^{20})_2$, and $C_{1-6}$ aminoalkyl.

287. The compound or salt of claim 286, wherein the heterocycle of $R^1$ is selected from



, and , each of which is optionally substituted.

288. The compound or salt of any one of claims 285 to 287, wherein $R^1$ is selected



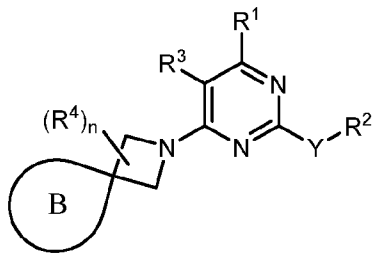
and .

289. The compound or salt of claims 1 to 40, or 48 to 175, or 288, wherein $R^1$ is selected from  .

290. The compound or salt of any one of claims 1 to 40, or 48 to 170, wherein $R^1$ is hydrogen.

291. The compound or salt of any one of claims 1 to 40, or 48 to 290, wherein n is 0.

292. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a RTK-MAPK pathway inhibitor and a compound of Formula (I-A):



Formula (I-A),

or a pharmaceutically acceptable salt thereof wherein:

$R^1$ is selected from 8- to 10-membered heterocycle, wherein the 8- to 10-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, $-OR^{20}$, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)R^{20}$, =O, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$

$_{6}$ alkyl-$SO_2R^{20}$, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, $-B(OR^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, and $C_3$-$C_{12}$ carbocycle;

B is selected from a 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle, wherein the 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle are each optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, =O, $-N(R^{21})_2$, $-B(OR^{21})_2$, $-OR^{21}$, $-SR^{21}$, $-S(O)_2(R^{21})$, $-S(O)_2N(R^{21})_2$, $-NR^{21}S(O)_2R^{21}$, $-C(O)N(R^{21})_2$, $-C(O)NR^{21}OR^{21}$, $-N(R^{21})C(O)R^{21}$, $-N(R^{21})C(O)N(R^{21})_2$, $-N(R^{21})C(O)OR^{21}$, $-C(O)R^{21}$, $C(O)OR^{21}$, $-OC(O)R^{21}$, $-OC(O)N(R^{21})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

Y is selected from a bond, and -O-;

$R^2$ is selected from heterocycle, aryl, $C_1$-$C_6$ alkyl, -L-heterocycle, -L-$N(R^{23})_2$, -L-$OR^{23}$, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-$NHC(=NH)NH_2$, -L-$C(O)N(R^{23})_2$, -L-$C_1$-$C_6$ haloalkyl, -L-$OR^{23}$, -L-$NR^{23}C(O)$-aryl, -L-COOH, -L-$NR^{23}S(O)_2(R^{23})$, -L-$S(O)_2N(R^{23})_2$, -L-$N(R^{23})C(O)(OR^{23})$, -L-$OC(O)N(R^{23})_2$, and -L-$C(=O)OC_1$-$C_6$ alkyl, wherein the heterocycle, the heterocycle portion of -L-heterocycle, and the cycloalkyl portion of the -L-cycloalkyl are each optionally substituted with one or more $R^6$, and wherein the aryl, aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$;

$R^3$ is selected from hydrogen, halogen, -CN, $-NO_2$, $-N(R^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

each $R^4$ is independently selected from halogen, $-NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

n is selected from 0, 1, 2, 3, and 4;

each $R^5$ is independently selected from hydrogen and $C_1$-$C_6$ alkyl;

each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, $=CH_2$, $=NO$-$C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, -$N(R^5)S(O)_2(R^5)$, -Q-phenyl, -Q-phenyl$SO_2F$, -NHC(O)phenyl, -NHC(O)phenyl$SO_2F$, $C_1$-$C_3$ alkyl substituted pyrazolyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, -$C(O)N(R^5)_2$, tert-butyldimethylsilyloxy$CH_2$-, -$N(R^5)_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$ alkyl)C(=O), oxo, ($C_1$-$C_3$ haloalkyl)C(=O)-, -$SO_2F$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC_1$-$C_6$ alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)C_1$-$C_6$ alkyl, -$CH_2$(pyrazolyl), -$CH_2NHSO_2C_1$-$C_6$ alkyl, -$CH_2OC(O)$heterocycle, -$OC(O)N(R^5)_2$, -OC(O)NH($C_1$-$C_3$ alkyl)O($C_1$-$C_3$ alkyl), -OC(O)NH($C_1$-$C_3$ alkyl)O($C_1$-$C_3$ alkyl)phenyl($C_1$-$C_3$ alkyl)$N(CH_3)_2$, -OC(O)NH($C_1$-$C_3$ alkyl)O($C_1$-$C_3$ alkyl)phenyl, -OC(O)heterocycle, -O-$C_1$-$C_3$ alkyl, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, and -$CH_2$heterocycle, wherein the phenyl of -NHC(O)phenyl and -OC(O)NH($C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl)phenyl are optionally substituted with one or more substituents selected from -C(O)H and OH, and wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo and hydroxy; and wherein the heterocycle of -$CH_2$heterocyclyl is optionally substituted with oxo;

each Q is selected from a bond, S, and O;

each $R^7$ is independently selected from halogen, hydroxy, HC(=O)-, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, -$C(O)N(R^5)_2$, and -$N(R^5)_2$;

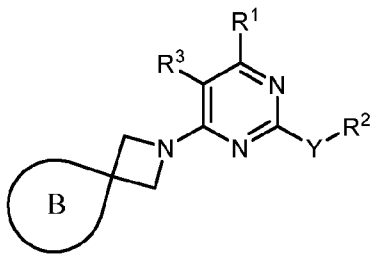
each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, hydroxy, $C_{1-6}$ alkoxy, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle, and 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

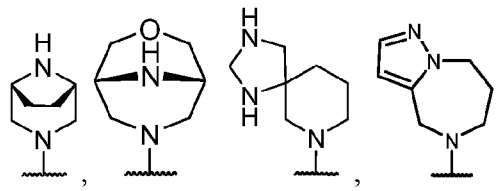
each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle.

293. The compound or salt of claim 292, wherein Formula (I-A) is represented by Formula (I-B),



Formula (I-B),

or a pharmaceutically acceptable salt thereof wherein:

wherein $R^1$ is selected from  , each of which is optionally substituted with one or more substituents independently selected from halogen, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)R^{20}$, =O, and 5- to 12-membered heterocycle, wherein the 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, $-OR^{20}$, $-N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl;

Y is -O-;

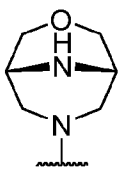
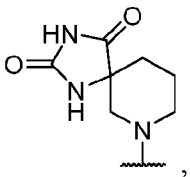
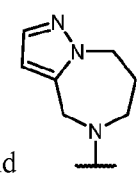
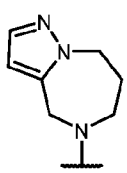
$R^2$ is selected from -L-heterocycle, and -L-$N(R^{23})_2$, wherein the heterocycle portion of -L-heterocycle is optionally substituted with one or more $R^6$.

B is selected from a 7- to 15-membered heterocycle, wherein the 7- to 15-membered heterocycle is optionally substituted with one or more substituents independently selected from

halogen, -CN, =O, -N($R^{21}$)$_2$, -O$R^{21}$, $C_{1-6}$ alkyl-N($R^{20}$)$_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, and $C_{2-6}$ alkynyl;

$R^3$ is selected from hydrogen, halogen, -CN, -N($R^{20}$)$_2$, -O$R^{20}$, -C(O)$R^{20}$, $C_{1-6}$ alkyl-N($R^{20}$)$_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl; and

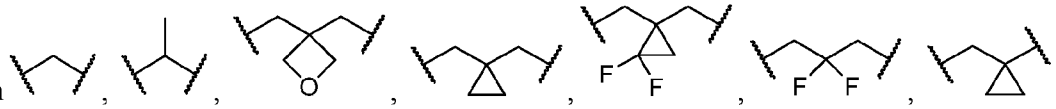
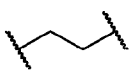
each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, and $C_{3-12}$ carbocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, and oxo.

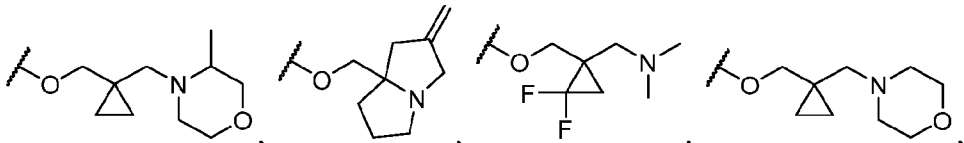
294. The compound or salt of claims 292 or 293, wherein $R^1$ is selected from  ,  ,  , and  , wherein  , is optionally substituted with one or more substituents independently selected from halogen, -S(O)$_2$($R^{20}$), -C(O)N($R^{20}$)$_2$, -$C_{1-6}$ alkyl(=NO$R^{20}$), -C(O)$R^{20}$, =O, and 5- to 9-membered heterocycle, wherein the 5- to -membered heterocycle are each optionally substituted independently with one or more $R^{1*}$; and

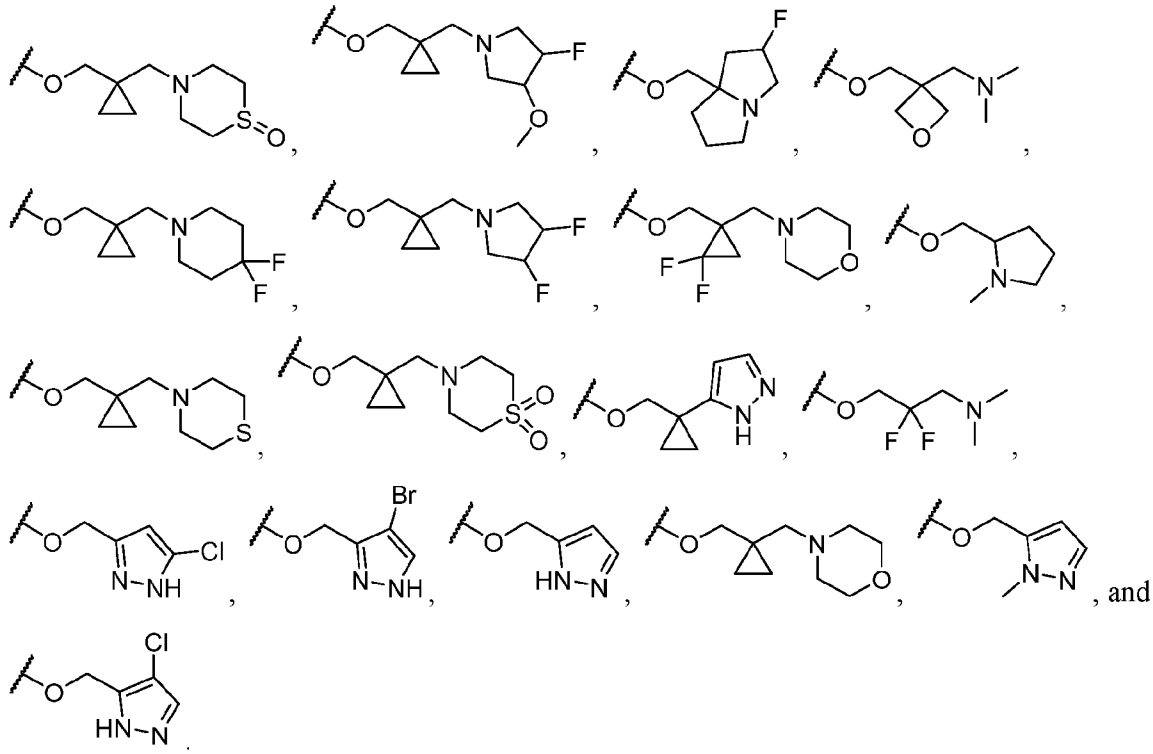
each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

295. The compound or salt of any one of claims 292 to 294, wherein Y is -O-.

296. The compound or salt of any one of claims 292 to 295, wherein each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, and $C_1$-$C_4$ alkyl; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 4- to 6-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 6-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen.

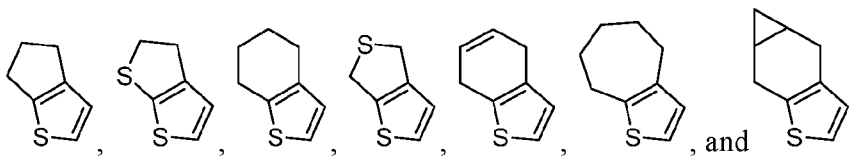
297. The compound or salt of any one of claims 292 to 296, wherein each L is selected from  , and  .

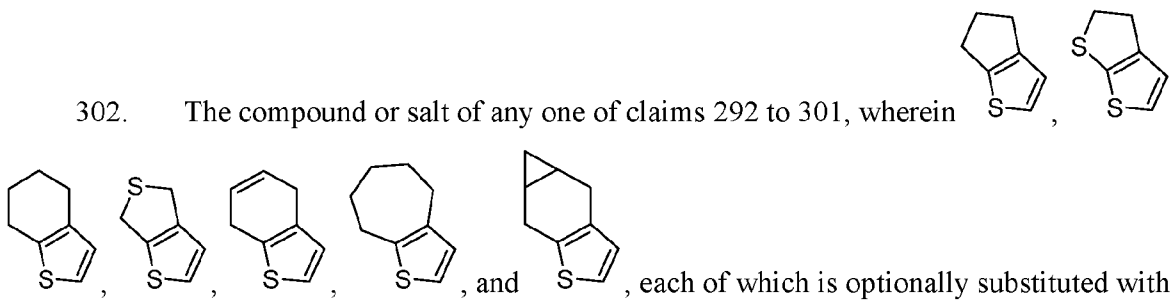
298. The compound or salt of any one of claims 292 to 297, wherein Y-$R^2$ is selected from  ,



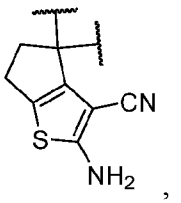
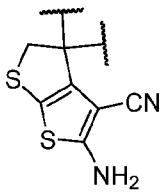
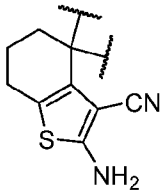
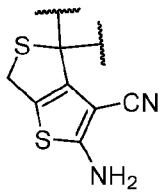
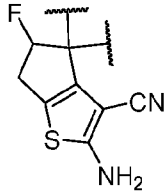
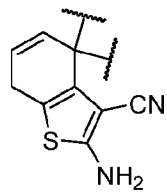
299. The compound or salt of any one of claims 292 to 298, wherein B is selected from an optionally substituted 8- to 10-membered heterocycle.

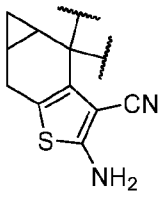
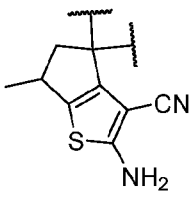
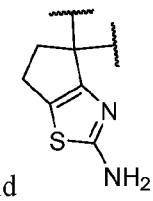
300. The compound or salt of claim 299, wherein the 8- to 10-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -CN, -$NH_2$, and $C_{1-6}$ alkyl.

301. The compound or salt of any one of claims 292 to 300, wherein the heterocycle of B is selected from  .

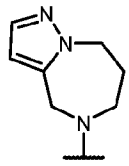
302. The compound or salt of any one of claims 292 to 301, wherein  , each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -$NH_2$, and $C_{1-6}$ alkyl.

303. The compound or salt of any one of claims 292 to 302, wherein B is selected from

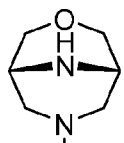







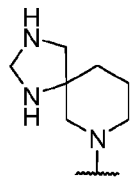


, and  .

304. The compound or salt of any one of claims 292 to 303, wherein $R^3$ is -CN.

305. The compound or salt of any one of claims 292 to 304, wherein $R^1$ is  , which is optionally substituted with one or more substituents.

306. The compound or salt of any one of claims 292 to 304, wherein $R^1$ is  .

307. The compound or salt of any one of claims 292 to 304, wherein $R^1$ is  .

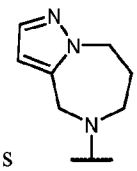
308. The compound or salt of any one of claims 292 to 304, wherein $R^1$ is  .

309. The compound or salt of any one of claims 292 to 308, wherein the one or more optional substituents of $R^1$ are independently selected from halogen, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)R^{20}$ =O, and 5- to 9-membered heterocycle, wherein the 5- to -membered heterocycle are each optionally substituted independently with one or more $R^{1*}$.

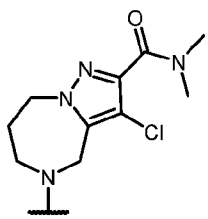
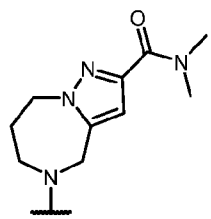
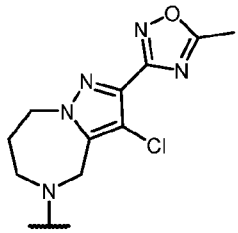
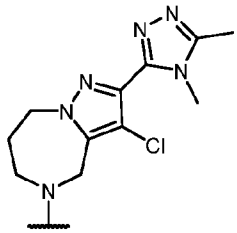
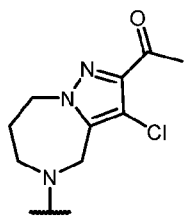
310. The compound or salt of any one of claims 292 to 308, wherein the one or more optional substituents of $R^1$ are independently selected from halogen, $-S(O)_2(R^{20})$, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)R^{20}$, =O, and 5- to 9-membered heterocycle, wherein the 5- to -membered heterocycle are each optionally substituted independently with one or more $R^{1*}$.

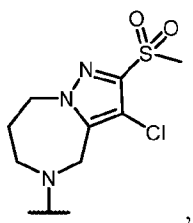
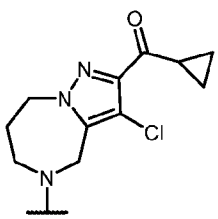
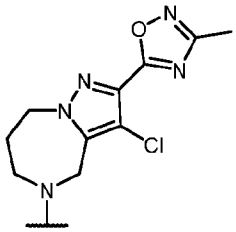
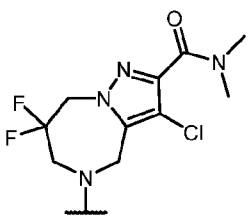
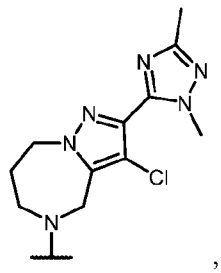
311. The compound or salt of any one of claims 292 to 308, wherein the one or more optional substituents of $R^1$ are independently selected from halogen, $-C(O)N(R^{20})_2$, $-C_{1-6}$ alkyl(=$NOR^{20}$), $-C(O)R^{20}$, and 5- to 9-membered heterocycle, wherein the 5- to -membered heterocycle are each optionally substituted independently with one or more $R^{1*}$.

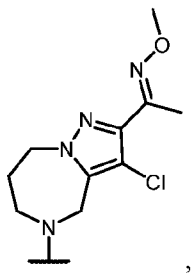
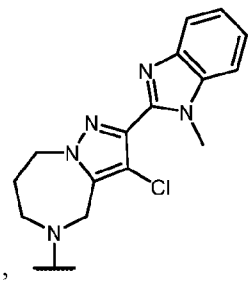
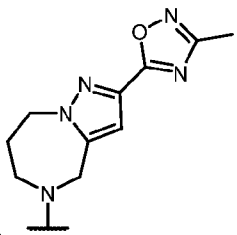
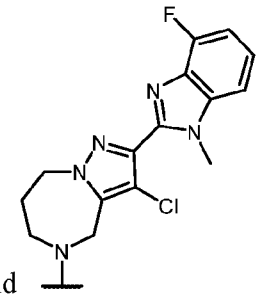
312. The compound or salt of claim 311, wherein each $R^{1*}$ is independently selected from halogen, $C_{1-6}$ haloalkyl, and $C_{1-6}$ alkyl.

313. The compound or salt of any one of claims 292 to 305, wherein $R^1$ is  , which is subtituted with at least one substituent.

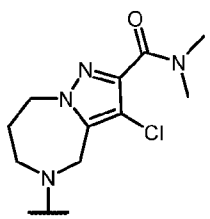
314. The compound or salt of any one of claims 292 to 305, wherein $R^1$ is

 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,  ,  , and  .

315. The compound or salt of any one of claims 292 to 305, wherein $R^1$ is

 .

316. A pharmaceutical composition comprising the compound of any one of claims 1 to 315 and a pharmaceutically acceptable excipient.

317. A method of treating a disease or disorder, using a compound or salt of any one of claims 1 to 315 or a pharmaceutical composition of claim 316.

318. A method of inhibiting KRas G12D and/or other G12 mutants, using a compound or salt of any one of claims 1 to 315 or a pharmaceutical composition of claim 316.

319. A method of inhibiting KRas G12D and/or other G12 mutants, using a compound or salt of any one of claims 1 to 315 or a pharmaceutical composition of claim 316.

320. A method of inhibiting KRas G12D and/or other G12 alleles, using a compound or salt of any one of claims 1 to 315 or a pharmaceutical composition of claim 316.

321. A method of inhibiting KRas G12D and/or other alleles, using a compound or salt of any one of claims 1 to 315 or a pharmaceutical composition of claim 316.

322. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a RTK-MAPK pathway inhibitor and a compound of Formulas (I), (I-A), or (I-B)wherein the compound is selected from: compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

323. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a RAF-MEK-ERK pathway inhibitor and a compound of Formulas (I), (I-A), or (I-B)wherein the compound is selected from: compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

324. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a ERBB family inhibitor and a compound of Formulas (I), (I-A), or (I-B)wherein the compound is selected from: compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100,

101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

325. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of a EGFR inhibitor and a compound of Formulas (I), (I-A), or (I-B) wherein the compound is selected from: compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

326. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of an SHP-2 inhibitor and a compound of Formulas (I), (I-A), or (I-B) wherein the compound is selected from: compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

327. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of an SOS1 inhibitor and a compound of Formulas (I), (I-A), or (I-B), wherein the compound is selected from: compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 74A, 74B, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, and 111, or a pharmaceutically acceptable salt of anyone thereof.

328. The method of any one of claims 322 to 327, wherein the compound of Formulas (I), (I-A), or (I-B) is selected from compound 2, 3, 4, 14, 25, and 74, or a pharmaceutically acceptable salt of anyone thereof.

329. The method of any one of claims 322 to 327, wherein the compound of Formulas (I), (I-A), or (I-B) is selected from compound 2, or a pharmaceutically acceptable salt of thereof.

330. The method of any one of claims 322 to 327, wherein the compound of Formulas (I), (I-A), or (I-B) is selected from compound 3, or a pharmaceutically acceptable salt of thereof.

331. The method of any one of claims 322 to 327, wherein the compound of Formulas (I), (I-A), or (I-B) is selected from compound 4, or a pharmaceutically acceptable salt of thereof.

332. The method of any one of claims 322 to 327, wherein the compound of Formulas (I), (I-A), or (I-B) is selected from compound 14, or a pharmaceutically acceptable salt of thereof.

333. The method of any one of claims 322 to 327, wherein the compound of Formulas (I), (I-A), or (I-B) is selected from compound 25, or a pharmaceutically acceptable salt of thereof

334. The method of any one of claims 322 to 327, wherein the compound of Formulas (I), (I-A), or (I-B) is selected from compound 74, or a pharmaceutically acceptable salt of thereof.

335. The method of any one of claims 322 to 333, wherein the combination exhibits synergy.

336. The method of any one of claims 322 to 325 & 328 to 333, wherein the inhibitor is selected from the group consisting of afatinib, dacomitinib, poziotinib, erlotinib, gefitinib, sapitinib, tarloxotinib, and cetuximab.

337. The method of any one of claims 322 to 325 and 328 to 333, wherein the inhibitor is cetuximab.

338. The method of claim of any one of claims 322 to 337, wherein the combination exhibits synergy.

339. The method of claims 322 or 337, wherein the therapeutically effective amount of the combination of the inhibitor and the compound or salt results in an increased duration of overall survival, an increased duration of progression free survival, an increase in tumor growth regression, an increase in tumor growth inhibition, an increased duration of stable disease in the subjects relative to treatment with only the compound or salt, or any combination thereof.

340. The method of any one of claims 322 to 339, wherein the therapeutically effective amount of the compound or salt of the combination is between about 0.01 to 100 mg/kg per day.

341. The method of any one of claims 322 to 340, wherein the therapeutically effective amount of the compound or salt in the combination is between about 0.1 to 50 mg/kg per day.

342. The method of any one of claims 322 to 341, wherein the therapeutically effective amount of the inhibitor of the combination is between about 0.01 to 100 mg/kg per day.

343. The method of any one of claims 322 to 342, wherein the therapeutically effective amount of the inhibitor of the combination is between about 0.1 to 50 mg/kg per day.

344. The method of any one of claims 322 to 343, wherein the inhibitor and the compound or salt are administered on different days.

345. The method of any one of claims 322 to 344, wherein the compound or salt is administered at a maximum tolerated dose.

346. The method of any one of claims 322 to 345, wherein the inhibitor is administered at a maximum tolerated dose.

347. The method of any one of claims 322 to 346, wherein the inhibitor and the compound or salt are each administered at a maximum tolerated dose.

348. The method of claim 322, wherein the RTK-MAPK pathway inhibitor is a RAF-MEK-ERK pathway inhibitor.

349. The method of claim 322, wherein the RTK-MAPK pathway inhibitor is a ERBB family inhibitor.

350. The method of claim 322 or 349, wherein the inhibitor is selected from the group consisting of afatinib, dacomitinib, poziotinib, erlotinib, gefitinib, sapitinib, tarloxotinib, and cetuximab.

351. The method of claim 322 or 350, wherein the inhibitor is cetuximab.

352. The method of claim 322, wherein the RTK-MAPK pathway inhibitor is an epidermal growth factor receptor (EGFR) inhibitor.

353. The method of claim 322, wherein the RTK-MAPK pathway inhibitor is a SHP-2 inhibitor.

354. The method of claim 353, wherein the SHP-2 inhibitor is SHP-099 (6-(4-Amino-4-methylpiperidin-l-yl)-3-(2,3-dichlorophenyl)pyrazin-2-amine dihydrochloride); RMC-4550 (3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazin-2-yl)methanol), RMC-4360 or TNO155 (Novartis).

355. The method of claim 354, wherein the SHP-2 inhibitor is RMC-4550.

356. The method of claim 354, wherein the SHP-2 inhibitor is RMC-4360.

357. The method of claim 354, wherein the SHP-2 inhibitor is TNO155.

358. The method of claim 354, wherein the SHP-2 inhibitor is SHP-099.

359. The method of claim 322, wherein the RTK-MAPK pathway inhibitor is a SOS1 inhibitor.

360. The method of claim 359, wherein the SOS1 inhibitor is BI-3406.

361. The method of any one of claims 322 to 360, wherein the RTK-MAPK pathway inhibitor is administered orally.

362. The method of any one of claims 322 to 361, wherein the cancer is selected from:

Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma;

Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma;

Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma);

Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma);

Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma;

Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma;

Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors;

Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma);

Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma);

Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma);

Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and

Adrenal glands: neuroblastoma.

363. The method of any one of claims 322 to 362, wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer.

364. The method of any one of claims 322 to 362, wherein the cancer is non-small cell lung cancer.

365. The method of any one of claims 322 to 362, wherein the cancer is small cell lung cancer.

366. The method of any one of claims 322 to 362, wherein the cancer is colorectal cancer.

367. The method of any one of claims 322 to 362, wherein the cancer is rectal cancer.

368. The method of any one of claims 322 to 362, wherein the cancer is pancreatic cancer.

369. The method of any one of claims 322 to 362, wherein the cancer is a solid tumor cancer.

370. The method of any one of claims 322 to 369, wherein the cancer is selected from a KRas mutant-associated cancer.

371. The method of any one of claims 322 to 369, wherein the cancer is selected from a KRas wildtype-associated cancer.

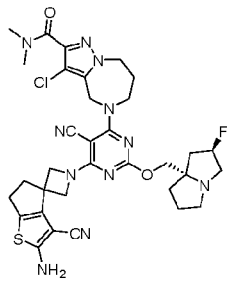
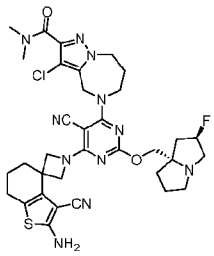
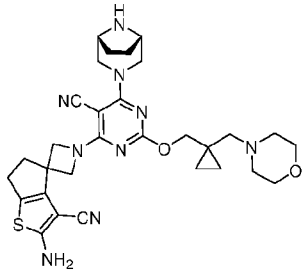
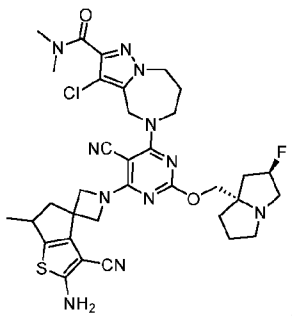
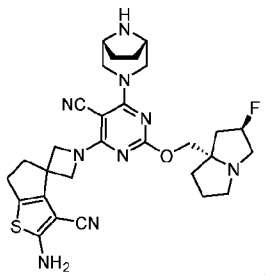
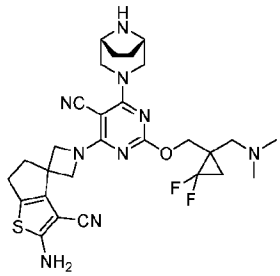
372. The method of any one of claims 322 to 369, wherein the cancer is selected from a KRas G12D-associated cancer, a KRas G12V-associated cancer, and a KRas wildtype-associated cancer.

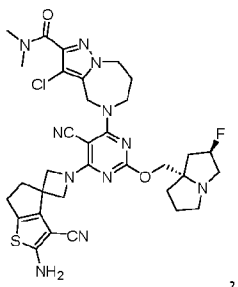
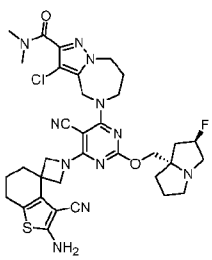
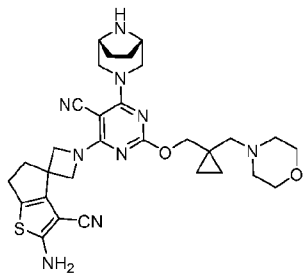
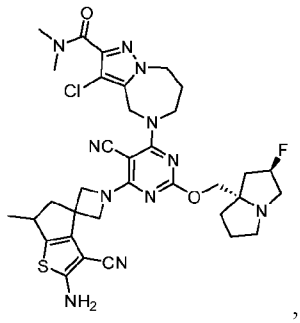
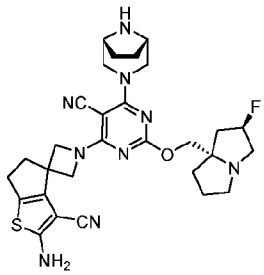
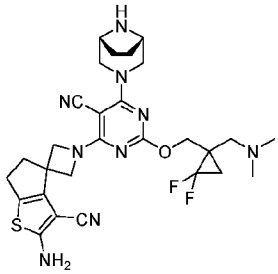
373. The method of any one of claims 322 to 369, wherein the cancer is a KRas G12D-associated cancer.

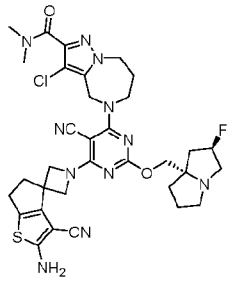
374. The method of any one of claims 322 to 369, wherein the cancer is a KRas G12V-associated cancer.

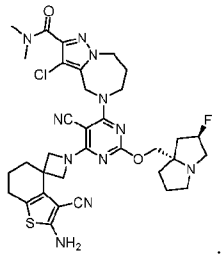
375. The method of any one of claims 322 to 369, wherein the cancer is a KRas wildtype-associated cancer.

376. The method of any one of claims 322 to 369, wherein the RTK-MAPK pathway inhibitor synergistically increases the sensitivity of cancer cells to the compound or salt.

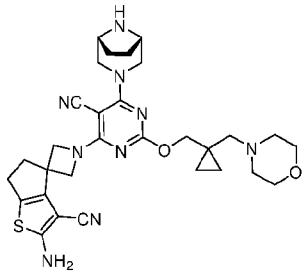
377. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination of cetuximab and a compound selected from  ,  ,  ,  ,  , and  , or a pharmaceutically acceptable salt of any one thereof.

378. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of cetuximab and a compound selected from  ,  ,  ,  ,  , and  , or a pharmaceutically acceptable salt of any one thereof.

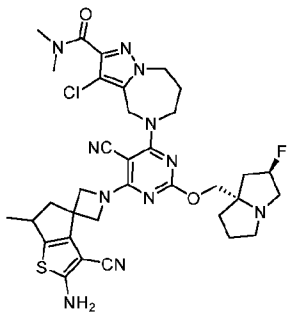
379. The method of claims 377 or 378, wherein the compound is  .

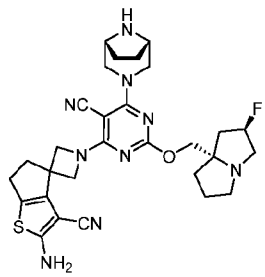
380. The method of claims 377 or 378, wherein the compound is  .

381. The method of claims 377 or 378, wherein the compound is

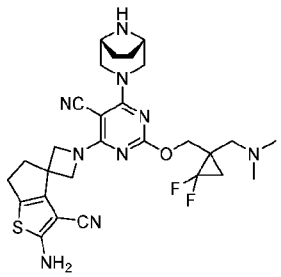
 .

382. The method of claims 377 or 378, wherein the compound is

 .

383. The method of claims 377 or 378, wherein the compound is  .

384. The method of claims 377 or 378, wherein the compound is



385. The method of any one of claims 377 to 384, wherein cetuximab synergistically increases the sensitivity of the cancer cells to the compound.

386. The method of any one of claims 377 to 385, wherein the cancer is selected from:

Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma;

Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma;

Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma);

Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma);

Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma;

Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma;

Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors;

Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma);

Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma);

Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma);

Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and

Adrenal glands: neuroblastoma.

387. The method of any one of claims 377 to 385, wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer.

388. The method of any one of claims 377 to 385, wherein the cancer is non-small cell lung cancer.

389. The method of any one of claims 377 to 385, wherein the cancer is small cell lung cancer.

390. The method of any one of claims 377 to 385, wherein the cancer is colorectal cancer.

391. The method of any one of claims 377 to 385, wherein the cancer is rectal cancer.

392. The method of any one of claims 377 to 385, wherein the cancer is pancreatic cancer.

393. The method of any one of claims 377 to 385, wherein the cancer is a solid tumor cancer.

394. The method of any one of claims 377 to 393, wherein cetuximab and the compound or salt are administered on different days.

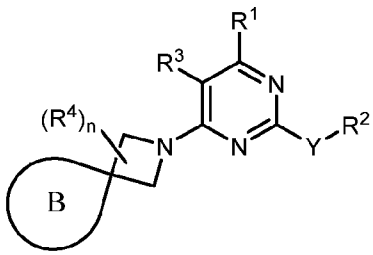
395. The method of any one of claims 377 to 394, wherein the combination is administered on different days.

396. A pharmaceutical composition, comprising a therapeutically effective amount of a combination of cetuximab and the compound of claim 377 to 384, and a pharmaceutically acceptable excipient.

397. A kit comprising the pharmaceutical composition of claim 394 for treating cancer in a subject.

398. A kit comprising: a) a pharmaceutical composition comprising cetuximab and b) a pharmaceutical composition comprising a compound of any one of claims 377-384 for treating cancer in a subject.

399. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of an RTK-MAPK pathway inhibitor and a compound of Formula (I):




Formula (I),

or a pharmaceutically acceptable salt thereof wherein:

B is selected from a 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle, wherein the 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle are each optionally substituted with one or more substituents independently selected from halogen, -CN, -$NO_2$, =O, -$N(R^{21})_2$, -$B(OR^{21})_2$, -$OR^{21}$, -$SR^{21}$, -$S(O)_2(R^{21})$, -$S(O)_2N(R^{21})_2$, -$NR^{21}S(O)_2R^{21}$, -$C(O)N(R^{21})_2$, -$C(O)NR^{21}OR^{21}$, -$N(R^{21})C(O)R^{21}$, -$N(R^{21})C(O)N(R^{21})_2$, -$N(R^{21})C(O)OR^{21}$, -$C(O)R^{21}$, $C(O)OR^{21}$, -$OC(O)R^{21}$, -$OC(O)N(R^{21})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

$R^1$ is selected from hydrogen and 5- to 15-membered heterocycle, wherein the 5- to 15-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, -$B(OR^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$C(=NR^{20})N(R^{20})_2$, -$C_{1-6}$ alkyl($=NOR^{20}$), -$C(O)NR^{20}OR^{20}$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$N(R^{20})_2$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, -$NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl,

$C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl-$SO_2R^{20}$, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle, wherein the $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, -$B(OR^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$C(O)NR^{20}OR^{20}$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$N(R^{20})_2$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, -$NO_2$, =O, =$N(R^{20})$, =$NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, and $C_3$-$C_{12}$ carbocycle;

Y is selected from a bond, -O-, -S-, and -$N(R^5)$-;

$R^2$ is selected from heterocycle, aryl, $C_1$-$C_6$ alkyl, -L-heterocycle, -L-$N(R^{23})_2$, -L-$OR^{23}$, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-$NHC(=NH)NH_2$, -L-$C(O)N(R^{23})_2$, -L-$C_1$-$C_6$ haloalkyl, -L-$OR^{23}$, -L-$NR^{23}C(O)$-aryl, -L-COOH, -L-$NR^{23}S(O)_2(R^{23})$, -L-$S(O)_2N(R^{23})_2$, -L-$N(R^{23})C(O)(OR^{23})$, -L-$OC(O)N(R^{23})_2$, and -L-$C(=O)OC_1$-$C_6$ alkyl, wherein the heterocycle, the heterocycle portion of -L-heterocycle, and the cycloalkyl portion of the -L-cycloalkyl are each optionally substituted with one or more $R^6$, and wherein the aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$;

$R^3$ is selected from hydrogen, halogen, -CN, -$NO_2$, -$N(R^{20})_2$, -$OR^{20}$, -$SR^{20}$, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, -$C(O)N(R^{20})_2$, -$N(R^{20})C(O)R^{20}$, -$N(R^{20})C(O)N(R^{20})_2$, -$N(R^{20})C(O)OR^{20}$, -$C(O)R^{20}$, -$C(O)OR^{20}$, -$OC(O)R^{20}$, -$OC(O)N(R^{20})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

each $R^4$ is independently selected from halogen, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

n is selected from 0, 1, 2, 3, and 4;

each $R^5$ is independently selected from hydrogen and $C_1$-$C_6$ alkyl;

each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, =$CH_2$, =NO-$C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, -$N(R^5)S(O)_2(R^5)$, -Q-phenyl, -Q-phenyl$SO_2F$, -NHC(O)phenyl, - NHC(O)phenyl$SO_2F$, $C_1$-$C_3$ alkyl substituted pyrazolyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, -$C(O)N(R^5)_2$, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, -$C(O)N(R^5)_2$, tert-butyldimethylsilyloxy$CH_2$-, -$N(R^5)_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$

alkyl)C(=O), oxo, ($C_1$-$C_3$ haloalkyl)C(=O)-, -$SO_2F$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC_1$-$C_6$ alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)C_1$-$C_6$ alkyl, -$CH_2$(pyrazolyl), -$CH_2NHSO_2C_1$-$C_6$ alkyl, -$CH_2OC(O)$heterocycle, -$OC(O)N(R^5)_2$, -$OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl), -$OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl($C_1$-$C_3$ alkyl)$N(CH_3)_2$, -$OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl, -$OC(O)$heterocycle, -O-$C_1$-$C_3$ alkyl, -$S(O)_2(R^{20})$, -$S(O)_2N(R^{20})_2$, -$S(O)N(R^{20})_2$, -$S(O)R^{20}(=NR^{20})$, -$NR^{20}S(O)_2R^{20}$, and -$CH_2$heterocycle, wherein the phenyl of -NHC(O)phenyl and -$OC(O)NH(C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl)phenyl are optionally substituted with one or more substituents selected from -C(O)H and OH, and wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo and hydroxy; and wherein the heterocycle of -$CH_2$heterocyclyl is optionally substituted with oxo;

each Q is selected from a bond, S, and O;

each $R^7$ is independently selected from halogen, hydroxy, HC(=O)-, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, -$C(O)N(R^5)_2$, and -$N(R^5)_2$;

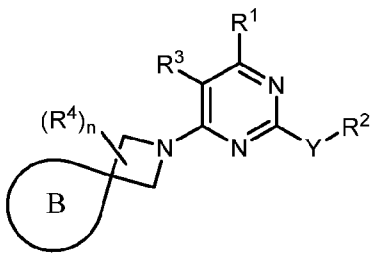
each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, hydroxy, $C_{1-6}$ alkoxy, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle, and 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -$N(C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, $-NO_2$, $-NH_2$, $-N(C_{1-6}\text{ alkyl})_2$, $C_{1-10}$ alkyl, $-C_{1-10}$ haloalkyl, $-O-C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle.

400. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of cetuximab and a compound of Formula (I):




Formula (I),

or a pharmaceutically acceptable salt thereof wherein:

B is selected from a 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle, wherein the 7- to 15-membered heterocycle and $C_7$-$C_{15}$ carbocycle are each optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, =O, $-N(R^{21})_2$, $-B(OR^{21})_2$, $-OR^{21}$, $-SR^{21}$, $-S(O)_2(R^{21})$, $-S(O)_2N(R^{21})_2$, $-NR^{21}S(O)_2R^{21}$, $-C(O)N(R^{21})_2$, $-C(O)NR^{21}OR^{21}$, $-N(R^{21})C(O)R^{21}$, $-N(R^{21})C(O)N(R^{21})_2$, $-N(R^{21})C(O)OR^{21}$, $-C(O)R^{21}$, $C(O)OR^{21}$, $-OC(O)R^{21}$, $-OC(O)N(R^{21})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

$R^1$ is selected from hydrogen and 5- to 15-membered heterocycle, wherein the 5- to 15-membered heterocycle is optionally substituted with one or more substituents independently selected from halogen, $-B(OR^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-C(=NR^{20})N(R^{20})_2$, $-C_{1-6}$ alkyl$(=NOR^{20})$, $-C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl-$SO_2R^{20}$, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle, wherein the $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle are each optionally substituted independently with one or more $R^{1*}$;

each $R^{1*}$ is independently selected from halogen, $-B(OR^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, -

$C(O)NR^{20}OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $-NO_2$, =O, $=N(R^{20})$, $=NO(R^{20})$, -CN, -NHCN, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, and $C_3$-$C_{12}$ carbocycle;

Y is selected from a bond, -O-, -S-, and $-N(R^5)-$;

$R^2$ is selected from heterocycle, aryl, $C_1$-$C_6$ alkyl, -L-heterocycle, -L-$N(R^{23})_2$, -L-$OR^{23}$, -L-aryl, -L-heteroaryl, -L-cycloalkyl, -L-$NHC(=NH)NH_2$, -L-$C(O)N(R^{23})_2$, -L-$C_1$-$C_6$ haloalkyl, -L-$OR^{23}$, -L-$NR^{23}C(O)$-aryl, -L-COOH, -L-$NR^{23}S(O)_2(R^{23})$, -L-$S(O)_2N(R^{23})_2$, -L-$N(R^{23})C(O)(OR^{23})$, -L-$OC(O)N(R^{23})_2$, and -L-$C(=O)OC_1$-$C_6$ alkyl, wherein the heterocycle, the heterocycle portion of -L-heterocycle, and the cycloalkyl portion of the -L-cycloalkyl are each optionally substituted with one or more $R^6$, and wherein the aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl portion of -L-$NR^{23}C(O)$-aryl, the aryl of the -L-aryl, and the heteroaryl of -L-heteroaryl are each optionally substituted with one or more $R^7$;

$R^3$ is selected from hydrogen, halogen, -CN, $-NO_2$, $-N(R^{20})_2$, $-OR^{20}$, $-SR^{20}$, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-OC(O)R^{20}$, $-OC(O)N(R^{20})_2$, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxyalkyl, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_3$-$C_{12}$ carbocycle and 5- to 12-membered heterocycle;

each $R^4$ is independently selected from halogen, $-NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkyl-$N(R^{20})_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ cyanoalkyl, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

n is selected from 0, 1, 2, 3, and 4;

each $R^5$ is independently selected from hydrogen and $C_1$-$C_6$ alkyl;

each $R^6$ is independently selected from halogen, hydroxy, $C_1$-$C_3$ hydroxyalkyl, $C_1$-$C_3$ alkyl, oxo, $C_1$-$C_3$ haloalkyl, $C_1$-$C_3$ alkoxy, cyano, $=CH_2$, $=NO$-$C_1$-$C_3$ alkyl, $C_1$-$C_3$ aminoalkyl, $-N(R^5)S(O)_2(R^5)$, -Q-phenyl, -Q-phenyl$SO_2F$, -NHC(O)phenyl, -NHC(O)phenyl$SO_2F$, $C_1$-$C_3$ alkyl substituted pyrazolyl, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, $-C(O)N(R^5)_2$, -$C_1$-$C_3$ alkyl-$N(R^5)_2$, $-C(O)N(R^5)_2$, tert-butyldimethylsilyloxy$CH_2$-, $-N(R^5)_2$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkyl-, ($C_1$-$C_3$ alkyl)C(=O), oxo, ($C_1$-$C_3$ haloalkyl)C(=O)-, $-SO_2F$, ($C_1$-$C_3$ alkoxy)$C_1$-$C_3$ alkoxy, $-CH_2OC(O)N(R^5)_2$, $-CH_2NHC(O)OC_1$-$C_6$ alkyl, $-CH_2NHC(O)N(R^5)_2$, $-CH_2NHC(O)C_1$-$C_6$ alkyl, $-CH_2$(pyrazolyl), $-CH_2NHSO_2C_1$-$C_6$ alkyl, $-CH_2OC(O)$heterocycle, $-OC(O)N(R^5)_2$, $-OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl), $-OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl($C_1$-$C_3$ alkyl)$N(CH_3)_2$, $-OC(O)NH(C_1$-$C_3$ alkyl)$O(C_1$-$C_3$ alkyl)phenyl, -OC(O)heterocycle, -O-$C_1$-$C_3$ alkyl, $-S(O)_2(R^{20})$, $-S(O)_2N(R^{20})_2$, $-S(O)N(R^{20})_2$, $-S(O)R^{20}(=NR^{20})$, $-NR^{20}S(O)_2R^{20}$, and -

$CH_2$heterocycle, wherein the phenyl of -NHC(O)phenyl and -OC(O)NH($C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl)phenyl are optionally substituted with one or more substituents selected from -C(O)H and OH, and wherein the alkyl of -O-$C_1$-$C_3$ alkyl is optionally substituted with substituents selected from heterocycle, oxo and hydroxy; and wherein the heterocycle of -$CH_2$heterocyclyl is optionally substituted with oxo;

each Q is selected from a bond, S, and O;

each $R^7$ is independently selected from halogen, hydroxy, HC(=O)-, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ hydroxyalkyl, -$C_1$-$C_3$ alkyl-N($R^5$)$_2$, -C(O)N($R^5$)$_2$, and -N($R^5$)$_2$;

each L is independently selected from a $C_1$-$C_4$ alkylene optionally substituted with one or more substituents independently selected from halogen, hydroxy, $C_{1-6}$ alkoxy, $C_1$-$C_4$ hydroxyalkyl, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ carbocycle, and 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-N($R^{20}$)$_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, $C_{1-6}$ haloalkyl; and wherein optionally two substituents on the same carbon atom of L come together to form a $C_3$-$C_6$ carbocycle or 3- to 8-membered heterocycle, wherein the $C_3$-$C_6$ carbocycle and 3- to 8-membered heterocycle are each optionally substituted with one or more substituents independently selected from halogen, -OH, -$NO_2$, =O, =S, -CN, $C_{1-6}$ alkyl-N($R^{20}$)$_2$, $C_{1-6}$ aminoalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ hydroxyalkyl, and $C_{1-6}$ haloalkyl;

each $R^{20}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{21}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle;

each $R^{23}$ is independently selected from hydrogen; and $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -OH, -CN, -$NO_2$, -$NH_2$, -N($C_{1-6}$ alkyl)$_2$, $C_{1-10}$ alkyl, -$C_{1-10}$ haloalkyl, -O-$C_{1-10}$ alkyl, oxo, $C_{3-12}$ carbocycle, and 3- to 12-membered heterocycle.

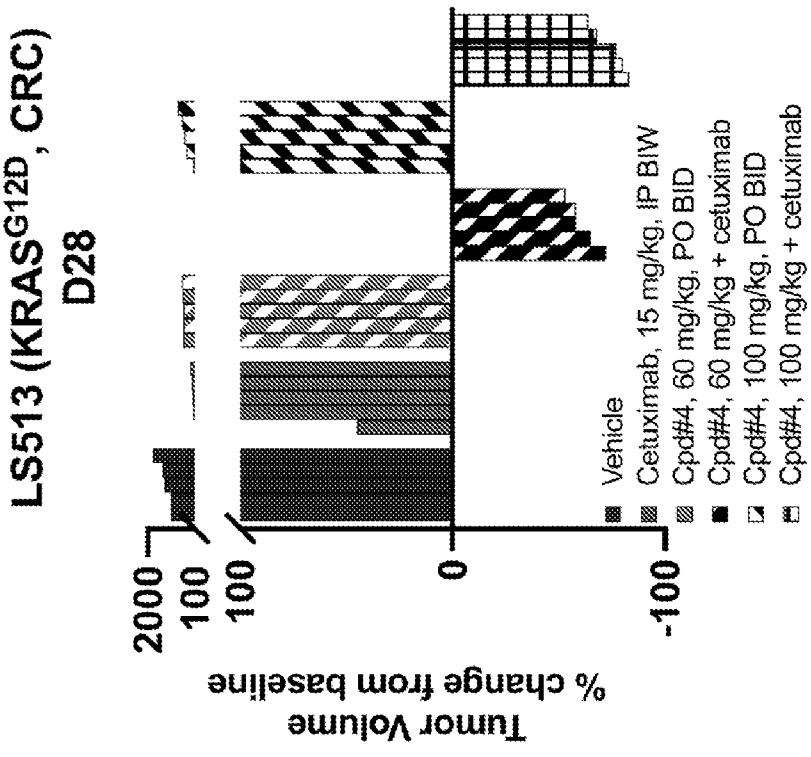

LS513 (KRAS$^{G12D}$, CRC)
D28
Tumor Volume
% change from baseline
2000
100
100
0
-100
Vehicle
Cetuximab, 15 mg/kg, IP BIW
Cpd#4, 60 mg/kg, PO BID
Cpd#4, 60 mg/kg + cetuximab
Cpd#4, 100 mg/kg, PO BID
Cpd#4, 100 mg/kg + cetuximab

FIG. 1A

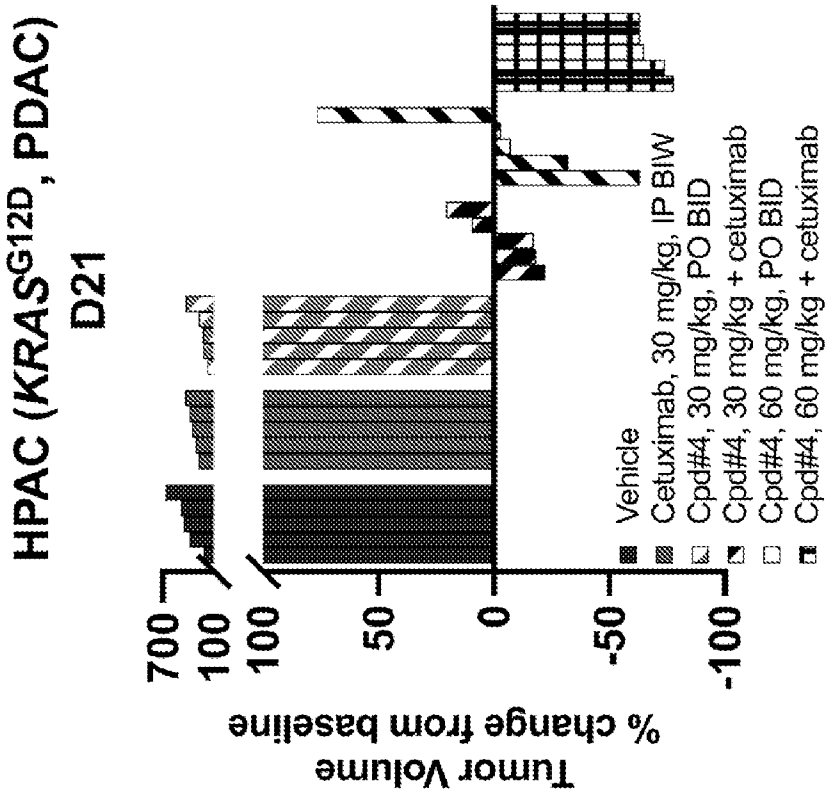

HPAC (KRAS$^{G12D}$, PDAC)
D21
Tumor Volume
% change from baseline
700
100
100
50
0
-50
-100
Vehicle
Cetuximab, 30 mg/kg, IP BIW
Cpd#4, 30 mg/kg, PO BID
Cpd#4, 30 mg/kg + cetuximab
Cpd#4, 60 mg/kg, PO BID
Cpd#4, 60 mg/kg + cetuximab

FIG. 1B

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/056246

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K31/506 A61K31/551 A61K31/5517 A61K39/395 A61K45/06
A61P35/00 C07K16/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y,P | WO 2023/230190 A1 (QUANTA THERAPEUTICS INC [US]) 30 November 2023 (2023-11-30)<br>claims 1-315<br>the whole document | 1-400 |
| Y | US 2023/103007 A1 (PACHTER JONATHAN A [US] ET AL) 30 March 2023 (2023-03-30)<br>claims 1-9, 23-29,32<br>the whole document | 1-400 |
| Y | CA 3 220 619 A1 (NOVARTIS AG [CH])<br>29 December 2022 (2022-12-29)<br>claims 1,6<br>the whole document | 1-400 |

-/--

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 21 February 2025 | 28/02/2025 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Langer, Oliver |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/056246

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2022/241265 A1 (SYNDAX PHARMACEUTICALS INC [US]; VITAE PHARMACEUTICALS LLC [US] ET AL.) 17 November 2022 (2022-11-17)<br>claims 51-61<br>page 137, last paragraph<br>examples 3-6<br>the whole document<br>----- | 1-400 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/056246

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2023230190 A1 | 30-11-2023 | AU 2023276596 A1 | 02-01-2025 |
| | | IL 317601 A | 01-02-2025 |
| | | US 2024199650 A1 | 20-06-2024 |
| | | WO 2023230190 A1 | 30-11-2023 |
| US 2023103007 A1 | 30-03-2023 | AU 2021213753 A1 | 04-08-2022 |
| | | BR 112022015161 A2 | 11-10-2022 |
| | | CA 3168648 A1 | 05-08-2021 |
| | | CN 115279376 A | 01-11-2022 |
| | | EP 4096671 A1 | 07-12-2022 |
| | | IL 295117 A | 01-09-2022 |
| | | JP 2023513015 A | 30-03-2023 |
| | | KR 20230011908 A | 25-01-2023 |
| | | US 2023103007 A1 | 30-03-2023 |
| | | WO 2021154929 A1 | 05-08-2021 |
| CA 3220619 A1 | 29-12-2022 | AU 2022299651 A1 | 14-12-2023 |
| | | BR 112023026408 A2 | 05-03-2024 |
| | | CA 3220619 A1 | 29-12-2022 |
| | | EP 4358953 A1 | 01-05-2024 |
| | | IL 308279 A | 01-01-2024 |
| | | JP 2024526145 A | 17-07-2024 |
| | | KR 20240024938 A | 26-02-2024 |
| | | TW 202317100 A | 01-05-2023 |
| | | US 2024366567 A1 | 07-11-2024 |
| | | WO 2022269525 A1 | 29-12-2022 |
| WO 2022241265 A1 | 17-11-2022 | AR 125866 A1 | 23-08-2023 |
| | | AU 2022274325 A1 | 05-10-2023 |
| | | BR 112023023463 A2 | 30-01-2024 |
| | | CA 3213074 A1 | 17-11-2022 |
| | | CL 2023003327 A1 | 03-05-2024 |
| | | CN 117956992 A | 30-04-2024 |
| | | EP 4337203 A1 | 20-03-2024 |
| | | IL 308476 A | 01-01-2024 |
| | | JP 2024517945 A | 23-04-2024 |
| | | KR 20240047338 A | 12-04-2024 |
| | | TW 202311262 A | 16-03-2023 |
| | | US 2023021684 A1 | 26-01-2023 |
| | | US 2024400564 A1 | 05-12-2024 |
| | | WO 2022241265 A1 | 17-11-2022 |