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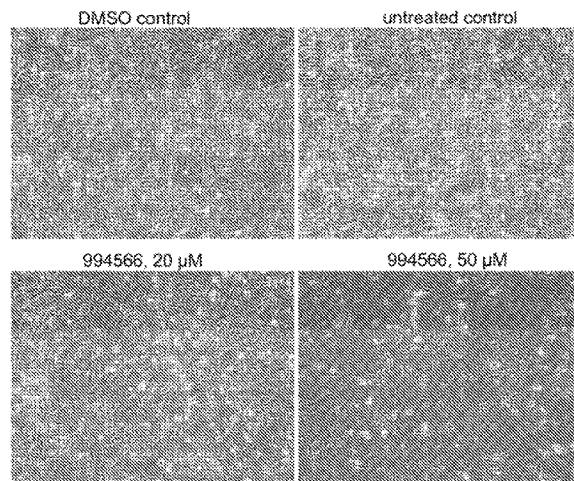
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(54) Title: K-RAS MODULATORS

FIG. 37



(57) Abstract: Provided herein, *inter alia*, are methods and compounds for inhibiting K-Ras and for treating cancer.

K-Ras Modulators

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/157,915,

5 filed May 6, 2015, and U.S. Provisional Application No. 62/158,356, filed May 7, 2015 which are incorporated herein by reference in their entirety and for all purposes.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED AS AN ASCII FILE

[0002] The Sequence Listing written in file 48536-569001WO_ST25.txt, created May 3,

10 2016, 10,641 bytes, machine format IBM-PC, MS Windows operating system, is hereby incorporated by reference.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0003] This invention was made with government support under Contract No.

15 HHSN261200800001E awarded by the National Cancer Institute. The government has certain rights in the invention.

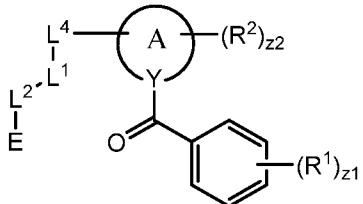
BACKGROUND OF THE INVENTION

[0004] K-Ras is the most frequently mutated oncogene in human cancer. Past attempts to directly modulate the activity of this enzyme have been unsuccessful. Ras proteins are small guanine nucleotide-binding proteins that act as molecular switches by cycling between active GTP-bound and inactive GDP-bound conformations. The Ras proteins play a critical role in the regulation of cell proliferation, differentiation, and survival. Dysregulation of the Ras signaling pathway is almost invariably associated with disease. Hyper-activating somatic mutations in Ras are among the most common lesions found in human cancer. Although mutation of any one of the three Ras isoforms (K-Ras, N-Ras, or H-Ras) has been shown to lead to oncogenic transformation, K-Ras mutations are by far the most common in human cancer. For example, K-Ras mutations are known to be often associated with pancreatic, colorectal and non-small-cell lung carcinomas. Similarly, H-Ras mutations are common in cancers such as papillary thyroid cancer, lung cancers and skin cancers. Finally, N-Ras mutations occur frequently in hepatocellular carcinoma. There is a need in the art for effective Ras inhibitors and anticancer compounds. Disclosed herein are solutions to these and other problems in the art.

BRIEF SUMMARY OF THE INVENTION

[0005] Described herein, inter alia, is the use of covalent (e.g. reversible or irreversible) modulators to target a Ras (e.g., K-Ras) protein, including but not limited to oncogenic mutants.

[0006] In an aspect is provided a compound having the formula:



(I) wherein, Y is N or CH; Ring A is a C₃-C₇ cycloalkyl or 3 to 7 membered heterocycloalkyl; R¹ is independently halogen, CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR⁷R⁸, -NHNR⁷R⁸, -ONR⁷R⁸, -NHC=(O)NHNR⁷R⁸, -NHC(O)NR⁷R⁸, -N(O)_{m1}, -NR⁷R⁸, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR⁷R⁸, -OR¹⁰, -NR⁷SO₂R¹⁰, -NR⁷C(O)R⁹, -NR⁷C(O)OR⁹, -NR⁷OR⁹, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted alkyl, 5 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R¹ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; L¹ is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene; L² is a 10 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, 15 -NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or 20 unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene; L⁴ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁴-, -NR⁴C(O)-, -C(O)NR⁴-, -SO₂NR⁴-, -NR⁴SO₂-, -NR⁴SO₂-, -OC(O)NR⁴-, -NR⁴C(O)O-, substituted or unsubstituted C₁-C₃ alkylene, substituted or 25 unsubstituted 2 to 3 membered heteroalkylene; E is an electrophilic moiety; R² is independently oxo, halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -SO₂Cl, -SO_{n2}R¹⁴, -SO_{v2}NR¹¹R¹², -NHNR¹¹R¹², -ONR¹¹R¹², -NHC=(O)NHNR¹¹R¹², -NHC(O)NR¹¹R¹², -N(O)_{m2}, -NR¹¹R¹², -C(O)R¹⁴, -C(O)-OR¹⁴, -C(O)NR¹¹R¹², -OR¹⁵, -

NR¹¹SO₂R¹⁵, -NR¹¹C(O)R¹⁴, -NR¹¹C(O)OR¹⁴, -NR¹¹OR¹⁴, -OCX²₃, -OCHX²₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R² substituents or two R² substituents bonded to the same atom may optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl; R⁴ is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R⁷, R⁸, R⁹, R¹⁰, R^{7B}, R^{8B}, R^{9B}, R^{10B}, 10 R¹¹, R¹², R¹⁴, and R¹⁵ are independently hydrogen, halogen, -CX₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX₃, -OCHX₂, -CHX₂, -CH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R⁷ and R⁸ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R¹¹ and R¹² substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X, 15 X¹, and X² is independently -F, -Cl, -Br, or -I; n1, n2, v1, and v2 are independently an integer from 0 to 4; m1 and m2 are independently an integer from 1 to 2; z1 is independently an integer from 0 to 5; and z2 is independently an integer from 0 to 10.

[0007] In another aspect is provided a pharmaceutical composition including a compound described herein and a pharmaceutically acceptable excipient.

25 [0008] In another aspect, a method of treating a disease in a patient in need of such treatment is provided. In embodiments, the disease is cancer.

[0009] In another aspect is provided a method of reducing the level of activity of a K-Ras protein (e.g., human K-Ras 4B), the method including contacting the K-Ras protein with a compound described herein (including in embodiments, examples, figures, and tables).

30 [0010] In another aspect, a method of modulating a K-Ras protein is provided. The method including contacting the K-Ras protein with an effective amount of a compound described herein (including in embodiments, examples, figures, and tables).

[0011] In another aspect is provided, a K-Ras protein covalently (e.g., reversibly or irreversibly) bonded to a compound, for example a compound as described herein (including modulators, inhibitors, or in embodiments, examples, and tables).

BRIEF DESCRIPTION OF THE DRAWINGS

- 5 [0012] FIGS. 1A-1C. LC-MS data from screen with His-K-Ras 4B (G12V) and (G12V/C185S). K refers to His-K-Ras 4B (G12V) (24823 Da) not bound to compound. B refers to His-K-Ras 4B (G12V) (24899 Da) bound to βMe. C: His-K-Ras 4B (G12V) (25114.5 Da for 3G4 vs. 25178Da for 6B9) bound to tethering compound. Kmut refers to His-K-Ras 4B (G12V/C185S) (24808 Da) not bound to compound.
- 10 [0013] FIGS. 2A-2D. Exemplary compounds from screen and derivatives thereof, 3G4 (phenyl thiazole containing compound) and derivatives wherein disulfide of 3G4 replaced with alternative electrophilic moieties. FIG. 2A depicts the structure of SMDC 917069, also referred to herein as 3G4. FIG. 2B depicts the structure of SMDC 963109. FIG. 2C depicts the structure of SMDC 963108. FIG. 2D depicts the structure of SMDC 963107.
- 15 [0014] FIGS. 3A-3C. Exemplary compounds from screen and derivatives thereof, including 6B9 (nipecotic acid derivative), 3G4 (phenyl thiazole containing compound); disulfide moiety of 6B9 was replaced with other electrophilic moieties, including tetrafluoro-phenoxy (FB9, also referred to herein as SMDC 959899) or difluoro-phenoxy (53, also referred to herein as SMDC 963153); disulfide of 3G4 replaced with alternative electrophilic moieties.
- 20 [0015] FIGS. 4A-4D Exemplary compounds from screen and derivatives thereof, including 6B9 (nipecotic acid derivative and derivatives wherein the disulfide moiety of 6B9 was replaced with other electrophilic moieties, including tetrafluoro-phenoxy (FB9) or difluoro-phenoxy (53). Derivatives of 6B9 with other electrophilic moieties.
- [0016] FIGS. 5A-5B. Exemplary compounds capable of binding to K-Ras.
- 25 [0017] FIGS. 6A-6B. Compound FB9; electrophile is the tetra fluorophenoxy-group which is also the leaving group after the thioether linkage between the cysteine thiol and the rest of FB9, depicted in FIG. 6B.
- [0018] FIG. 7A-7B. In Vitro Prenylation Assays with Purified K-Ras and FTase or GGTase. A fluorescent substrate for farnesyl transferase, 3,7-dimethyl-8-(7-nitro-benzo[1,2,5]oxadiazol-4-ylamino)-octa-2,6-diene-1-pyrophosphate (NBD-GPP), has similar kinetics as the natural

substrate for farnesyl pyrophosphate. FIG. 7A is with concentrations of 3G4. FIG. 7B is with concentrations of 6B9.

[0019] FIGS. 8A-8B. In vitro prenylation with 6B9 tethering compound.

[0020] FIG. 9. In vitro prenylation comparing N-Ras with different compounds; 1. KRAS4B wt CT; 2. KRAS4B mut CT; 3. 50 μ M 6B9; 4. 20 μ M 6B9; 5. 8 μ M 6B9; 6. 3.2 μ M 6B9; 7. 1.3 μ M 6B9; and 8. 0.5 μ M 6B9. A fluorescent substrate for farnesyl transferase, 3,7-dimethyl-8-(7-nitro-benzo[1,2,5]oxadiazol-4-ylamino) -octa-2,6-diene-1- pyrophosphate (NBD-GPP), has similar kinetics as the natural substrate for farnesyl pyrophosphate.

[0021] FIG. 10. BIACore Experiment with 3G4 on K-Ras 4B; Surface Plasmon Resonance (SPR) and ForteBio/Octet Experiment showing whether 3G4 and 6B9 Fragment (LB9) had a

secondary non-covalent interaction site in K-Ras 4B; experiment should show whether compounds interact with K-Ras 4B at 2 sites (e.g., the covalent site which is the CAAX-box cysteine and a non-covalent site); SPR experiments with K-Ras 4B G12V/C185S so that only possible non-covalent interaction; binding curve of 3G4 with K-Ras 4B G12V/C185S; Binding Curve of Compound 3G4 with K-Ras C186S, demonstrating potential non-covalent interaction.

[0022] FIGS. 11A-11B. ForteBio / Octet Assays; Measures compound binding to protein: association versus dissociation, steady state; Tested Avi-tagged Kras G12D with Fragments of FB9 and FB9D (parts of FB9/FB9D that make non-covalent interactions); LB9: = fragment of FB9; DB9: = fragment of FB9D; Avi-tagged K-Ras G12D was loaded with GTPyS/Mg; Curve with LB9 better than with DB9; Kd for LB9 around 17 μ M.

[0023] FIGS. 12A-12B. Measuring Conformational Changes Induced by Adding 3G4; Second Harmonic Generation (SHG) Experiments; SHG experiments were designed in order to see whether compound 3G4 induces any conformational change in K-Ras 4B; FPLC purified K-Ras was labelled either with EDA-GTP-ATTO 390, a fluorescent GTP analog, or PyMPO-

Maleimide, a fluorescent dye that labels cysteines, or PyMPO-SE, another fluorescent dye that labels amines; Labeled K-Ras 4B was immobilized via His-tag on the surface of a chip and the experiments were performed in the presence of DMSO or 3G4 compound; 2 experiments with K-Ras 4B G12V/C185S labelled either with EDA-GTP-ATTO 390 or PyMPO-Maleimide. Fluorescent dyes, EDA-GTP-ATT0 390 and PyMPO-Maleimide, that have second harmonic generation activity were used.

[0024] FIGS. 13A-13E. Binding Assay of FB9 to either GTPyS or GDP bound K-Ras G12D; Binding of FB9 to His-tagged K-Ras wt, G12D, G12V and His-tagged K-Ras G12V/C185S was

compared; Proteins were loaded with GTPyS/Mg; Binding reaction with FB9 was done at RT for 4 hours; Rec full length G12D became loaded with either GDP or GTPyS and Mg²⁺; ~10μM protein was bound to 100μM electrophile compound at RT and time points were taken after 5 and 23 hours; Compound 6B9 had a tetrafluoro-phenoxy electrophile modification (FB9);

5 Compound bound better when K-Ras was in complex with GTPyS/Mg²⁺; In the case of K-Ras / GDP/Mg²⁺ the protein got significantly labelled at a second site after 5h. FIG. 13B and FIG. 13D were performed after 5 hours. FIG. 13C and FIG. 13E were performed at 23 hours.

[0025] FIG. 14A-14D. Binding of Electrophilic 6B9 Derivative (FB9) to Different Oncogenic His-K-Ras 4B.

10 [0026] FIGS. 15A-15D. Experiments with Stereoisomers of Difluorophenoxy-6B9; Kras G12D/GTPyS/Mg²⁺, DMSO control, 2h incubation at RT; The binding of FB9 to Kras G12D was compared with the stereoisomers of Difluorophenoxy-6B9 (53, 54); FB9 bound 100% after 2h incubation; Difluorophenoxy-6B9 (compound ‘53’) bound to about 62% compared to FB9 under the same condition; The stereoisomer (‘54’) of compound ‘53’ bound to roughly 35% compared to FB9 which is roughly 50% of compound ‘53’; Partial stereospecific interaction.

15 [0027] FIGS. 16A-16B. Binding Comparison of FB9 and FB9D to K-Ras (G12D), GTPyS/Mg; Original compound (FB9): 50μM for 2.5h at RT; The binding of FB9 with its enantiomer FB9D was also compared; FB9 bound about 25-30% better than FB9D, shows partial stereoselectivity.

20 [0028] FIGS. 17A-17B. Modifications of 3G4 (phenyl thiazole) and relative binding as determined by mass spectrometry. FIG. 17B depicts the extent of the KRas labeling relative to compound TC-1.

[0029] FIGS. 18A-18B. Additional Modifications of 3G4 and mass spectrometry binding assays.

25 [0030] FIGS. 19A-19C. Different Electrophiles of Compound 3G4 (Tetrafluoro-phenoxy-3G4, Difluoro-phenoxy-3G4, Fimethyl-phenoxy-3G4); certain electrophilic modifications resulted in reduced binding in the present assay; 3G4 may find different pocket than 6B9 (e.g., makes different contacts or interactions).

30 [0031] FIGS. 20A-20C. Reactivity of Tetrafluorophenoxy-6B9 (FB9) with BME; experiment was done with 1mM FB9 and minus or plus 5mM BME at 37°C. Time points were taken at 0,

18, and 55 minutes; graphs show the area under curve vs time; analysis of the reduction of the free compound peak shows about 25% product coming up after 55 minutes.

[0032] FIGS. 21A-21C. Interaction of FB9 with Kras in the absence or presence of BME; at RT for the indicated times; titrating in BME results in reactivity of the compound being reduced;

5 BME itself did not react with the protein.

[0033] FIG. 22. Cell Based Assays with G12D expressing RAS-less MEFS; Ras-less cells exogenously expressing K-Ras G12D were stimulated with EGF for 30 and 60 minutes.

Concomitantly FB9 was added at various concentrations. Similar experiments were done with pancreatic cell lines expressing various oncogenic mutations. Changes at K-Ras protein levels
10 are visible. Growth curves were also performed.

[0034] FIG. 23. Time course EGF stimulation in combination with FB9 treatment (L3.6pl G12D).

[0035] FIG. 24. Stimulation with EGF in combination with FB9, Erlotinib, Carfilzomib treatment (L3.6pl G12D).

15 [0036] FIGS. 25A-25B. Time course EGF stimulation in combination with FB9 treatment (L3.6pl G12D).

[0037] FIG. 26. Time course EGF stimulation in combination with FB9 treatment (L3.6pl G12D).

20 [0038] FIG. 27. Comparing Gel Mobility and Antibody Reactivity of Different Purified K-Ras 4B Forms. E. Coli: unprocessed K-ras 4B purified from E. coli. Fme: processed K-ras 4B purified from SF9 cells. FB9: unprocessed K-ras 4B labeled with FB9 to about 70%.

[0039] FIG. 28. Time Course: Short and Long.

25 [0040] FIG. 29. Different Extraction Techniques and Antibody Comparison. Experiment #1 and #2 were performed at the same time, and in the same media solutions and cells (L3.6pl (G12D)); pellet fraction did not completely go into solution. The pellet fraction recognized by the Santa Cruz antibody shows two bands. The upper band is K-Ras.

[0041] FIG. 30. Growth Curves with human pancreatic cancer cell lines over 24 hours:EGF plus FB9, or EGF plus FB9 plus Erlotinib.

30 [0042] FIG. 31. Growth Curves with human pancreatic cancer cell lines over 24 hours:EGF plus FB9, or EGF plus FB9 plus Erlotinib.

[0043] FIGS. 32A-32B. FIG. 32A: K-ras 4B wild type C-terminus: Compound 3G4. FIG. 32B: K-ras 4B mutant C-terminus (C185S): compound 3G4.

[0044] FIG. 33. Identification of Kras G12D bound to tetrafluorophenoxy-6B9.

[0045] FIG. 34. Time Course: Short and Long.

5 [0046] FIG. 35. Cell uptake experiment showing stability of 994566 in MiaPaCa-2 cells within 24-h. Cells plated 1×10^6 on Petri dishes were treated, with 994566 in complete medium). Cells were collected into 200 μ l acetonitrile, lysate was centrifuged 15,000g x 15 min, filtered into HPLC vials and analyzed by LC/MS for the presence of the parent compound.

10 [0047] FIG. 36. Modification of fmeKRAS4b by FB9. Recombinant fmeKRAS4b was loaded with GDP or GppNHP (a nonhydrolyzable analogue of GTP), then reacted with FB9 at 37 °C for 100 min. The MALDI-TOF analysis revealed that covalent modification of the protein by FB9 (350 Da mass addition) was more pronounced when GTP analogue was present.

15 [0048] FIG. 37. Vinyl sulfonamide analogue of FB9, compound 994566, inhibited proliferation of mouse embryonic fibroblasts (MEF) expressing Kras4B G12D. Cells were serum-starved overnight, followed by treatment with 994566 and EGF (30 ng/ml). Medium was changed to complete (10% FBS) after 8 h, then compound was added again. Images were taken after 72 h in culture.

20 [0049] FIGS. 38A-38B. FIG. 38A: Vinyl sulfonamide analogue of FB9, compound 994566, decreased Kras protein expression in mouse embryonic fibroblasts (MEF) expressing Kras4B G12D. Cells were serum-starved overnight, followed by treatment with 994566 and EGF (30 ng/ml). Medium was changed to complete (10% FBS) after 8 h, then compound was added again. Cell lysates were collected after 96 h in culture. FIG. 38B: Structures of vinyl acrylamide (left) and vinyl sulfonamide (right) analogues of FB9.

25 [0050] FIG. 39. Vinyl sulfonamide analogue of FB9, compound 994566, decreased Kras protein expression in mouse embryonic fibroblasts (MEF) expressing Kras4B G12D after 24-h treatment. Cells were serum-starved overnight, followed by treatment with 994566 or 994565, followed immediately by EGF (30 ng/ml). Cells harvested after 24 h were processed for Western blot analysis.

30 [0051] FIG. 40. Conformations of the protein showing H95 is on the surface and exposed as drug-accessible.

[0052] FIG. 41. Control sample. Mouse lung epithelial cell line stably transduced with HA-tagged Kras4B G12V was used in this experiment. HA-Kras4BG12V expression was induced with doxycycline for 48h, then cells were treated with a close analogue of FB9, compound 993784. Kras protein was purified from cell lysate using immunoaffinity chromatography followed by SDS-PAGE, then subjected to MALDI-TOF analysis of modification to Kras protein. Characteristic fragment of peptide modified with the compound was detected (bottom panel). This fragment was not present in the control sample (second panel from the top).

[0053] FIG. 42. Sequence of KRAS4b used in MALDI-TOF experiments

GMTEYKLVVVGAGGVGKSALTIQLIQNHFVDEYDPTIEDSYRKQVVIDGETCLLDILDT
10 AGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDSEDVPMVLVGN
KCDLPSRTVDTKQAQDLARSYGIPFIETSAKTRQGVDDAFYTLVREIRKHKEKMSKDGK
KKKKKSHTKCVIM (SEQ ID NO:1).

[0054] FIG. 43. MALDI-TOF spectra of KRAS4B (SEQ ID NO:1) modified by FB9.

[0055] FIG. 44. MALDI-TOF MS (linear mode) of the Glu-C digest (overnight, RT) of FB9-modified full-size (1-188) KRAS4b. The sequences listed within FIG. 44 are DIHHYRE (SEQ ID NO:2), GKKKKKKSKTKCVIM (SEQ ID NO:3), and KMSKDGKKKKKSHTKCVIM (SEQ ID NO:4).

[0056] FIGS. 45A-45B. Identification of residues modified by FB9 on KRAS 4b. FIG. 45A: Peptides obtained after digestion by Glu-C were further digested by trypsin. FIG. 45B: Common fragments and a comparison of fragmentation spectra of peptides 969.485 and 1320.614.

[0057] FIGS. 46A-46B. FIG. 46A: The sequence of the protein used for experiment, specifically GGTEYKLVVVGAGGVGKSALTIQLIQNHFVDEYDPTIEDSYRKQVVIDGETC
LLDILDTAGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDSEDVP
MVLVGNKCDLPSRTVDTKQAQDLARSYGIPFIETSAKTRQGVDDAFYTLVREIRKHKEK
25 MSKDGKKKKKSHTK (SEQ ID NO:5). FIG. 46B: MALDI-TOF spectrum of the FME-Kras4b protein modified by FB9.

[0058] FIG. 47. MALDI-TOF analysis of peptides modified by FB9 in Kras4b. The sequences listed within FIG. 47 are SFEDIHHYR (SEQ ID NO:6), SFEDIHHYREQIKR (SEQ ID NO:7), SFEDIHHYREQIK (SEQ ID NO:8), and DSEDVPMVLVGNKCDLPSR (SEQ ID NO:9).

I. Definitions

[0059] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

5 [0060] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., -CH₂O- is equivalent to -OCH₂-.

[0061] The term “alkyl,” by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, 10 which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C₁-C₁₀ means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), 15 ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

20 [0062] The term “alkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -CH₂CH₂CH₂CH₂- . Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer 25 carbon atoms. The term “alkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0063] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., selected from the group consisting of O, N, P, 30 Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized). The heteroatom(s) (e.g., O, N, P, S, B, As, or Si) may be placed at any interior position of the heteroalkyl group or at the position at which

the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂, -S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, -O-CH₃, -O-CH₂-CH₃, and -CN. Up to 5 two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃.

[0064] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-.

For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)₂R'- represents both -C(O)₂R'- and -R'C(O)₂-.

As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R'', -OR', -SR', and/or -SO₂R'. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R'' or the like, it will be understood that the terms heteroalkyl and -NR'R'' are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R'' or the like.

[0065] The terms “cycloalkyl” and “heterocycloalkyl,” by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl,” respectively. Cycloalkyl and heteroalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule.

Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A

“cycloalkylene” and a “heterocycloalkylene,” alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0066] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as

“haloalkyl” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0067] The term “acyl” means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0068] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term “heteroaryl” refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An “arylene”

and a “heteroarylene,” alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

[0069] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a

5 single atom. The individual rings within spirocyclic rings may be identical or different.

Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocyclic

10 rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene

wherein each ring may be the same or different substituted heterocycloalkylene). When referring

15 to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0070] The symbol “~~” denotes the point of attachment of a chemical moiety to the

20 remainder of a molecule or chemical formula.

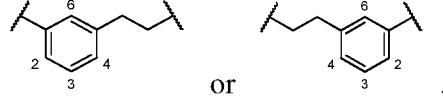
[0071] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon

atom.

[0072] The term “alkylarylene” as an arylene moiety covalently bonded to an alkylene moiety

(also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the

25 formula:



[0073] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the

alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, -N₃, -CF₃, -

CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂CH₃, -SO₃H, , -

30 OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted C₁-C₅

alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0074] Each of the above terms (e.g., “alkyl,” “heteroalkyl,” “aryl,” and “heteroaryl”) includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0075] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R'', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR''R'', -NR'C(O)₂R', -NR-C(NR'R''R'')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R'', -ONR'R'', -NR'C(O)NR''R''R''', -CN, -NO₂, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R'', R''', and R''''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R''''' group when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term “alkyl” is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂CH₃, and the like).

[0076] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R'', -SR', -halogen, -SiR'R''R'', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR''R'', -NR'C(O)₂R', -NR-C(NR'R''R'')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R'', -ONR'R'', -NR'C(O)NR''R''R''', -CN, -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to the total number of open valences on the

aromatic ring system; and where R', R'', R''', and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described

5 herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' groups when more than one of these groups is present.

[0077] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case,

10 the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent),

15 and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of

20 any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more

25 hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0078] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring

structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

- 5 [0079] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-,-S(O)₂NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CRR')_s-X'-(C"R"R"')_d-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituents R, R', 10 R", and R''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.
- 15

- [0080] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0081] A "substituent group," as used herein, means a group selected from the following moieties:

- (A) oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O) NH₂, -NHSO₂H, -NHC=(O)H, 25 -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and
- (B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:
- 30 (i) oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O) NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted

heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

- 5 (a) oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O) NH₂, -NSO₂H, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and
- 10 (b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O) NH₂, -NSO₂H, -NHC= (O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.
- 15

[0082] A “size-limited substituent” or “ size-limited substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0083] A “lower substituent” or “ lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀

aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0084] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0085] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₂₀ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₈ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0086] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some

embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₈ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₇ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0087] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0088] As used herein, the term “isomers” refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0089] The term “tautomer,” as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0090] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0091] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0092] Unless otherwise stated, structures depicted herein are also meant 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 ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0093] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I), or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0094] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0095] "Analog," or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0096] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C₁-C₂₀ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C₁-C₂₀ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0097] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group

is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol or additional number may be used to distinguish each appearance of that particular R group. For example, where multiple R¹³ substituents are present, each R¹³ substituent may be distinguished as R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc. is defined within the scope of the definition of R¹³ and optionally differently.

[0098] A “detectable moiety” as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The

10 detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dyes, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

[0099] Description of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently

20 unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

25 [0100] The term “pharmaceutically acceptable salts” is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a

sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge *et al.*, 5 “Pharmaceutical Salts”, *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0101] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, 15 methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, propionate, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0102] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0103] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0104] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In 5 general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0105] The terms “polypeptide,” “peptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which 10 one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

[0106] A polypeptide, or a cell is “recombinant” when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous 15 location, *e.g.*, in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence 20 that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0107] “Co-administer” it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient.

25 Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (*e.g.* to reduce metabolic degradation). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, 30 ointments, pastes, jellies, paints, powders, and aerosols.

[0108] A “cell” as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known

methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not

- 5 limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, *spodoptera*) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

[0109] The terms “treating” or “treatment” refers to any indicia of success in the treatment or amelioration of an injury, disease, pathology or condition, including any objective or subjective

- 10 parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams,

- 15 and/or a psychiatric evaluation. For example, the certain methods presented herein successfully treat cancer by decreasing the incidence of cancer and or causing remission of cancer. In some embodiments of the compositions or methods described herein, treating cancer includes slowing the rate of growth or spread of cancer cells, reducing metastasis, or reducing the growth of metastatic tumors. The term "treating" and conjugations thereof, include prevention of an injury, 20 pathology, condition, or disease.

[0110] An “effective amount” is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (*e.g.* achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce signaling pathway, reduce one or more symptoms of a disease or condition (*e.g.* reduce signaling pathway

- 25 stimulated by GTP bound Ras (*e.g.* K-Ras), reduce the signaling pathway activity of Ras, , reduce the signaling pathway activity of K-Ras, reduce the signaling pathway activity of K-Ras4A, reduce the signaling pathway activity of K-Ras4B, reduce the signaling pathway activity of H-Ras, reduce the signaling pathway activity of N-Ras, reduce the signaling pathway activity of a mutant K-Ras, inhibit the binding of K-Ras to SOS, inhibit the binding of K-Ras to a GEF, 30 reduce the localization of K-Ras to a membrane, reduce the prenylation of K-Ras, inhibit the localization of K-Ras to a membrane, inhibit the prenylation of K-Ras). An example of an “effective amount” is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a

“therapeutically effective amount.” A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A “prophylactically effective amount” of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g.,

- 5 preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An
- 10 “activity decreasing amount,” as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A “function disrupting amount,” as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist (e.g. disrupt the protein-protein interaction between K-Ras and a signaling pathway binding protein such as
- 15 PI3K, disrupt the interaction of K-Ras and GEF, disrupt the interaction of K-Ras and SOS, disrupt the interaction of K-Ras with Raf, disrupt the localization of K-Ras to a membrane, disrupt the prenylation of K-Ras). The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and*
- 20 *Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and Remington: *The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

- [0111] “Control” or “control experiment” is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity (e.g. signaling pathway) of a protein (e.g. Ras, K-Ras, mutant K-Ras, K-Ras G12C, K-Ras G12D, K-Ras G13C, K-Ras G13D, K-Ras G12V, K-Ras G12S) in the absence of a compound as described herein (including embodiments, examples, figures, or Tables).

- [0112] “Contacting” is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules, or cells) to become sufficiently proximal to react, interact or physically touch. It

should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0113] The term “contacting” may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme (e.g. Ras, K-Ras, H-Ras, N-Ras, K-Ras4A, K-Ras4B, mutant Ras, mutant K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S). In some embodiments, the protein may be K-Ras. In some embodiments, the protein may be a mutant K-Ras (e.g. K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S). In some embodiments, the protein may be K-Ras4A. In some embodiments, the protein may be K-Ras4B. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway.

[0114] As defined herein, the term “inhibition”, “inhibit”, “inhibiting” and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein (e.g. decreasing the signaling pathway stimulated by GTP bound Ras (e.g. K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S), nucleotide exchange, effector protein binding, effector protein activation, guanine exchange factor (GEF) binding, SOS binding, GEF-facilitated nucleotide exchange, phosphate release, nucleotide release, nucleotide binding, membrane localization, prenylation of the protein) relative to the activity or function of the protein in the absence of the inhibitor. In some embodiments inhibition refers to reduction of a disease or symptoms of disease. In some embodiments, inhibition refers to a reduction in the activity of a signal transduction pathway or signaling pathway (e.g. reduction of a pathway involving GTP bound Ras (e.g. K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S), reduction of a pathway involving mutant K-Ras (e.g. K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S)). Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating the signaling pathway or enzymatic activity or the amount of a protein (e.g. K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S). In some embodiments, inhibition refers to inhibition of interactions of Ras (K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S) with signaling pathway binding partners (e.g. PI3K, SOS, Raf). In some embodiments, inhibition refers to inhibition of interactions of Ras with a GEF (e.g. SOS). In some embodiments,

inhibition refers to inhibition of Ras prenylation. In some embodiments, inhibition refers to inhibition of Ras localization. In some embodiments, inhibition refers to inhibition of Ras membrane localization.

[0115] The term “modulator” refers to a composition that increases or decreases the level of a target molecule or the function (e.g., effector protein binding, effector protein activation, guanine exchange factor (GEF) binding, SOS binding, prenylation, localization) of a target molecule or the physical state (e.g. Ras subcellular localization, Ras post-translational processing, Ras post-translational modifications (prenylation)) of the target of the molecule (e.g. a target may be K-Ras and the function may be to hydrolyze GTP or activate a signaling pathway that is activated by GTP bound K-Ras, interaction of K-Ras with protein binding partners (e.g. PI3K, SOS, Raf)) relative to the absence of the composition. In some embodiments, a K-Ras disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with K-Ras (e.g. cancer, metastatic cancer) relative to the absence of the compound. A K-Ras modulator is a compound that increases or decreases the activity or function or level of activity or level of function of K-Ras or level of K-Ras or level of K-Ras in a particular physical state relative to the absence of the compound. A mutant K-Ras modulator is a compound that increases or decreases the activity or function or level of activity or level of function of mutant K-Ras or level of mutant K-Ras or level of mutant K-Ras in a particular physical state relative to the absence of the compound. A K-Ras G12C modulator, K-Ras G12D modulator, K-Ras G13C modulator, K-Ras G12V modulator, K-Ras G12S modulator, or K-Ras G13D modulator is a compound that increases or decreases the activity or function or level of activity or level of function of that particular mutant K-Ras or level of that particular mutant K-Ras or level of that particular mutant K-Ras in a particular physical state relative to the absence of the compound. A K-Ras inhibitor is a compound that decreases the activity or function or level of activity or level of function of K-Ras or level of K-Ras or level of K-Ras in a particular physical state relative to the absence of the compound. A mutant K-Ras inhibitor is a compound that decreases the activity or function or level of activity or level of function of mutant K-Ras or level of mutant K-Ras or level of mutant K-Ras in a particular physical state relative to the absence of the compound. A K-Ras G12C inhibitor, K-Ras G12D inhibitor, K-Ras G13C inhibitor, K-Ras G12V inhibitor, K-Ras G12S inhibitor, or K-Ras G13D inhibitor is a compound that decreases the activity or function or level of activity or level of function of that particular mutant K-Ras or level of that particular mutant K-Ras or level of that particular mutant K-Ras in a particular physical state relative to the absence of the compound.

[0116] The term “modulate” is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. “Modulation” refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a

5 property or function of the target molecule or the amount of the target molecule.

[0117] “Patient” or “subject in need thereof” refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals.

10 In some embodiments, a patient is human.

[0118] “Disease” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. In some embodiments, the disease is a disease related to (e.g. caused by) a Ras. In some embodiments, the disease is a disease related to (e.g. caused by) a K-Ras (e.g. K-Ras G12C, G13C, G12D,

15 G12V, G12S, or G13D) or aberrant K-Ras signaling pathway activity (e.g. lung cancer, breast cancer, colon cancer, colorectal cancer, pancreatic cancer, leukemia). Examples of diseases, disorders, or conditions include, but are not limited to cancer. Examples of diseases, disorders, or conditions include, but are not limited to MYH-associated polyposis. In some instances,

“disease” or “condition” refers to cancer. In some instances, “disease” or “condition” refers to

20 MYH-associated polyposis. In some further instances, “cancer” refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin’s

25 lymphomas (e.g., Burkitt’s, Small Cell, and Large Cell lymphomas), Hodgkin’s lymphoma, leukemia (including AML, ALL, and CML), or multiple myeloma.

[0119] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas.

Exemplary cancers that may be treated with a compound or method provided herein include

30 cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma

multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant

5 hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0120] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocytemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia,

20 hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia,

25 Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[0121] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma,

embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[0122] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungual melanoma, or superficial spreading melanoma.

[0123] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatous, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epidermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniform carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma

mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma,

- 5 carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, or
10 carcinoma villosum.

[0124] “Ras associated cancer” (also referred to herein as “Ras related cancer”) refers to a cancer caused by aberrant Ras activity or signaling. A “cancer associated with aberrant K-Ras activity” (also referred to herein as “K-Ras related cancer”) is a cancer caused by aberrant K-Ras activity or signaling (e.g. a mutant K-Ras). K-Ras related cancers may include lung cancer, non-
15 small cell lung cancer, breast cancer, leukemia, pancreatic cancer, colon cancer, colorectal cancer. Other cancers that are associated with aberrant activity of one or more of Ras, K-Ras, H-Ras, N-Ras, mutant K-Ras (including K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G12V, K-Ras G12S, K-Ras G13D mutants), mutant N-Ras, and mutant H-Ras are well known in the art and determining such cancers are within the skill of a person of skill in the art.

20 [0125] “Pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing
25 osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0126] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it.

Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and

5 lozenges can be used as solid dosage forms suitable for oral administration.

[0127] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and

10 transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal).

Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery

include, but are not limited to, the use of liposomal formulations, intravenous infusion,

transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is

15 administered at the same time, just prior to, or just after the administration of one or more

additional therapies, for example cancer therapies such as chemotherapy, hormonal therapy,

radiotherapy, or immunotherapy. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one

20 compound). Thus, the preparations can also be combined, when desired, with other active

substances (*e.g.* to reduce metabolic degradation). The compositions of the present invention can

be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions,

suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0128] The term "administer (or administering) a Ras inhibitor" means administering a

25 compound that inhibits the activity or level (*e.g.* amount) or level of a signaling pathway of one or more Ras proteins (*e.g.* a Ras inhibitor, K-Ras inhibitor, N-Ras inhibitor, H-Ras inhibitor, mutant K-Ras inhibitor, K-Ras G12C inhibitor, K-Ras G12V inhibitor, K-Ras G12S inhibitor, K-

Ras G13C inhibitor, K-Ras G12D inhibitor, K-Ras G13D inhibitor) to a subject. Administration

may include, without being limited by mechanism, allowing sufficient time for the Ras inhibitor

30 to reduce the activity of one or more Ras proteins or for the Ras inhibitor to reduce one or more symptoms of a disease (*e.g.* cancer, wherein the Ras inhibitor may arrest the cell cycle, slow the cell cycle, reduce DNA replication, reduce cell replication, reduce cell growth, reduce

metastasis, or cause cell death). The term "administer (or administering) a K-Ras inhibitor"

means administering a compound that inhibits the activity or level (e.g. amount) or level of a signaling pathway of one or more K-Ras proteins (K-Ras, mutant K-Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G12D, K-Ras G13C, K-Ras G13D).

[0129] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating a disease associated with cells expressing a particular Ras, K-Ras, mutant K-Ras (e.g. cancer), or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0130] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another.

[0131] As a non-limiting example, the compounds described herein can be co-administered with conventional chemotherapeutic agents including alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiopeta, nitrosoureas, etc.), anti-metabolites (e.g., 5-fluorouracil, azathioprine, methotrexate, leucovorin, capecitabine, cytarabine, floxuridine, fludarabine, gemcitabine, pemetrexed, raltitrexed, etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.), platinum-based compounds (e.g. cisplatin, oxaloplatin, carboplatin, etc.), and the like.

[0132] The compounds described herein can also be co-administered with conventional hormonal therapeutic agents including, but not limited to, steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, tamoxifen, and gonadotropin-releasing hormone agonists (GnRH) such as goserelin.

[0133] Additionally, the compounds described herein can be co-administered with conventional immunotherapeutic agents including, but not limited to, immunostimulants (e.g.,

Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (*e.g.*, anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (*e.g.*, anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), and radioimmunotherapy (*e.g.*, anti-CD20 monoclonal antibody conjugated to ^{111}In , ^{90}Y , or ^{131}I , *etc.*).

[0134] In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc , ^{64}Cu , ^{67}Cu , ^{89}Sr , ^{86}Y , ^{87}Y , ^{90}Y , ^{105}Rh , ^{111}Ag , ^{111}In , $^{117\text{m}}\text{Sn}$, ^{149}Pm , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi , optionally conjugated to antibodies directed against tumor antigens.

[0135] In therapeutic use for the treatment of cancer, compound utilized in the pharmaceutical compositions of the present invention may be administered at the initial dosage of about 0.001 mg/kg to about 1000 mg/kg daily. A daily dose range of about 0.01 mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 200 mg/kg, or about 1 mg/kg to about 100 mg/kg, or about 10 mg/kg to about 50 mg/kg, can be used. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound or drug being employed. For example, dosages can be empirically determined considering the type and stage of cancer diagnosed in a particular patient. The dose administered to a patient, in the context of the present invention, should be sufficient to affect a beneficial therapeutic response in the patient over time. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a compound in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

[0136] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0137] The term “associated” or “associated with” in the context of a substance or substance activity or function associated with a disease (*e.g.* a protein associated disease, a cancer associated with aberrant Ras activity, K-Ras associated cancer, mutant K-Ras associated cancer, activated K-Ras associated cancer, K-Ras G12C associated cancer, K-Ras G12V associated

cancer, K-Ras G12S associated cancer, K-Ras G13C associated cancer, K-Ras G12D associated cancer, K-Ras G13D associated cancer) means that the disease (e.g. cancer) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, a cancer associated with aberrant Ras activity or

5 function may be a cancer that results (entirely or partially) from aberrant Ras activity or function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or a cancer wherein a particular symptom of the disease is caused (entirely or partially) by aberrant Ras activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a cancer associated with 10 aberrant Ras activity or function or a Ras associated cancer, may be treated with a Ras modulator or Ras inhibitor, in the instance where increased Ras activity or function (e.g. signaling pathway activity) causes the cancer. For example, a cancer associated with K-Ras G12V may be a cancer that a subject with K-Ras G12V is at higher risk of developing as compared to a subject without K-Ras G12V.

15 [0138] The term “aberrant” as used herein refers to different from normal. When used to describe enzymatic activity, aberrant refers to activity that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described 20 herein), results in reduction of the disease or one or more disease symptoms.

[0139] “Anti-cancer agent” is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent 25 identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, 30 AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g.,

hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine,

5 Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.),

10 platinum-based compounds (e.g. cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g.

15 U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossyphol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.),

20 geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide;

25 angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole;

CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol;

5 cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; daclizimab; decitabine; dehydrodideamin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaiquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol;

10 duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflorenthine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate;

15 galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole;

20 isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin;

25 loxoribine; lurtotecan; lutetium texaphyrin; lysozyme; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone;

30 mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; molidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetylglucosamine; N-substituted benzamides; nafarelin; nargrestip; naloxone+pentazocine; napavine; naphterpin; nartograstim; nedaplatin;

nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin;

acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium;

5 bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone

10 propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enoplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine

15 hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rIL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol;

20 maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedopa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate;

25 perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium;

30 tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamicrine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine

sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-5 10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone 10 A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists 15 (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies 20 (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ¹¹¹In, ⁹⁰Y, or ¹³¹I, etc.), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, 25 vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (IressaTM), erlotinib (TarcevaTM), cetuximab (ErbituxTM), lapatinib (TykerbTM), panitumumab (VectibixTM), vandetanib (CaprelsaTM), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP- 30 724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, Ras inhibitors, or the like.

[0140] “Chemotherapeutic” or “chemotherapeutic agent” is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0141] The term “Electrophilic” as used herein refers to a chemical group that is capable of accepting electron density. An “electrophilic substituent”, “electrophilic chemical moiety”, or “electrophilic moiety” refers to an electron-poor chemical group, substituent, or moiety (monovalent chemical group), which may react with an electron-donating group, such as a nucleophile, by accepting an electron pair or electron density to form a bond. In some embodiments, the electrophilic substituent of the compound is capable of reacting with a cysteine residue. In some embodiments, the electrophilic substituent is capable of forming a covalent bond with a cysteine residue (e.g., K-ras cysteine residue, residue corresponding to C185 of human K-Ras 4B) and may be referred to as a “covalent cysteine modifier moiety” or “covalent cysteine modifier substituent”. The covalent bond formed between the electrophilic substituent and the sulphydryl group of the cysteine may be a reversible or irreversible bond. In some

10
15
embodiments, the electrophilic substituent is capable of forming a covalent bond with a histidine residue (e.g., K-ras histidine residue, residue corresponding to H95 of human K-Ras 4B) and may be referred to as a “covalent histidine modifier moiety” or “covalent histidine modifier substituent”. The covalent bond formed between the electrophilic substituent and the histidine may be a reversible or irreversible bond.

20 **[0142]** “Nucleophilic” as used herein refers to a chemical group that is capable of donating electron density.

[0143] The term “Ras” refers to one or more of the family of human Ras GTPase proteins (e.g. K-Ras, H-Ras, N-Ras). The term “K-Ras” refers to the nucleotide sequences or proteins of human K-Ras (e.g. human K-Ras4A (NP_203524.1), human K-Ras4B (NP_004976.2), or both K-Ras4A and K-Ras4B). The term “K-Ras” includes both the wild-type form of the nucleotide sequences or proteins as well as any mutants thereof. In some embodiments, “K-Ras” is wild-type K-Ras. In some embodiments, “K-Ras” is one or more mutant forms. The term “K-Ras” XYZ refers to a nucleotide sequence or protein of a mutant K-Ras wherein the Y numbered amino acid of K-Ras that has an X amino acid in the wildtype instead has a Z amino acid in the mutant (e.g. K-Ras G12C has a G in wildtype protein but a C in the K-Ras G12C mutant protein). In some embodiments K-Ras refers to K-Ras4A and K-Ras4B. In some embodiments, K-Ras refers to K-Ras4A. In some embodiments, K-Ras refers to K-Ras4B. In embodiments K-Ras refers to a protein having an amino acid sequence described herein.

[0144] The term “Ras inhibitor test compound” as used herein refers to a compound that is being characterized in an assay for the ability to inhibit an activity, function, or level (e.g. amount) of a Ras protein. The term “K-Ras inhibitor test compound” as used herein refers to a compound that is being characterized in an assay for the ability to inhibit an activity, function, or level (e.g. amount) of K-Ras protein.

[0145] The term “signaling pathway” as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propagated to other signaling pathway components. For example, binding of a K-Ras with a compound as described herein may result in a change in one or more protein-protein interactions of the K-Ras or interactions between the K-Ras and a membrane, resulting in changes in cell growth, proliferation, or survival.

[0146] An amino acid residue in a protein "corresponds" to a given residue when it occupies the same essential structural position within the protein as the given residue. For example, a selected residue in a selected protein corresponds to Gly 12 of Human K-Ras4A or Human K-Ras 4B or both when the selected residue occupies the same essential spatial or other structural relationship as Gly 12 in Human K-Ras4A or Human K-Ras 4B or both. In some embodiments, where a selected protein is aligned for maximum homology with the Human K-Ras4A or Human K-Ras 4B protein, the position in the aligned selected protein aligning with Gly 12 is said to correspond to Gly 12. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, e.g., where the structure of the selected protein is aligned for maximum correspondence with the Human K-Ras4A or Human K-Ras 4B protein and the overall structures compared. In this case, an amino acid that occupies the same essential position as Gly 12 in the structural model is said to correspond to the Gly 12 residue. Another example is wherein a selected residue in a selected protein corresponds to C185 of Human K-Ras 4B when the selected residue (e.g., cysteine residue) occupies essential the same sequence, spatial, or other structural position within the protein as C185 in Human K-Ras 4B.

[0147] The terms “unsubstituted vinyl sulfone moiety”, “unsubstituted vinyl sulfonamide moiety”, “unsubstituted fluoro(C₁-C₄)alkylketone moiety”, “unsubstituted chloro(C₁-C₄)alkylketone moiety”, “unsubstituted acrylamide moiety”, “unsubstituted disulfide moiety”, “unsubstituted thiol moiety”, “unsubstituted phosphonate moiety”, “unsubstituted aldehyde moiety”, “unsubstituted enone moiety”, “unsubstituted diazomethylketone moiety”,

“unsubstituted diazomethylamide moiety”, “unsubstituted cyanocyclopropyl carboxamide moiety”, “unsubstituted epoxide moiety”, “unsubstituted epoxyketone moiety”, “unsubstituted epoxyamide moiety”, “unsubstituted aryl aldehyde moiety”, “unsubstituted aryl dialdehyde moiety”, “unsubstituted dialdehyde moiety”, “unsubstituted nitrogen mustard moiety”,

5 “unsubstituted propargyl moiety”, or “unsubstituted propargylamide moiety” are used according to their plain ordinary chemical meaning and refer to those monovalent chemical groups named having the lowest molecular weight for each such group while obeying the rules of chemical valency. A substituted form of one of the named groups may be substituted with one or more of any of the substituent groups described herein while obeying the rules of chemical valency.

10 [0148] H-Ras WT Human

[0149] MTEYKLVVVG AGGVGKSAIT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHQYREQI
KRVKDSDDVP MVLVGNKCDL AARTVESRQA QDLARSYGIP YIETSAKTRQ
GVEDAFYTLV REIRQHKLKLNPPDESGPG CMSCKCVLS (SEQ ID NO:10)

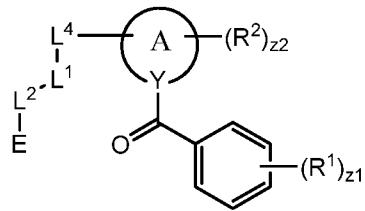
15 [0150] K-Ras 4A WT Human

[0151] mteyklvvvg aggvgksalt iqqliqnhfvd eydptiedsy rkqvvidget clldildtag qeeysamrdq
ymrtgegflc vfainntksf edihhyreqi krvkdsedvp mvlgvgnkcdl psrtvdtkqa qdlarsygip fietsaktrq
rvedafytlv reirqyrlkk iskeektpgc vkikkciim (SEQ ID NO:11)

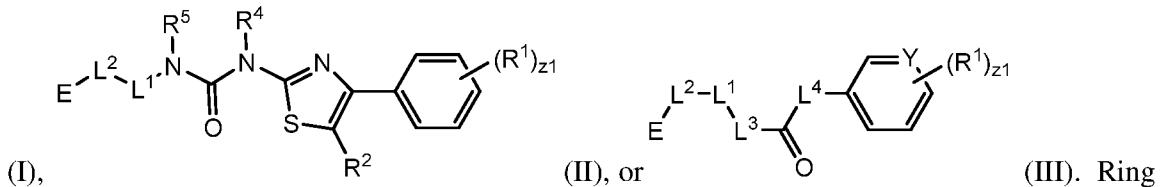
[0152] K-Ras 4B WT Human

20 [0153] mteyklvvvg aggvgksalt iqqliqnhfvd eydptiedsy rkqvvidget clldildtag qeeysamrdq
ymrtgegflc vfainntksf edihhyreqi krvkdsedvp mvlgvgnkcdl psrtvdtkqa qdlarsygip fietsaktrq
gvddafytlv reirkhkekmskdgkkkkk sktkcvim (SEQ ID NO:12)

II. Compounds



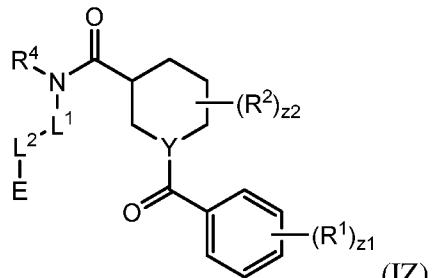
[0154] In an aspect is provided a compound having the formula:



A is a C₃-C₇ cycloalkyl or 3 to 7 membered heterocycloalkyl. Y is N or CH or C. R¹ is independently halogen, CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR⁷R⁸, -NHNR⁷R⁸, -ONR⁷R⁸, -NHC=(O)NHNR⁷R⁸, -NHC(O)NR⁷R⁸, -N(O)_{m1}, -NR⁷R⁸, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR⁷R⁸, -OR¹⁰, -NR⁷SO₂R¹⁰, -NR⁷C(O)R⁹, -NR⁷C(O)OR⁹, -NR⁷OR⁹, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R¹ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. L¹ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7A}-, -NR^{7A}C(O)-, -C(O)NR^{7A}-, -SO₂NR^{7A}-, -NR^{7A}SO₂-, -OC(O)NR^{7A}-, -NR^{7A}C(O)O-, -CR^{9A}=NO-, -ON=CR^{9A}-, -NR^{8A}C(O)NR^{7A}-, -NR^{8A}C(=NR^{10A})NR^{7A}-, -NR^{8A}C(=NR^{10A})-, -C(=NR^{10A})NR^{7A}-, -OC(=NR^{10A})-, -C(=NR^{10A})O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. L³ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁵-, -NR⁵C(O)-, -C(O)NR⁵-, -SO₂NR⁵-, -

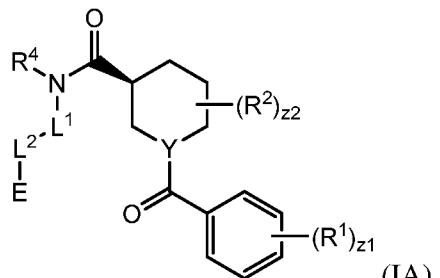
NR⁵SO₂-, -OC(O)NR⁵-, -NR⁵C(O)O-, substituted or unsubstituted C₁-C₆ alkylene, substituted or unsubstituted 2 to 6 membered heteroalkylene. L⁴ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁴-, -NR⁴C(O)-, -C(O)NR⁴-, -SO₂NR⁴-, -NR⁴SO₂-, -NR⁴SO₂-, -OC(O)NR⁴-, -NR⁴C(O)O-, substituted or unsubstituted C₁-C₃ alkylene, substituted or unsubstituted 2 to 3 membered heteroalkylene. E is an electrophilic moiety. R² is independently hydrogen, oxo, halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -SO₂Cl, -SO_{n2}R¹⁴, -SO_{v2}NR¹¹R¹², -NHNR¹¹R¹², -ONR¹¹R¹², -NHC=(O)NHNR¹¹R¹², -NHC(O)NR¹¹R¹², -N(O)_{m2}, -NR¹¹R¹², -C(O)R¹⁴, -C(O)-OR¹⁴, -C(O)NR¹¹R¹², -OR¹⁵, -NR¹¹SO₂R¹⁵, -NR¹¹C(O)R¹⁴, -NR¹¹C(O)OR¹⁴, -NR¹¹OR¹⁴, -OCX²₃, -OCHX²₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R² substituents or two R² substituents bonded to the same atom may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R⁴ is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R⁵ is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R⁷, R⁸, R⁹, R¹⁰, R^{7A}, R^{8A}, R^{9A}, R^{10A}, R^{7B}, R^{8B}, R^{9B}, R^{10B}, R¹¹, R¹², R¹⁴, and R¹⁵ are independently hydrogen, halogen, -CX₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX₃, -OCHX₂, -CHX₂, -CH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R⁷ and R⁸ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R¹¹ and R¹² substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. Each X, X¹, and X² is independently -F, -Cl, -Br, or -I. The symbols n1, n2, v1, and v2 are independently an integer from 0 to 4. The symbols m1 and m2 are independently an integer.

from 1 to 2. The symbol z1 is independently an integer from 0 to 5. The symbol z2 is independently an integer from 0 to 10.



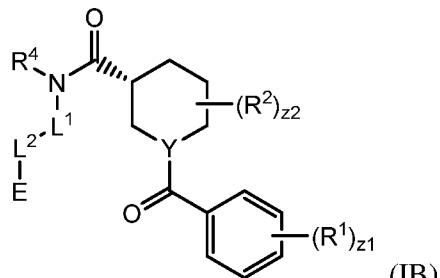
[0155] In embodiments, the compound has the formula:

R¹, R², R⁴, L¹, L², E, Y z1 and z2 are as described herein.



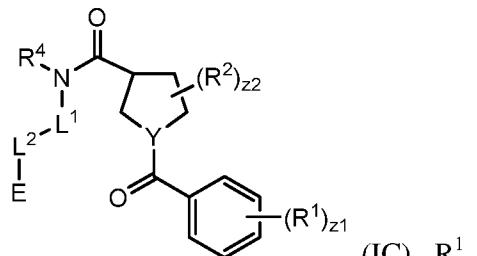
5 [0156] In embodiments, the compound has the formula:

R¹, R², R⁴, L¹, L², E, Y z1 and z2 are as described herein.



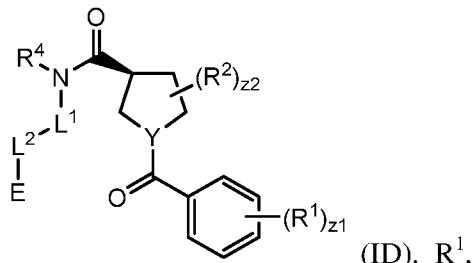
[0157] In embodiments, the compound has the formula:

R¹, R², R⁴, L¹, L², E, Y z1 and z2 are as described herein.

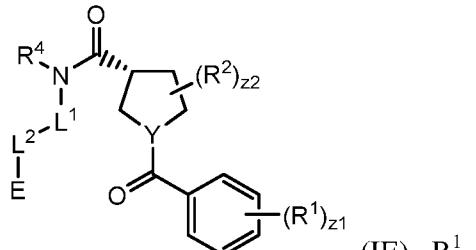


[0158] In embodiments, the compound has the formula:

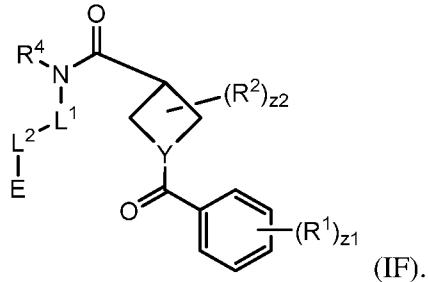
10 R², R⁴, L¹, L², E, Y z1 and z2 are as described herein.



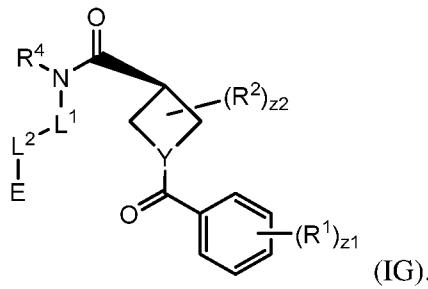
[0159] In embodiments, the compound has the formula: (ID). R^1 , R^2 , R^4 , L^1 , L^2 , E , $Y z1$ and $z2$ are as described herein.



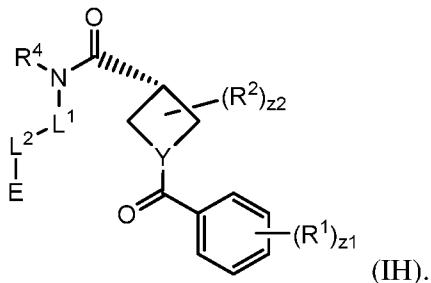
[0160] In embodiments, the compound has the formula: (IE). R^1 , R^2 , R^4 , L^1 , L^2 , E , $Y z1$ and $z2$ are as described herein.



5 [0161] In embodiments, the compound has the formula: (IF). R^1 , R^2 , R^4 , L^1 , L^2 , E , $Y z1$ and $z2$ are as described herein.

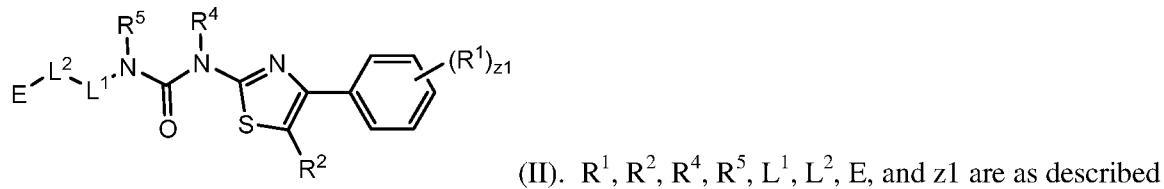


[0162] In embodiments, the compound has the formula: (IG). R^1 , R^2 , R^4 , L^1 , L^2 , E , $Y z1$ and $z2$ are as described herein.

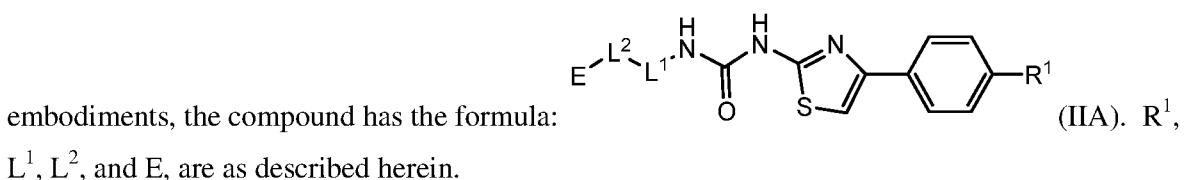


[0163] In embodiments, the compound has the formula:
 $R^1, R^2, R^4, L^1, L^2, E, Y z1$ and $z2$ are as described herein.

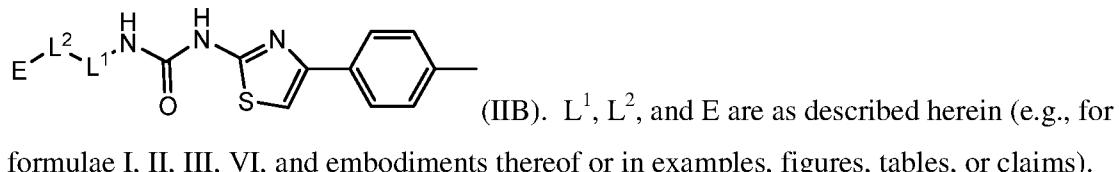
[0164] In embodiments, the compound has the formula:



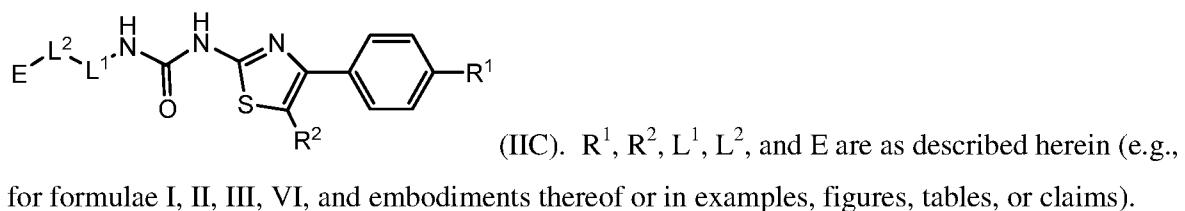
[0165] In embodiments of the compound of formula II, R^2, R^4 , and R^5 are hydrogen. In



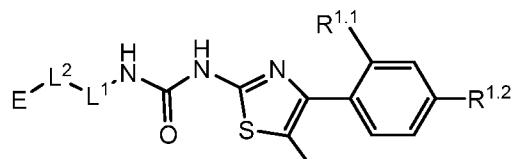
[0166] In embodiments, the compound has the formula:



[0167] In embodiments, the compound has the formula:



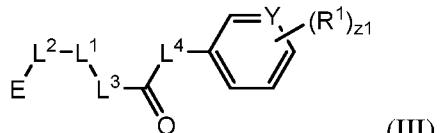
[0168] In embodiments, the compound has the formula:



(IID). R^1 , R^2 , L^1 , L^2 , and E are as described herein

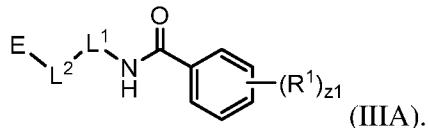
(e.g., for formulae I, II, III, VI, VI, and embodiments thereof or in examples, figures, tables, or claims). $R^{1.1}$ and $R^{1.2}$ have the values of R^1 . $R^{1.1}$ and $R^{1.2}$ may be optionally different halogens

5 (e.g., F and/or Cl). R^1 may be halogen (e.g., F or Cl). R^2 may be unsubstituted methyl.



[0169] In embodiments, the compound has the formula:

R^1 , L^1 , L^2 , L^3 , L^4 , E , Y , and $z1$ are as described herein.



[0170] In embodiments, the compound has the formula:

R^1 , L^1 , L^2 , E , and $z1$ are as described herein.

10 **[0171]** In embodiments, L^3 is a

bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHCH(CH₃)C(O)NH-, or unsubstituted C₁-C₃ alkylene. In embodiments, L^4 is a bond, -CH₂O-, -C(O)-, -NH-, or -O-. In embodiments, L^3 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(CH₃)C(O)NH-, or unsubstituted C₁-C₃ alkylene and L^4 is a bond, -CH₂O-, -C(O)-, -NH-, or -O-. In embodiments, L^3 is a bond. In embodiments, L^3 is a bond. In embodiments, L^3 is -O-. In embodiments, L^3 is -C(O)-. In embodiments, L^3 is -S-. In embodiments, L^3 is -SO-. In embodiments, L^3 is -S(O)₂-. In embodiments, L^3 is -NR⁵- . In embodiments, L^3 is -NH-. In embodiments, L^3 is -NR⁵C(O)- . In embodiments, L^3 is -NHC(O)- . In embodiments, L^3 is -C(O)NR⁵- . In embodiments, L^3 is -C(O)NH-. In embodiments, L^3 is -SO₂NR⁵- . In embodiments, L^3 is -SO₂NH-. In embodiments, L^3 is -NR⁵SO₂- . In embodiments, L^3 is -NHSO₂- . In embodiments, L^3 is -OC(O)NR⁵- . In embodiments, L^3 is -OC(O)NH-. In embodiments, L^3 is -NR⁵C(O)O-. In embodiments, L^3 is -NHC(O)O-. In embodiments, L^3 is substituted or unsubstituted C₁-C₆ alkylene. In embodiments, L^3 is substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^3 is unsubstituted methylene. In embodiments, L^3 is a bond.

[0172] In embodiments, L⁴ is a bond. In embodiments, L⁴ is -O-. In embodiments, L⁴ is -C(O)-. In embodiments, L⁴ is -S-. In embodiments, L⁴ is -SO-. In embodiments, L⁴ is -S(O)₂- . In embodiments, L⁴ is -NR⁴- . In embodiments, L⁴ is -NR⁴C(O)- . In embodiments, L⁴ is -C(O)NR⁴- . In embodiments, L⁴ is -SO₂NR⁴- . In embodiments, L⁴ is -NR⁴SO₂- . In
5 embodiments, L⁴ is -OC(O)NR⁴- . In embodiments, L⁴ is -NR⁴C(O)O- . In embodiments, L⁴ is substituted or unsubstituted C₁-C₃ alkylene. In embodiments, L⁴ is substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L⁴ is -NH-. In embodiments, L⁴ is -NHC(O)- . In
10 embodiments, L⁴ is -C(O)NH- . In embodiments, L⁴ is -SO₂NH- . In embodiments, L⁴ is -NHSO₂- . In embodiments, L⁴ is -NHSO₂- . In embodiments, L⁴ is -OC(O)NH- . In
15 embodiments, L⁴ is -NHC(O)O- . In embodiments, L⁴ is unsubstituted C₁-C₃ alkylene. In
embodiments, L⁴ is unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L⁴ is -CH₂NH- . In
20 embodiments, L⁴ is an unsubstituted methylene.

[0173] In embodiments, Ring A is a C₃-C₇ cycloalkyl. In embodiments, Ring A is a 3 to 7 membered heterocycloalkyl. In embodiments, Ring A is a C₅-C₇ cycloalkyl. In embodiments,
15 Ring A is a 5 to 7 membered heterocycloalkyl. In embodiments, Ring A is a C₃ cycloalkyl. In
embodiments, Ring A is a C₄ cycloalkyl. In embodiments, Ring A is a C₅ cycloalkyl. In
embodiments, Ring A is a C₆ cycloalkyl. In embodiments, Ring A is a C₇ cycloalkyl. In
embodiments, Ring A is a saturated C₃ cycloalkyl. In embodiments, Ring A is a saturated C₄
20 cycloalkyl. In embodiments, Ring A is a saturated C₅ cycloalkyl. In embodiments, Ring A is a
saturated C₆ cycloalkyl. In embodiments, Ring A is a saturated C₇ cycloalkyl. In
embodiments, Ring A is an unsaturated C₃ cycloalkyl. In embodiments, Ring A is an unsaturated C₄
25 cycloalkyl. In embodiments, Ring A is an unsaturated C₅ cycloalkyl. In embodiments, Ring A is an
unsaturated C₆ cycloalkyl. In embodiments, Ring A is an unsaturated C₇ cycloalkyl. In
embodiments, Ring A is a 3 membered heterocycloalkyl. In embodiments, Ring A is a 4
membered heterocycloalkyl. In embodiments, Ring A is a 5 membered heterocycloalkyl. In
embodiments, Ring A is a 6 membered heterocycloalkyl. In embodiments, Ring A is a 7
membered heterocycloalkyl. In embodiments, Ring A is a saturated 3 membered
30 heterocycloalkyl. In embodiments, Ring A is a saturated 4 membered heterocycloalkyl. In
embodiments, Ring A is a saturated 5 membered heterocycloalkyl. In embodiments, Ring A is a
saturated 6 membered heterocycloalkyl. In embodiments, Ring A is a saturated 7 membered
heterocycloalkyl. In embodiments, Ring A is an unsaturated 3 membered heterocycloalkyl. In
embodiments, Ring A is an unsaturated 4 membered heterocycloalkyl. In embodiments, Ring A is an
unsaturated 5 membered heterocycloalkyl. In embodiments, Ring A is an unsaturated 6
membered heterocycloalkyl. In embodiments, Ring A is an unsaturated 7 membered

heterocycloalkyl. In embodiments, Ring A is an aziridinyl. In embodiments, Ring A is an azirinyl. In embodiments, Ring A is a diaziridinyl. In embodiments, Ring A is a diazirinyl. In embodiments, Ring A is an azetidinyl. In embodiments, Ring A is an azetyl. In embodiments, Ring A is a diazetidinyl. In embodiments, Ring A is adiazetyl. In embodiments, Ring A is a piperidinyl. In embodiments, Ring A is pyrrolidinyl. In embodiments, Ring A is azepanyl. In embodiments, Ring A is a N-piperidinyl. In embodiments, Ring A is N-pyrrolidinyl. In embodiments, Ring A is N-azepanyl. In embodiments, Ring A is a 1-piperidinyl. In embodiments, Ring A is 1-pyrrolidinyl. In embodiments, Ring A is 1-azepanyl. In embodiments, Ring A is piperazinyl. In embodiments, Ring A is imidazolidinyl. In embodiments, Ring A is pyrazolidinyl. In embodiments, Ring A is oxazolidinyl. In embodiments, Ring A is isoxazolidinyl. In embodiments, Ring A is thiazolidinyl. In embodiments, Ring A is isothiazolidinyl. In embodiments, Ring A is pyridinyl. In embodiments, Ring A is pyranyl. In embodiments, Ring A is thiopyranyl. In embodiments, Ring A is oxanyl. In embodiments, Ring A is thianyl. In embodiments, Ring A is morpholinyl. In embodiments, Ring A is thiomorpholinyl. In embodiments, Ring A is dioxanyl. In embodiments, Ring A is dithianyl. In embodiments, Ring A is diazinyl. In embodiments, Ring A is oxazinyl. In embodiments, Ring A is thiazinyl. In embodiments, Ring A is dioxinyl. In embodiments, Ring A is dithiinyl.

[0174] In embodiments, Y is CH. In embodiments, Y is N. In embodiments, Y is C.

[0175] In embodiments, R¹ is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹ is independently halogen or -OCH₃. In embodiments, R¹ is substituted or unsubstituted C₁-C₆ alkyl. In embodiments, R¹ is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R¹ is substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹ is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹ is substituted or unsubstituted C₆ aryl. In

embodiments, R¹ is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹ is independently halogen. In embodiments, R¹ is independently -CX¹₃. In embodiments, R¹ is independently -CHX¹₂. In embodiments, R¹ is independently -CH₂X¹. In embodiments, R¹ is independently -OH. In embodiments, R¹ is independently -SH. In embodiments, R¹ is independently -COOH. In embodiments, R¹ is independently -OCX¹₃. In embodiments, R¹ is independently -OCHX¹₂. In embodiments, R¹ is independently -CH₃. In embodiments, R¹ is independently -CH₂CH₃. In embodiments, R¹ is independently -OCH₃. In embodiments, R¹ is independently -OCH₂CH₃. In embodiments, R¹ is independently -SCH₃. In embodiments, R¹ is independently -SCH₂CH₃. In embodiments, R¹ is independently -Cl or -OCH₃. In 5 embodiments, R¹ is independently halogen, -CX¹₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -OCX¹₃, -OCHX¹₂, -CHX¹₂, -CH₂X¹, substituted or unsubstituted C₁-C₈ alkyl, or substituted or unsubstituted 10 2 to 8 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹ is independently halogen, -CX¹₃, -CN, unsubstituted C₁-C₄ alkyl, or unsubstituted 15 2 to 4 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or unsubstituted tert-butyl. In embodiments, R¹ is independently unsubstituted methyl. In embodiments, R¹ is independently unsubstituted ethyl. In embodiments, R¹ is independently 20 unsubstituted propyl. In embodiments, R¹ is independently unsubstituted n-propyl. In embodiments, R¹ is independently unsubstituted isopropyl. In embodiments, R¹ is independently unsubstituted butyl. In embodiments, R¹ is independently unsubstituted n-butyl. In embodiments, R¹ is independently unsubstituted isobutyl. In embodiments, R¹ is independently 25 unsubstituted tert-butyl. In embodiments, R¹ is independently unsubstituted pentyl. In embodiments, R¹ is independently unsubstituted hexyl. In embodiments, R¹ is independently unsubstituted heptyl. In embodiments, R¹ is independently unsubstituted octyl. In embodiments, R¹ is independently -F. In embodiments, R¹ is independently -Cl. In embodiments, R¹ is independently -Br. In embodiments, R¹ is independently -I. In embodiments, R¹ is independently 30 unsubstituted methoxy. In embodiments, R¹ is independently unsubstituted ethoxy. In embodiments, R¹ is independently -CF₃. In embodiments, R¹ is independently -CCl₃. In embodiments, R¹ is an unsubstituted isopropyl. In embodiments, R¹ is an unsubstituted phenyl. In embodiments, R¹ is an unsubstituted pyridyl. In embodiments, R¹ is independently halogen. In embodiments, R¹ is independently -CX¹₃. In embodiments, R¹ is independently -CHX¹₂. In embodiments, R¹ is independently -CH₂X¹. In embodiments, R¹ is

independently -CN. In embodiments, R¹ is independently -OH. In embodiments, R¹ is independently -NH₂. In embodiments, R¹ is independently -COOH. In embodiments, R¹ is independently -CONH₂. In embodiments, R¹ is independently -NO₂. In embodiments, R¹ is independently -SH. In embodiments, R¹ is independently -SO₂Cl. In embodiments, R¹ is independently -SO₃H. In embodiments, R¹ is independently -SO₄H. In embodiments, R¹ is independently -SO₂NH₂. In embodiments, R¹ is independently -NHNH₂. In embodiments, R¹ is independently -ONH₂. In embodiments, R¹ is independently -NHC(O)NHNH₂. In embodiments, R¹ is independently -NHC(O)NH₂. In embodiments, R¹ is independently -NHSO₂H. In embodiments, R¹ is independently -NHC(O)H. In embodiments, R¹ is independently -NHC(O)OH. In embodiments, R¹ is independently -NHOH. In embodiments, R¹ is independently -OCX¹₃. In embodiments, R¹ is independently -OCHX¹₂. In embodiments, R¹ is independently substituted or unsubstituted alkyl. In embodiments, R¹ is independently substituted or unsubstituted heteroalkyl. In embodiments, R¹ is independently substituted or unsubstituted cycloalkyl. In embodiments, R¹ is independently substituted or unsubstituted heterocycloalkyl. In embodiments, R¹ is independently substituted or unsubstituted aryl. In embodiments, R¹ is independently substituted or unsubstituted heteroaryl. In embodiments, R¹ is independently substituted alkyl. In embodiments, R¹ is independently substituted heteroalkyl. In embodiments, R¹ is independently substituted cycloalkyl. In embodiments, R¹ is independently substituted heterocycloalkyl. In embodiments, R¹ is independently substituted aryl. In embodiments, R¹ is independently substituted heteroaryl. In embodiments, R¹ is independently unsubstituted alkyl. In embodiments, R¹ is independently unsubstituted heteroalkyl. In embodiments, R¹ is independently unsubstituted cycloalkyl. In embodiments, R¹ is independently unsubstituted heterocycloalkyl. In embodiments, R¹ is independently unsubstituted aryl. In embodiments, R¹ is independently unsubstituted heteroaryl. In embodiments, R¹ is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R¹ is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R¹ is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹ is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹ is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R¹ is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R¹ is independently substituted C₁-C₈ alkyl. In embodiments, R¹ is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R¹ is independently substituted C₃-C₈ cycloalkyl. In embodiments, R¹ is independently substituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹ is independently substituted C₆-C₁₀ aryl. In embodiments, R¹ is independently

substituted 5 to 10 membered heteroaryl. In embodiments, R¹ is independently unsubstituted C₁-C₈ alkyl. In embodiments, R¹ is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹ is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹ is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R¹ is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R¹ is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R¹ is independently substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R¹ is independently substituted or unsubstituted C₃-C₆ cycloalkyl. In embodiments, R¹ is independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl.

5 In embodiments, R¹ is independently substituted or unsubstituted phenyl. In embodiments, R¹ is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹ is independently substituted C₁-C₄ alkyl. In embodiments, R¹ is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R¹ is independently substituted C₃-C₆ cycloalkyl. In embodiments, R¹ is independently substituted 3 to 6 membered heterocycloalkyl.

10 In embodiments, R¹ is independently substituted phenyl. In embodiments, R¹ is independently substituted 5 to 6 membered heteroaryl. In embodiments, R¹ is independently unsubstituted C₁-C₄ alkyl. In embodiments, R¹ is independently unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted C₃-C₆ cycloalkyl. In embodiments, R¹ is independently unsubstituted 3 to 6 membered heterocycloalkyl.

15 In embodiments, R¹ is independently substituted phenyl. In embodiments, R¹ is independently substituted 5 to 6 membered heteroaryl. In embodiments, R¹ is independently unsubstituted C₁-C₄ alkyl. In embodiments, R¹ is independently unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R¹ is independently unsubstituted C₃-C₆ cycloalkyl. In embodiments, R¹ is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R¹ is

20 independently unsubstituted phenyl. In embodiments, R¹ is independently unsubstituted 5 to 6 membered heteroaryl.

[0176] In embodiments, R^{1,1} is independently halogen, -CX^{1,1}₃, -CHX^{1,1}₂, -CH₂X^{1,1}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX^{1,1}₃, -OCHX^{1,1}₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1,1} is independently

25 substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1,1} is independently halogen, -CX^{1,1}₃, -CHX^{1,1}₂, -CH₂X^{1,1}, -OH, -SH, -COOH, -OCX^{1,1}₃, -OCHX^{1,1}₂, -CH₃, -CH₂CH₃, -OC H₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R^{1,1} is independently halogen or -OCH₃. In embodiments, R^{1,1} is substituted or unsubstituted C₁-C₆ alkyl. In embodiments, R^{1,1} is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^{1,1} is substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{1,1} is substituted or unsubstituted 3 to 8

30

membered heterocycloalkyl. In embodiments, R^{1.1} is substituted or unsubstituted C₆ aryl. In embodiments, R^{1.1} is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1.1} is independently halogen. In embodiments, R^{1.1} is independently -CX^{1.3}. In embodiments, R^{1.1} is independently -CHX^{1.2}. In embodiments, R^{1.1} is independently -CH₂X¹. In embodiments, 5 R^{1.1} is independently -OH. In embodiments, R^{1.1} is independently -SH. In embodiments, R^{1.1} is independently -COOH. In embodiments, R^{1.1} is independently -OCX^{1.3}. In embodiments, R^{1.1} is independently -OCHX^{1.2}. In embodiments, R^{1.1} is independently -CH₃. In embodiments, R^{1.1} is independently -CH₂CH₃. In embodiments, R^{1.1} is independently -OCH₃. In embodiments, R^{1.1} is independently -OCH₂CH₃. In embodiments, R^{1.1} is independently -SCH₃. In embodiments, R^{1.1} is independently -SCH₂CH₃. In embodiments, R^{1.1} is independently -Cl or -OCH₃. In 10 embodiments, R^{1.1} is independently halogen, -CX^{1.3}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -OCX^{1.3}, -OCHX^{1.2}, -CHX^{1.2}, -CH₂X¹, substituted or unsubstituted C₁-C₈ alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 15 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1.1} is independently halogen, -CX^{1.3}, -CN, unsubstituted C₁-C₄ alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^{1.1} is independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or unsubstituted tert-butyl. In embodiments, R^{1.1} is independently unsubstituted methyl. In 20 embodiments, R^{1.1} is independently unsubstituted ethyl. In embodiments, R^{1.1} is independently unsubstituted propyl. In embodiments, R^{1.1} is independently unsubstituted n-propyl. In embodiments, R^{1.1} is independently unsubstituted isopropyl. In embodiments, R^{1.1} is independently unsubstituted butyl. In embodiments, R^{1.1} is independently unsubstituted n-butyl. In 25 embodiments, R^{1.1} is independently unsubstituted isobutyl. In embodiments, R^{1.1} is independently unsubstituted tert-butyl. In embodiments, R^{1.1} is independently unsubstituted pentyl. In embodiments, R^{1.1} is independently unsubstituted hexyl. In embodiments, R^{1.1} is independently unsubstituted heptyl. In embodiments, R^{1.1} is independently unsubstituted octyl. In embodiments, R^{1.1} is independently -F. In embodiments, R^{1.1} is independently -Cl. In 30 embodiments, R^{1.1} is independently -Br. In embodiments, R^{1.1} is independently -I. In embodiments, R^{1.1} is independently unsubstituted methoxy. In embodiments, R^{1.1} is independently -CF₃. In embodiments, R^{1.1} is independently -CCl₃. In embodiments, R^{1.1} is an unsubstituted isopropyl. In embodiments, R^{1.1} is an unsubstituted phenyl. In embodiments, R^{1.1} is an unsubstituted pyridyl. In embodiments, R^{1.1} is independently halogen. In embodiments, R^{1.1} is

independently $-CX_3^1$. In embodiments, $R^{1.1}$ is independently $-CHX_2^1$. In embodiments, $R^{1.1}$ is independently $-CH_2X^1$. In embodiments, $R^{1.1}$ is independently $-CN$. In embodiments, $R^{1.1}$ is independently $-OH$. In embodiments, $R^{1.1}$ is independently $-NH_2$. In embodiments, $R^{1.1}$ is independently $-COOH$. In embodiments, $R^{1.1}$ is independently $-CONH_2$. In embodiments, $R^{1.1}$ is independently $-NO_2$. In embodiments, $R^{1.1}$ is independently $-SH$. In embodiments, $R^{1.1}$ is independently $-SO_2Cl$. In embodiments, $R^{1.1}$ is independently $-SO_3H$. In embodiments, $R^{1.1}$ is independently $-SO_4H$. In embodiments, $R^{1.1}$ is independently $-SO_2NH_2$. In embodiments, $R^{1.1}$ is independently $-NHNH_2$. In embodiments, $R^{1.1}$ is independently $-ONH_2$. In embodiments, $R^{1.1}$ is independently $-NHC(O)NHNH_2$. In embodiments, $R^{1.1}$ is independently $-NHC(O)NH_2$. In 5 embodiments, $R^{1.1}$ is independently $-NHSO_2H$. In embodiments, $R^{1.1}$ is independently $-NHC(O)H$. In embodiments, $R^{1.1}$ is independently $-NHC(O)OH$. In embodiments, $R^{1.1}$ is independently $-NHOH$. In embodiments, $R^{1.1}$ is independently $-OCX_3^1$. In embodiments, $R^{1.1}$ is independently $-OCHX_2^1$. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted alkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted heteroalkyl. In 10 embodiments, $R^{1.1}$ is independently substituted or unsubstituted cycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted heterocycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted aryl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted heteroaryl. In embodiments, $R^{1.1}$ is independently substituted alkyl. In embodiments, $R^{1.1}$ is independently substituted heteroalkyl. In embodiments, $R^{1.1}$ is independently substituted cycloalkyl. In 15 embodiments, $R^{1.1}$ is independently substituted heterocycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted aryl. In embodiments, $R^{1.1}$ is independently substituted heteroaryl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted heteroaryl. In embodiments, $R^{1.1}$ is independently unsubstituted alkyl. In embodiments, $R^{1.1}$ is independently unsubstituted heteroalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted cycloalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted 20 heterocycloalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted aryl. In embodiments, $R^{1.1}$ is independently unsubstituted heteroaryl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted 25 3 to 8 membered heterocycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, $R^{1.1}$ is independently substituted C₁-C₈ alkyl. In embodiments, $R^{1.1}$ is independently substituted 30 2 to 8 membered heteroalkyl. In embodiments, $R^{1.1}$ is independently substituted C₃-C₈ cycloalkyl. In embodiments, $R^{1.1}$ is independently substituted

substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{1.1} is independently substituted C₆-C₁₀ aryl. In embodiments, R^{1.1} is independently substituted 5 to 10 membered heteroaryl. In embodiments, R^{1.1} is independently unsubstituted C₁-C₈ alkyl. In embodiments, R^{1.1} is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^{1.1} is

5 independently unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{1.1} is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{1.1} is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R^{1.1} is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{1.1} is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R^{1.1} is independently substituted or unsubstituted 2 to 4 membered

10 heteroalkyl. In embodiments, R^{1.1} is independently substituted or unsubstituted C₃-C₆ cycloalkyl. In embodiments, R^{1.1} is independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{1.1} is independently substituted or unsubstituted phenyl. In embodiments, R^{1.1} is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1.1} is independently substituted C₁-C₄ alkyl. In embodiments, R^{1.1} is

15 independently substituted 2 to 4 membered heteroalkyl. In embodiments, R^{1.1} is independently substituted C₃-C₆ cycloalkyl. In embodiments, R^{1.1} is independently substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{1.1} is independently substituted phenyl. In embodiments, R^{1.1} is independently substituted 5 to 6 membered heteroaryl. In embodiments, R^{1.1} is independently unsubstituted C₁-C₄ alkyl. In embodiments, R^{1.1} is independently unsubstituted 2

20 to 4 membered heteroalkyl. In embodiments, R^{1.1} is independently unsubstituted C₃-C₆ cycloalkyl. In embodiments, R^{1.1} is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{1.1} is independently unsubstituted phenyl. In embodiments, R^{1.1} is independently unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1.1} is independently hydrogen.

25 [0177] In embodiments, R^{1.2} is independently halogen, -CX^{1.3}, -CHX^{1.2}, -CH₂X¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX^{1.3}, -OCHX^{1.2}, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl,

30 substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1.2} is independently halogen, -CX^{1.3}, -CHX^{1.2}, -CH₂X¹, -OH, -SH, -COOH, -OCX^{1.3}, -OCHX^{1.2}, -CH₃, -CH₂CH₃, -OC H₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R^{1.2} is independently halogen or -OCH₃.

In embodiments, R^{1,2} is substituted or unsubstituted C₁-C₆ alkyl. In embodiments, R^{1,2} is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^{1,2} is substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{1,2} is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{1,2} is substituted or unsubstituted C₆ aryl. In 5 embodiments, R^{1,2} is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1,2} is independently halogen. In embodiments, R^{1,2} is independently -CX^{1,3}. In embodiments, R^{1,2} is independently -CHX^{1,2}. In embodiments, R^{1,2} is independently -CH₂X¹. In embodiments, R^{1,2} is independently -OH. In embodiments, R^{1,2} is independently -SH. In embodiments, R^{1,2} is independently -COOH. In embodiments, R^{1,2} is independently -OCX^{1,3}. In embodiments, R^{1,2} is independently -OCHX^{1,2}. In embodiments, R^{1,2} is independently -CH₃. In embodiments, R^{1,2} is independently -CH₂CH₃. In embodiments, R^{1,2} is independently -OCH₃. In embodiments, R^{1,2} is independently -OCH₂CH₃. In embodiments, R^{1,2} is independently -SCH₃. In embodiments, R^{1,2} is independently -SCH₂CH₃. In embodiments, R^{1,2} is independently -Cl or -OCH₃. In 10 embodiments, R^{1,2} is independently halogen, -CX^{1,3}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -OCX^{1,3}, -OCHX^{1,2}, -CHX^{1,2}, -CH₂X¹, substituted or unsubstituted C₁-C₈ alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1,2} is independently halogen, -CX^{1,3}, -CN, 15 unsubstituted C₁-C₄ alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^{1,2} is independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or unsubstituted tert-butyl. In embodiments, R^{1,2} is independently unsubstituted methyl. In 20 embodiments, R^{1,2} is independently unsubstituted ethyl. In embodiments, R^{1,2} is independently unsubstituted propyl. In embodiments, R^{1,2} is independently unsubstituted n-propyl. In 25 embodiments, R^{1,2} is independently unsubstituted isopropyl. In embodiments, R^{1,2} is independently unsubstituted butyl. In embodiments, R^{1,2} is independently unsubstituted n-butyl. In embodiments, R^{1,2} is independently unsubstituted isobutyl. In embodiments, R^{1,2} is independently unsubstituted pentyl. In embodiments, R^{1,2} is independently unsubstituted hexyl. In embodiments, R^{1,2} is 30 independently unsubstituted heptyl. In embodiments, R^{1,2} is independently unsubstituted octyl. In embodiments, R^{1,2} is independently -F. In embodiments, R^{1,2} is independently -Cl. In embodiments, R^{1,2} is independently -Br. In embodiments, R^{1,2} is independently -I. In embodiments, R^{1,2} is independently unsubstituted methoxy. In embodiments, R^{1,2} is independently unsubstituted ethoxy. In embodiments, R^{1,2} is independently -CF₃. In

embodiments, R^{1,2} is independently -CCl₃. In embodiments, R^{1,2} is an unsubstituted isopropyl. In embodiments, R^{1,2} is an unsubstituted phenyl. In embodiments, R^{1,2} is an unsubstituted pyridyl. In embodiments, R^{1,2} is independently halogen. In embodiments, R^{1,2} is independently -CX^{1,3}. In embodiments, R^{1,2} is independently -CHX^{1,2}. In embodiments, R^{1,2} is independently -CH₂X¹. In embodiments, R^{1,2} is independently -CN. In embodiments, R^{1,2} is independently -OH. In embodiments, R^{1,2} is independently -NH₂. In embodiments, R^{1,2} is independently -COOH. In embodiments, R^{1,2} is independently -CONH₂. In embodiments, R^{1,2} is independently -NO₂. In embodiments, R^{1,2} is independently -SH. In embodiments, R^{1,2} is independently -SO₂Cl. In embodiments, R^{1,2} is independently -SO₃H. In embodiments, R^{1,2} is independently -SO₄H. In embodiments, R^{1,2} is independently -SO₂NH₂. In embodiments, R^{1,2} is independently -NHNH₂. In embodiments, R^{1,2} is independently -ONH₂. In embodiments, R^{1,2} is independently -NHC(O)NHNH₂. In embodiments, R^{1,2} is independently -NHC(O)NH₂. In embodiments, R^{1,2} is independently -NHSO₂H. In embodiments, R^{1,2} is independently -NHC(O)H. In embodiments, R^{1,2} is independently -NHOH. In embodiments, R^{1,2} is independently -OCX^{1,3}. In embodiments, R^{1,2} is independently -OCHX^{1,2}. In embodiments, R^{1,2} is independently substituted or unsubstituted alkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted heteroalkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted cycloalkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted heterocycloalkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted aryl. In embodiments, R^{1,2} is independently substituted or unsubstituted heteroaryl. In embodiments, R^{1,2} is independently substituted alkyl. In embodiments, R^{1,2} is independently substituted heteroalkyl. In embodiments, R^{1,2} is independently substituted cycloalkyl. In embodiments, R^{1,2} is independently substituted heterocycloalkyl. In embodiments, R^{1,2} is independently substituted aryl. In embodiments, R^{1,2} is independently substituted heteroaryl. In embodiments, R^{1,2} is independently unsubstituted alkyl. In embodiments, R^{1,2} is independently unsubstituted heteroalkyl. In embodiments, R^{1,2} is independently unsubstituted cycloalkyl. In embodiments, R^{1,2} is independently unsubstituted heterocycloalkyl. In embodiments, R^{1,2} is independently unsubstituted aryl. In embodiments, R^{1,2} is independently unsubstituted heteroaryl. In embodiments, R^{1,2} is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R^{1,2} is independently substituted or unsubstituted 5 to 10

membered heteroaryl. In embodiments, R^{1,2} is independently substituted C₁-C₈ alkyl. In embodiments, R^{1,2} is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R^{1,2} is independently substituted C₃-C₈ cycloalkyl. In embodiments, R^{1,2} is independently substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{1,2} is independently substituted 5 to 10 membered heteroaryl. In embodiments, R^{1,2} is independently unsubstituted C₁-C₈ alkyl. In embodiments, R^{1,2} is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^{1,2} is independently unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{1,2} is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{1,2} is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R^{1,2} is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{1,2} is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted C₃-C₆ cycloalkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{1,2} is independently substituted or unsubstituted phenyl. In embodiments, R^{1,2} is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1,2} is independently substituted C₁-C₄ alkyl. In embodiments, R^{1,2} is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R^{1,2} is independently substituted C₃-C₆ cycloalkyl. In embodiments, R^{1,2} is independently substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{1,2} is independently substituted phenyl. In embodiments, R^{1,2} is independently substituted 5 to 6 membered heteroaryl. In embodiments, R^{1,2} is independently unsubstituted C₁-C₄ alkyl. In embodiments, R^{1,2} is independently unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^{1,2} is independently unsubstituted C₃-C₆ cycloalkyl. In embodiments, R^{1,2} is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{1,2} is independently unsubstituted phenyl. In embodiments, R^{1,2} is independently unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{1,2} is independently hydrogen.

[0178] In embodiments, z1 is 2. In embodiments, z1 is 3. In embodiments, z1 is 0. In embodiments, z1 is 1. In embodiments, z1 is 4. In embodiments, z1 is 5.

[0179] In embodiments, R² is independently hydrogen, oxo, halogen, CX₃², -CHX₂², -CH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX₃², -OCHX₂², substituted or unsubstituted C₁-C₆ alkyl, substituted or

unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently oxo, halogen, CX²₃, -CHX²₂, -

- 5 CH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently hydrogen, halogen, CX²₃, -CHX²₂, -
- 10 CH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently hydrogen, halogen, CX²₃, -CHX²₂, -
- 15 halogen, -CX²₃, -CHX²₂, -CH₂X², --OH, -SH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -OC H₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R² is independently hydrogen, halogen, -CX²₃, -CHX²₂, -CH₂X², --OH, -SH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -OC H₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R² is independently hydrogen. In embodiments, R² is independently halogen. In embodiments, R² is independently unsubstituted methyl. In embodiments, two adjacent R² substituents or two R² substituents bonded to the same atom may 20 optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl. In embodiments, two adjacent R² substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R² is independently halogen, -CX²₃, -CHX²₂, -
- 25 CH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆

aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently halogen, -CX²₃, -CHX²₂, -CH₂X², -OH, -SH, -COOH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R² is independently halogen or -OCH₃.

5 In embodiments, R² is substituted or unsubstituted C₁-C₆ alkyl. In embodiments, R² is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R² is substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R² is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R² is substituted or unsubstituted C₆ aryl. In embodiments, R² is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments,

10 R² is independently halogen. In embodiments, R² is independently -CX²₃. In embodiments, R² is independently -CHX²₂. In embodiments, R² is independently -CH₂X². In embodiments, R² is independently -OH. In embodiments, R² is independently -SH. In embodiments, R² is independently -COOH. In embodiments, R² is independently -OCX²₃. In embodiments, R² is independently -OCHX²₂. In embodiments, R² is independently -CH₃. In embodiments, R² is independently -CH₂CH₃. In embodiments, R² is independently -OCH₃. In embodiments, R² is independently -OCH₂CH₃. In embodiments, R² is independently -SCH₃. In embodiments, R² is independently -SCH₂CH₃. In embodiments, R² is independently -Cl or -OCH₃. In

15 embodiments, R² is independently halogen, -CX²₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -OCX²₃, -OCHX²₂, -CHX²₂, -CH₂X², substituted or unsubstituted C₁-C₈ alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently halogen, -CX²₃, -CN, unsubstituted C₁-C₄ alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or

20 unsubstituted tert-butyl. In embodiments, R² is independently unsubstituted methyl. In embodiments, R² is independently unsubstituted ethyl. In embodiments, R² is independently unsubstituted propyl. In embodiments, R² is independently unsubstituted n-propyl. In embodiments, R² is independently unsubstituted isopropyl. In embodiments, R² is independently unsubstituted butyl. In embodiments, R² is independently unsubstituted n-butyl. In

25 embodiments, R² is independently unsubstituted isobutyl. In embodiments, R² is independently unsubstituted tert-butyl. In embodiments, R² is independently unsubstituted pentyl. In embodiments, R² is independently unsubstituted hexyl. In embodiments, R² is independently unsubstituted heptyl. In embodiments, R² is independently unsubstituted octyl. In embodiments,

R² is independently -F. In embodiments, R² is independently -Cl. In embodiments, R² is independently -Br. In embodiments, R² is independently -I. In embodiments, R² is independently unsubstituted methoxy. In embodiments, R² is independently unsubstituted ethoxy. In embodiments, R² is independently -CF₃. In embodiments, R² is independently -CCl₃.

5 In embodiments, R² is an unsubstituted isopropyl. In embodiments, R² is an unsubstituted phenyl. In embodiments, R² is an unsubstituted pyridyl. In embodiments, R² is independently halogen. In embodiments, R² is independently -CX²₃. In embodiments, R² is independently -CHX²₂. In embodiments, R² is independently -CH₂X². In embodiments, R² is independently -CN. In embodiments, R² is independently -OH. In embodiments, R² is

10 independently -NH₂. In embodiments, R² is independently -COOH. In embodiments, R² is independently -CONH₂. In embodiments, R² is independently -NO₂. In embodiments, R² is independently -SH. In embodiments, R² is independently -SO₂Cl. In embodiments, R² is independently -SO₃H. In embodiments, R² is independently -SO₄H. In embodiments, R² is independently -SO₂NH₂. In embodiments, R² is independently -NHNH₂. In embodiments, R² is

15 independently -ONH₂. In embodiments, R² is independently -NHC(O)NHNH₂. In embodiments, R² is independently -NHC(O)NH₂. In embodiments, R² is independently -NHSO₂H. In embodiments, R² is independently -NHC(O)H. In embodiments, R² is independently -NHC(O)OH. In embodiments, R² is independently -NHOH. In embodiments, R² is independently -OCX²₃. In embodiments, R² is independently -OCHX²₂. In embodiments, R²

20 is independently substituted or unsubstituted alkyl. In embodiments, R² is independently substituted or unsubstituted heteroalkyl. In embodiments, R² is independently substituted or unsubstituted cycloalkyl. In embodiments, R² is independently substituted or unsubstituted heterocycloalkyl. In embodiments, R² is independently substituted or unsubstituted aryl. In embodiments, R² is independently substituted or unsubstituted heteroaryl. In embodiments, R² is

25 independently substituted alkyl. In embodiments, R² is independently substituted heteroalkyl. In embodiments, R² is independently substituted cycloalkyl. In embodiments, R² is independently substituted heterocycloalkyl. In embodiments, R² is independently substituted aryl. In embodiments, R² is independently substituted heteroaryl. In embodiments, R² is independently unsubstituted alkyl. In embodiments, R² is independently unsubstituted heteroalkyl. In

30 embodiments, R² is independently unsubstituted cycloalkyl. In embodiments, R² is independently unsubstituted heterocycloalkyl. In embodiments, R² is independently unsubstituted aryl. In embodiments, R² is independently unsubstituted heteroaryl. In embodiments, R² is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R² is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R²

is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R² is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R² is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R² is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R² is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R² is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R² is independently substituted C₃-C₈ cycloalkyl. In embodiments, R² is independently substituted 3 to 8 membered heterocycloalkyl. In embodiments, R² is independently substituted C₆-C₁₀ aryl. In embodiments, R² is independently substituted 5 to 10 membered heteroaryl. In embodiments, R² is independently unsubstituted C₁-C₈ alkyl. In embodiments, R² is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R² is independently unsubstituted C₃-C₈ cycloalkyl. In embodiments, R² is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R² is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R² is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R² is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R² is independently substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently substituted or unsubstituted C₃-C₆ cycloalkyl. In embodiments, R² is independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R² is independently substituted or unsubstituted phenyl. In embodiments, R² is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently substituted C₁-C₄ alkyl. In embodiments, R² is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently substituted C₃-C₆ cycloalkyl. In embodiments, R² is independently substituted 3 to 6 membered heterocycloalkyl. In embodiments, R² is independently substituted phenyl. In embodiments, R² is independently substituted 5 to 6 membered heteroaryl. In embodiments, R² is independently unsubstituted C₁-C₄ alkyl. In embodiments, R² is independently unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently unsubstituted C₃-C₆ cycloalkyl. In embodiments, R² is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R² is independently unsubstituted phenyl. In embodiments, R² is independently unsubstituted 5 to 6 membered heteroaryl.

[0180] In embodiments, z2 is 0. In embodiments, z2 is 1. In embodiments, z2 is 2. In embodiments, z2 is 3. In embodiments, z2 is 4. In embodiments, z2 is 5. In embodiments, z2 is 6. In embodiments, z2 is 7. In embodiments, z2 is 8. In embodiments, z2 is 9. In embodiments, z2 is 10.

[0181] In embodiments, R⁴ is hydrogen. In embodiments, R⁵ is hydrogen. In embodiments, R⁴ is unsubstituted methyl. In embodiments, R⁴ is unsubstituted ethyl. In embodiments, R⁴ is unsubstituted propyl. In embodiments, R⁴ is unsubstituted butyl. In embodiments, R⁵ is unsubstituted methyl. In embodiments, R⁵ is unsubstituted ethyl. In embodiments, R⁵ is 5 unsubstituted propyl. In embodiments, R⁵ is unsubstituted butyl. In embodiments, R⁴ is substituted or unsubstituted alkyl. In embodiments, R⁴ is substituted or unsubstituted heteroalkyl. In embodiments, R⁴ is substituted or unsubstituted cycloalkyl. In embodiments, R⁴ is substituted or unsubstituted heterocycloalkyl. In embodiments, R⁴ is substituted or unsubstituted aryl. In embodiments, R⁴ is substituted or unsubstituted heteroaryl. In 10 embodiments, R⁵ is substituted or unsubstituted alkyl. In embodiments, R⁵ is substituted or unsubstituted heteroalkyl. In embodiments, R⁵ is substituted or unsubstituted cycloalkyl. In embodiments, R⁵ is substituted or unsubstituted heterocycloalkyl. In embodiments, R⁵ is substituted or unsubstituted aryl. In embodiments, R⁵ is substituted or unsubstituted heteroaryl.

[0182] In embodiments, L¹ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7A}-, - 15 NR^{7A}C(O)-, -C(O)NR^{7A}-, -SO₂NR^{7A}-, -NR^{7A}SO₂-, -OC(O)NR^{7A}-, - NR^{7A}C(O)O-, -CR^{9A}=NO-, -ON=CR^{9A}-, -NR^{8A}C(O)NR^{7A}-, -NR^{8A}C(=NR^{10A})NR^{7A}-, -NR^{8A}C(=NR^{10A})-, -C(=NR^{10A})NR^{7A}-, -OC(=NR^{10A})-, -C(=NR^{10A})O-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted 20 cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0183] In embodiments, L¹ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, - 25 NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted 30 heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0184] In embodiments, L¹ is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L¹ is a bond, unsubstituted C₁-C₄ alkylene, or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L¹ is a bond. In embodiments, L¹ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -

5 NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. In embodiments, L¹ is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. In embodiments, L¹ is a bond. In embodiments, L¹ is a bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C₁-C₄ alkylene, or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L¹ is -NH-. In embodiments, 10 L¹ is -CH(CH₂Cl)CH₂-. In embodiments, L¹ is -C(O)CH(CH₂Cl)CH₂-. In embodiments, L¹ is -NHC(O)CH(CH₂Cl)CH₂-. In embodiments, L¹ is halo-substituted C₁-C₄ alkylene. In 15 embodiments, L¹ is halo-substituted C₂-C₄ alkylene. In embodiments, L¹ is halo-substituted C₃-C₄ alkylene. In embodiments, L¹ is halo-substituted C₃ alkylene. In embodiments, L¹ is a bond. In embodiments, L¹ is -O-. In embodiments, L¹ is -C(O)-. In embodiments, L¹ is -S-. In 20 embodiments, L¹ is -SO-. In embodiments, L¹ is -S(O)₂-. In embodiments, L¹ is -NH-. In embodiments, L¹ is -NHC(O)-. In embodiments, L¹ is -C(O)NH-. In embodiments, L¹ is -SO₂NH-. In embodiments, L¹ is -NHSO₂-. In embodiments, L¹ is -OC(O)NH-. In 25 embodiments, L¹ is -NHC(O)O-. In embodiments, L¹ is -CH=NO-. In embodiments, L¹ is -ON=CH-. In embodiments, L¹ is -NHC(O)NH-. In embodiments, L¹ is -NHC(=NH)NH-. In embodiments, L¹ is -NHC(=NH)-. In embodiments, L¹ is -C(=NH)NH-. In embodiments, L¹ is -OC(=NH)-. In embodiments, L¹ is -C(=NH)O-. 30

[0185] In embodiments, L¹ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7A}-, -NR^{7A}C(O)-, -C(O)NR^{7A}-, -SO₂NR^{7A}-, -NR^{7A}SO₂-, -OC(O)NR^{7A}-, -NR^{7A}C(O)O-, -CR^{9A}=NO-, -ON=CR^{9A}-, -NR^{8A}C(O)NR^{7A}-, -NR^{8A}C(=NR^{10A})NR^{7A}-, -NR^{8A}C(=NR^{10A})-, -C(=NR^{10A})NR^{7A}-, -OC(=NR^{10A})-, -C(=NR^{10A})O-, R^{7A}-substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{7A}-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{7A}-substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{7A}-substituted or unsubstituted

heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{7A}-substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or R^{7A}-substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0186] In embodiments, L¹ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -

- 5 NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, R^{7A}-substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{7A}-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{7A}-substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{7A}-substituted or 10 unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{7A}-substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or R^{7A}-substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0187] In embodiments, L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -

- 15 NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted 20 cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0188] In embodiments, L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -

- 25 NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted 30 heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0189] In embodiments, L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or 5 unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. In embodiments, L² is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. In embodiments, L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -NHC(O)NH-, substituted or unsubstituted alkylene, or 10 substituted or unsubstituted heteroalkylene. In embodiments, L² is a bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C₁-C₄ alkylene, or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L² is a bond. In embodiments, 15 L² is -NH-. In embodiments, L² is -CH(CH₂Cl)CH₂- . In embodiments, L² is -C(O)CH(CH₂Cl)CH₂- . In embodiments, L² is -NHC(O)CH(CH₂Cl)CH₂- . In embodiments, L² is -NHC(O)-. In embodiments, L² is -NH-. In embodiments, L² is halo-substituted C₁-C₄ alkylene. In embodiments, L² is halo-substituted C₂-C₄ alkylene. In embodiments, L² is halo-substituted C₃-C₄ alkylene. In embodiments, L² is halo-substituted C₃ alkylene.

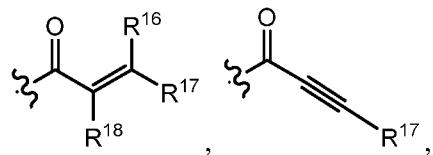
[0190] In embodiments, L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, R^{7B}-substituted or 20 unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{7B}-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{7B}-substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{7B}-substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{7B}-substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or R^{7B}-substituted or 25 unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, R^{7B}-substituted or 30 unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{7B}-substituted or

unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{7B}-substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{7B}-substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{7B}-substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or R^{7B}-substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

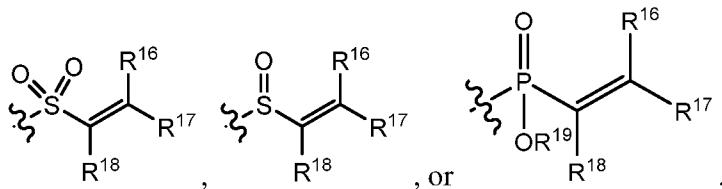


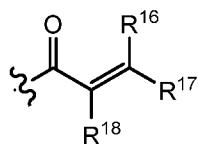
[0191] In embodiments, L² is . Ring C is a substituted or unsubstituted heterocycloalkylene or substituted or unsubstituted heteroarylene. In embodiments, Ring C is a substituted or unsubstituted 5 to 6 membered heterocycloalkylene or substituted or unsubstituted 10 5 to 6 membered heteroarylene. In embodiments, Ring C is an R^{7B}-substituted or unsubstituted heterocycloalkylene or R^{7B}-substituted or unsubstituted heteroarylene. In embodiments, Ring C is a R^{7B}-substituted or unsubstituted 5 to 6 membered heterocycloalkylene or R^{7B}-substituted or unsubstituted 5 to 6 membered heteroarylene.

[0192] In embodiments, E is a covalent cysteine modifier moiety. In embodiments, E is a

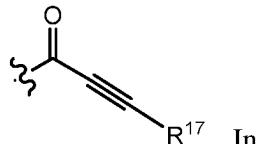


15 covalent histidine modifier moiety. In embodiments, E is

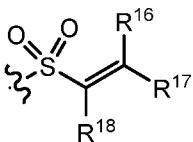




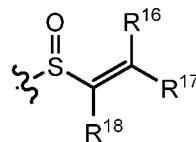
In embodiments, E is



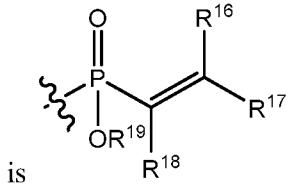
. In embodiments, , E is



embodiments, E is



. In embodiments, E is



is

[0193] R¹⁶ is independently hydrogen, halogen, CX¹⁶₃, -CHX¹⁶₂, -

- 5 CH₂X¹⁶, -CN, -SO₂Cl, -SO_{n16}R^{16D}, -SO_{v16}NR^{16A}R^{16B}, -NHNR^{16A}R^{16B}, -ONR^{16A}R^{16B},
-NHC=(O)NHNR^{16A}R^{16B},
-NHC(O)NR^{16A}R^{16B}, -N(O)_{m16}, -NR^{16A}R^{16B}, -C(O)R^{16C}, -C(O)-OR^{16C}, -C(O)NR^{16A}R^{16B}, -OR^{16D},
-NR^{16A}SO₂R^{16D}, -NR^{16A}C(O)R^{16C}, -NR^{16A}C(O)OR^{16C}, -NR^{16A}OR^{16C}, -OCX¹⁶₃, -OCHX¹⁶₂,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
10 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, substituted or unsubstituted heteroaryl. R¹⁷ is independently hydrogen,
-NHC(O)NR^{17A}R^{17B}, -N(O)_{m17}, -NR^{17A}R^{17B}, -C(O)R^{17C}, -C(O)-OR^{17C}, -C(O)NR^{17A}R^{17B}, -OR^{17D},
-NR^{17A}SO₂R^{17D}, -NR^{17A}C(O)R^{17C}, -NR^{17A}C(O)OR^{17C}, -NR^{17A}OR^{17C}, -OCX¹⁷₃, -OCHX¹⁷₂,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
15 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, substituted or unsubstituted heteroaryl. R¹⁸ is independently hydrogen,
halogen, CX¹⁸₃, -CHX¹⁸₂, -CH₂X¹⁸, -CN, -SO₂Cl, -SO_{n18}R^{18D}, -SO_{v18}NR^{18A}R^{18B}, -NHNR^{18A}R^{18B},
20 -ONR^{18A}R^{18B}, -NHC=(O)NHNR^{18A}R^{18B},
-NHC(O)NR^{18A}R^{18B}, -N(O)_{m18}, -NR^{18A}R^{18B}, -C(O)R^{18C}, -C(O)-OR^{18C}, -C(O)NR^{18A}R^{18B}, -OR^{18D},
-NR^{18A}SO₂R^{18D}, -NR^{18A}C(O)R^{18C}, -NR^{18A}C(O)OR^{18C}, -NR^{18A}OR^{18C}, -OCX¹⁸₃, -OCHX¹⁸₂,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
25 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, substituted or unsubstituted heteroaryl. R¹⁹ is independently hydrogen,

halogen, CX¹⁹₃, -CHX¹⁹₂, -CH₂X¹⁹, -CN, -SO₂Cl, -SO_{n19}R^{19D}, -SO_{v19}NR^{19A}R^{19B}, -NHR^{19A}R^{19B}, -ONR^{19A}R^{19B}, -NHC=(O)NHNR^{19A}R^{19B}, -NHC(O)NR^{19A}R^{19B}, -N(O)_{m19}, -NR^{19A}R^{19B}, -C(O)R^{19C}, -C(O)-OR^{19C}, -C(O)NR^{19A}R^{19B}, -OR^{19D}, -NR^{19A}SO₂R^{19D}, -NR^{19A}C(O)R^{19C}, -NR^{19A}C(O)OR^{19C}, -NR^{19A}OR^{19C}, -OCX¹⁹₃, -OCHX¹⁹₂,

- 5 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B}, R^{17C}, R^{17D}, R^{18A}, R^{18B}, R^{18C}, R^{18D}, R^{19A}, R^{19B}, R^{19C}, R^{19D}, are independently hydrogen, halogen, -CX₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX₃, -OCHX₂, -CHX₂, -CH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. Each X, X¹⁶, X¹⁷, X¹⁸ and X¹⁹ is independently -F, -Cl, -Br, or -I. The symbols n16, n17, n18, n19, v16, v17, v18, and v19 are independently an integer from 0 to 4. The symbols m16, m17, m18, and m19 are independently an integer from 1 to 2. In embodiments, R¹⁸ is -CN. In embodiments, R¹⁶ is unsubstituted methyl. In embodiments, R¹⁷ is unsubstituted methyl. In embodiments, R¹⁹ is unsubstituted methyl. In embodiments, R¹⁸ is hydrogen. In embodiments, R¹⁶ is hydrogen. In embodiments, R¹⁷ is hydrogen. In embodiments, R¹⁹ is hydrogen.

[0194] X may independently be -F. X may independently be -Cl. X may independently be -Br. X may independently be -I. X¹⁶ may independently be -F. X¹⁶ may independently be -Cl. X¹⁶ may independently be -Br. X¹⁶ may independently be -I. X¹⁷ may independently be -F. X¹⁷ may independently be -Cl. X¹⁷ may independently be -Br. X¹⁷ may independently be -I. X¹⁸ may independently be -F. X¹⁸ may independently be -Cl. X¹⁸ may independently be -Br.

X^{18} may independently be -I. X^{19} may independently be -F. X^{19} may independently be -Cl. X^{19} may independently be -Br. X^{19} may independently be -I.

[0195] n16 may independently be 0. n16 may independently be 1. n16 may independently be 2. n16 may independently be 3. n16 may independently be 4. n17 may independently be 0.

5 n17 may independently be 1. n17 may independently be 2. n17 may independently be 3. n17 may independently be 4. n18 may independently be 0. n18 may independently be 1. n18 may independently be 2. n18 may independently be 3. n18 may independently be 4. n19 may independently be 0. n19 may independently be 1. n19 may independently be 2. n19 may independently be 3. n19 may independently be 4.

10 [0196] v16 may independently be 0. v16 may independently be 1. v16 may independently be 2. v16 may independently be 3. v16 may independently be 4. v17 may independently be 0. v17 may independently be 1. v17 may independently be 2. v17 may independently be 3. v17 may independently be 4. v18 may independently be 0. v18 may independently be 1. v18 may independently be 2. v18 may independently be 3. v18 may independently be 4. v19 may independently be 0. v19 may independently be 1. v19 may independently be 2. v19 may independently be 3. v19 may independently be 4.

[0197] m16 may independently be 1. m16 may independently be 2. m17 may independently be 1. m17 may independently be 2. m18 may independently be 1. m18 may independently be 2. m19 may independently be 1. m19 may independently be 2.

20 [0198] In embodiments, R^{16} is hydrogen. In embodiments, R^{16} is halogen. In embodiments, R^{16} is CX^{16}_3 . In embodiments, R^{16} is $-CHX^{16}_2$. In embodiments, R^{16} is $-CH_2X^{16}$. In embodiments, R^{16} is -CN. In embodiments, R^{16} is $-SO_{n16}R^{16D}$. In embodiments, R^{16} is $-SO_{v16}NR^{16A}R^{16B}$. In embodiments, R^{16} is $-NHNR^{16A}R^{16B}$. In embodiments, R^{16} is $-ONR^{16A}R^{16B}$. In embodiments, R^{16} is $-NHC=(O)NHNR^{16A}R^{16B}$. In embodiments, R^{16} is $-NHC(O)NR^{16A}R^{16B}$. In embodiments, R^{16} is $-N(O)_{m16}$. In embodiments, R^{16} is $-NR^{16A}R^{16B}$. In embodiments, R^{16} is $-C(O)R^{16C}$. In embodiments, R^{16} is $-C(O)-OR^{16C}$. In embodiments, R^{16} is $-C(O)NR^{16A}R^{16B}$. In embodiments, R^{16} is $-OR^{16D}$. In embodiments, R^{16} is $-NR^{16A}SO_2R^{16D}$. In embodiments, R^{16} is $-NR^{16A}C(O)R^{16C}$. In embodiments, R^{16} is $-NR^{16A}C(O)OR^{16C}$. In embodiments, R^{16} is $-NR^{16A}OR^{16C}$. In embodiments, R^{16} is $-OCX^{16}_3$. In embodiments, R^{16} is $-OCHX^{16}_2$. In embodiments, R^{16} is substituted or unsubstituted alkyl. In embodiments, R^{16} is substituted or unsubstituted heteroalkyl. In embodiments, R^{16} is substituted or unsubstituted cycloalkyl. In embodiments, R^{16} is substituted or unsubstituted heterocycloalkyl. In

embodiments, R¹⁶ is substituted or unsubstituted aryl. In embodiments, R¹⁶ is substituted or unsubstituted heteroaryl. In embodiments, R¹⁶ is substituted alkyl. In embodiments, R¹⁶ is substituted heteroalkyl. In embodiments, R¹⁶ is substituted cycloalkyl. In embodiments, R¹⁶ is substituted heterocycloalkyl. In embodiments, R¹⁶ is substituted aryl. In embodiments, R¹⁶ is substituted heteroaryl. In embodiments, R¹⁶ is unsubstituted alkyl. In embodiments, R¹⁶ is unsubstituted heteroalkyl. In embodiments, R¹⁶ is unsubstituted cycloalkyl. In embodiments, R¹⁶ is unsubstituted heterocycloalkyl. In embodiments, R¹⁶ is unsubstituted aryl. In

5 embodiments, R¹⁶ is unsubstituted heteroaryl. In embodiments, R¹⁶ is unsubstituted methyl. In embodiments, R¹⁶ is unsubstituted ethyl. In embodiments, R¹⁶ is unsubstituted propyl. In

10 embodiments, R¹⁶ is unsubstituted isopropyl. In embodiments, R¹⁶ is unsubstituted butyl. In embodiments, R¹⁶ is unsubstituted tert-butyl. In embodiments, R¹⁶ is -CH₂Ph. In embodiments, R¹⁶ is independently halogen, -CX¹⁶₃, -CHX¹⁶₂, -

15 CH₂X¹⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -

20 NHC(O)OH, -NHOH, -OCX¹⁶₃, -OCHX¹⁶₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁶ is independently

25 halogen, -CX¹⁶₃, -CHX¹⁶₂, -CH₂X¹⁶, -OH, -SH, -COOH, -OCX¹⁶₃, -OCHX¹⁶₂, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R¹⁶ is independently halogen or -OCH₃. In embodiments, R¹⁶ is substituted or unsubstituted C₁-C₆ alkyl. In embodiments, R¹⁶ is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R¹⁶ is substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹⁶ is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹⁶ is substituted or unsubstituted C₆ aryl. In

30 embodiments, R¹⁶ is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁶ is independently halogen. In embodiments, R¹⁶ is independently -CX¹⁶₃. In embodiments, R¹⁶ is independently -CHX¹⁶₂. In embodiments, R¹⁶ is independently -CH₂X¹⁶. In embodiments, R¹⁶ is independently -OH. In embodiments, R¹⁶ is independently -SH. In embodiments, R¹⁶ is independently -COOH. In embodiments, R¹⁶ is independently -OCX¹⁶₃. In embodiments, R¹⁶ is independently -OCHX¹⁶₂. In embodiments, R¹⁶ is independently -CH₃. In embodiments, R¹⁶ is independently -CH₂CH₃. In embodiments, R¹⁶ is independently -OCH₃. In embodiments, R¹⁶ is independently -OCH₂CH₃. In embodiments, R¹⁶ is independently -SCH₃. In embodiments, R¹⁶ is independently -SCH₂CH₃. In embodiments, R¹⁶ is independently -Cl or -OCH₃. In

embodiments, R¹⁶ is independently halogen, -CX¹⁶₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -OCX¹⁶₃, -OCHX¹⁶₂, -CHX¹⁶₂, -CH₂X¹⁶, substituted or unsubstituted C₁-C₈ alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 5 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁶ is independently halogen, -CX¹⁶₃, -CN, unsubstituted C₁-C₄ alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R¹⁶ is independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or unsubstituted tert-butyl. In embodiments, R¹⁶ is independently unsubstituted methyl. In embodiments, R¹⁶ is independently unsubstituted ethyl. In embodiments, R¹⁶ is independently unsubstituted propyl. In embodiments, R¹⁶ is independently unsubstituted n-propyl. In embodiments, R¹⁶ is independently unsubstituted isopropyl. In embodiments, R¹⁶ is independently unsubstituted butyl. In embodiments, R¹⁶ is independently unsubstituted n-butyl. In embodiments, R¹⁶ is independently unsubstituted isobutyl. In embodiments, R¹⁶ is independently unsubstituted tert-butyl. In embodiments, R¹⁶ is independently unsubstituted pentyl. In embodiments, R¹⁶ is independently unsubstituted hexyl. In embodiments, R¹⁶ is independently unsubstituted heptyl. In embodiments, R¹⁶ is independently unsubstituted octyl. In embodiments, R¹⁶ is independently -F. In embodiments, R¹⁶ is independently -Cl. In embodiments, R¹⁶ is independently -Br. In embodiments, R¹⁶ is independently -I. In embodiments, R¹⁶ is independently unsubstituted methoxy. In embodiments, R¹⁶ is independently unsubstituted ethoxy. In embodiments, R¹⁶ is independently -CF₃. In embodiments, R¹⁶ is independently -CCl₃. In embodiments, R¹⁶ is an unsubstituted isopropyl. In embodiments, R¹⁶ is an unsubstituted phenyl. In embodiments, R¹⁶ is an unsubstituted pyridyl. In embodiments, R¹⁶ is independently halogen. In embodiments, R¹⁶ is independently -CX¹⁶₃. In embodiments, R¹⁶ is independently -CHX¹⁶₂. In embodiments, R¹⁶ is independently -CH₂X¹⁶. In embodiments, R¹⁶ is independently -CN. In embodiments, R¹⁶ is independently -OH. In embodiments, R¹⁶ is independently -NH₂. In embodiments, R¹⁶ is independently -COOH. In embodiments, R¹⁶ is independently -CONH₂. In embodiments, R¹⁶ is independently -NO₂. In embodiments, R¹⁶ is independently -SH. In embodiments, R¹⁶ is independently -SO₂Cl. In embodiments, R¹⁶ is independently -SO₃H. In embodiments, R¹⁶ is independently -SO₄H. In embodiments, R¹⁶ is independently -SO₂NH₂. In embodiments, R¹⁶ is independently -NHNH₂. In embodiments, R¹⁶ is independently -ONH₂. In embodiments, R¹⁶ is independently -NHC(O)NHNH₂. In embodiments, R¹⁶ is independently -NHC(O)NH₂. In embodiments, R¹⁶ is independently -NHSO₂H. In embodiments, R¹⁶ is independently -NHC(O)H. In

embodiments, R¹⁶ is independently -NHC(O)OH. In embodiments, R¹⁶ is independently -NHOH. In embodiments, R¹⁶ is independently -OCX¹⁶₃. In embodiments, R¹⁶ is independently -OCHX¹⁶₂. In embodiments, R¹⁶ is independently substituted or unsubstituted alkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted heteroalkyl. In 5 embodiments, R¹⁶ is independently substituted or unsubstituted cycloalkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted heterocycloalkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted aryl. In embodiments, R¹⁶ is independently substituted or unsubstituted heteroaryl. In embodiments, R¹⁶ is independently substituted alkyl. In embodiments, R¹⁶ is independently substituted heteroalkyl. In embodiments, R¹⁶ is 10 independently substituted cycloalkyl. In embodiments, R¹⁶ is independently substituted heterocycloalkyl. In embodiments, R¹⁶ is independently substituted aryl. In embodiments, R¹⁶ is independently substituted heteroaryl. In embodiments, R¹⁶ is independently unsubstituted alkyl. In embodiments, R¹⁶ is independently unsubstituted heteroalkyl. In embodiments, R¹⁶ is independently unsubstituted cycloalkyl. In embodiments, R¹⁶ is independently unsubstituted heterocycloalkyl. In embodiments, R¹⁶ is independently unsubstituted aryl. In embodiments, R¹⁶ is independently unsubstituted heteroaryl. In embodiments, R¹⁶ is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted 15 2 to 8 membered heteroalkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R¹⁶ is independently substituted or unsubstituted 20 5 to 10 membered heteroaryl. In embodiments, R¹⁶ is independently substituted C₁-C₈ alkyl. In embodiments, R¹⁶ is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R¹⁶ is independently substituted C₃-C₈ cycloalkyl. In embodiments, R¹⁶ is independently 25 substituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹⁶ is independently substituted C₆-C₁₀ aryl. In embodiments, R¹⁶ is independently substituted 5 to 10 membered heteroaryl. In embodiments, R¹⁶ is independently unsubstituted C₁-C₈ alkyl. In embodiments, R¹⁶ is independently unsubstituted 30 2 to 8 membered heteroalkyl. In embodiments, R¹⁶ is independently unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹⁶ is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹⁶ is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R¹⁶ is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R¹⁶ is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted 35 2 to 4 membered heteroalkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted C₃-C₆ cycloalkyl. In embodiments, R¹⁶ is

independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R¹⁶ is independently substituted or unsubstituted phenyl. In embodiments, R¹⁶ is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁶ is independently substituted C₁-C₄ alkyl. In embodiments, R¹⁶ is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R¹⁶ is independently substituted C₃-C₆ cycloalkyl. In embodiments, R¹⁶ is independently substituted 3 to 6 membered heterocycloalkyl. In embodiments, R¹⁶ is independently substituted phenyl. In embodiments, R¹⁶ is independently substituted 5 to 6 membered heteroaryl. In embodiments, R¹⁶ is independently unsubstituted C₁-C₄ alkyl. In embodiments, R¹⁶ is independently unsubstituted 2 to 4 membered heteroalkyl. In 10 embodiments, R¹⁶ is independently unsubstituted C₃-C₆ cycloalkyl. In embodiments, R¹⁶ is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R¹⁶ is independently unsubstituted phenyl. In embodiments, R¹⁶ is independently unsubstituted 5 to 6 membered heteroaryl.

15 [0199] In embodiments, R^{16A} is hydrogen. In embodiments, R^{16A} is -CX₃. In embodiments, R^{16A} is -CN. In embodiments, R^{16A} is -COOH. In embodiments, R^{16A} is -CONH₂. In embodiments, R^{16A} is -CHX₂. In embodiments, R^{16A} is -CH₂X. In embodiments, R^{16A} is unsubstituted methyl. In embodiments, R^{16A} is unsubstituted ethyl. In embodiments, R^{16A} is unsubstituted propyl. In embodiments, R^{16A} is unsubstituted isopropyl. In embodiments, R^{16A} is unsubstituted butyl. In embodiments, R^{16A} is unsubstituted tert-butyl.

20 [0200] In embodiments, R^{16B} is hydrogen. In embodiments, R^{16B} is -CX₃. In embodiments, R^{16B} is -CN. In embodiments, R^{16B} is -COOH. In embodiments, R^{16B} is -CONH₂. In embodiments, R^{16B} is -CHX₂. In embodiments, R^{16B} is -CH₂X. In embodiments, R^{16B} is unsubstituted methyl. In embodiments, R^{16B} is unsubstituted ethyl. In embodiments, R^{16B} is unsubstituted propyl. In embodiments, R^{16B} is unsubstituted isopropyl. In embodiments, R^{16B} is 25 unsubstituted butyl. In embodiments, R^{16B} is unsubstituted tert-butyl.

[0201] In embodiments, R^{16C} is hydrogen. In embodiments, R^{16C} is -CX₃. In embodiments, R^{16C} is -CN. In embodiments, R^{16C} is -COOH. In embodiments, R^{16C} is -CONH₂. In embodiments, R^{16C} is -CHX₂. In embodiments, R^{16C} is -CH₂X. In embodiments, R^{16C} is unsubstituted methyl. In embodiments, R^{16C} is unsubstituted ethyl. In embodiments, R^{16C} is unsubstituted propyl. In embodiments, R^{16C} is unsubstituted isopropyl. In embodiments, R^{16C} is 30 unsubstituted butyl. In embodiments, R^{16C} is unsubstituted tert-butyl.

[0202] In embodiments, R^{16D} is hydrogen. In embodiments, R^{16D} is -CX₃. In embodiments, R^{16D} is -CN. In embodiments, R^{16D} is -COOH. In embodiments, R^{16D} is -CONH₂. In embodiments, R^{16D} is -CHX₂. In embodiments, R^{16D} is -CH₂X. In embodiments, R^{16D} is unsubstituted methyl. In embodiments, R^{16D} is unsubstituted ethyl. In embodiments, R^{16D} is 5 unsubstituted propyl. In embodiments, R^{16D} is unsubstituted isopropyl. In embodiments, R^{16D} is unsubstituted butyl. In embodiments, R^{16D} is unsubstituted tert-butyl.

[0203] In embodiments, R¹⁷ is hydrogen. In embodiments, R¹⁷ is halogen. In embodiments, R¹⁷ is CX¹⁷₃. In embodiments, R¹⁷ is -CHX¹⁷₂. In embodiments, R¹⁷ is -CH₂X¹⁷. In embodiments, R¹⁷ is -CN. In embodiments, R¹⁷ is -SO_{n17}R^{17D}. In embodiments, R¹⁷ is 10 -SO_{v17}NR^{17A}R^{17B}. In embodiments, R¹⁷ is -NHNR^{17A}R^{17B}. In embodiments, R¹⁷ is -ONR^{17A}R^{17B}. In embodiments, R¹⁷ is -NHC=(O)NHNR^{17A}R^{17B}. In embodiments, R¹⁷ is -NHC(O)NR^{17A}R^{17B}. In embodiments, R¹⁷ is -N(O)_{m17}. In embodiments, R¹⁷ is -NR^{17A}R^{17B}. In embodiments, R¹⁷ is -C(O)R^{17C}. In embodiments, R¹⁷ is -C(O)-OR^{17C}. In embodiments, R¹⁷ is 15 -C(O)NR^{17A}R^{17B}. In embodiments, R¹⁷ is -OR^{17D}. In embodiments, R¹⁷ is -NR^{17A}SO₂R^{17D}. In embodiments, R¹⁷ is -NR^{17A}C(O)R^{17C}. In embodiments, R¹⁷ is -NR^{17A}C(O)OR^{17C}. In embodiments, R¹⁷ is -NR^{17A}OR^{17C}. In embodiments, R¹⁷ is -OCX¹⁷₃. In embodiments, R¹⁷ is 20 -OCHX¹⁷₂. In embodiments, R¹⁷ is substituted or unsubstituted alkyl. In embodiments, R¹⁷ is substituted or unsubstituted heteroalkyl. In embodiments, R¹⁷ is substituted or unsubstituted cycloalkyl. In embodiments, R¹⁷ is substituted or unsubstituted heterocycloalkyl. In embodiments, R¹⁷ is substituted or unsubstituted aryl. In embodiments, R¹⁷ is substituted or 25 unsubstituted heteroaryl. In embodiments, R¹⁷ is substituted alkyl. In embodiments, R¹⁷ is substituted heteroalkyl. In embodiments, R¹⁷ is substituted cycloalkyl. In embodiments, R¹⁷ is substituted heterocycloalkyl. In embodiments, R¹⁷ is substituted aryl. In embodiments, R¹⁷ is substituted heteroaryl. In embodiments, R¹⁷ is 30 unsubstituted alkyl. In embodiments, R¹⁷ is unsubstituted heteroalkyl. In embodiments, R¹⁷ is unsubstituted cycloalkyl. In embodiments, R¹⁷ is unsubstituted heterocycloalkyl. In embodiments, R¹⁷ is unsubstituted aryl. In embodiments, R¹⁷ is unsubstituted heteroaryl. In embodiments, R¹⁷ is unsubstituted methyl. In embodiments, R¹⁷ is unsubstituted ethyl. In embodiments, R¹⁷ is unsubstituted propyl. In embodiments, R¹⁷ is unsubstituted isopropyl. In embodiments, R¹⁷ is unsubstituted butyl. In embodiments, R¹⁷ is unsubstituted tert-butyl. In embodiments, R¹⁷ is -CH₂Ph.

[0204] In embodiments, R^{17A} is hydrogen. In embodiments, R^{17A} is -CX₃. In embodiments, R^{17A} is -CN. In embodiments, R^{17A} is -COOH. In embodiments, R^{17A} is -CONH₂. In embodiments, R^{17A} is -CHX₂. In embodiments, R^{17A} is -CH₂X. In embodiments, R^{17A} is

unsubstituted methyl. In embodiments, R^{17A} is unsubstituted ethyl. In embodiments, R^{17A} is unsubstituted propyl. In embodiments, R^{17A} is unsubstituted isopropyl. In embodiments, R^{17A} is unsubstituted butyl. In embodiments, R^{17A} is unsubstituted tert-butyl.

[0205] In embodiments, R^{17B} is hydrogen. In embodiments, R^{17B} is -CX₃. In embodiments, 5 R^{17B} is -CN. In embodiments, R^{17B} is -COOH. In embodiments, R^{17B} is -CONH₂. In

embodiments, R^{17B} is -CHX₂. In embodiments, R^{17B} is -CH₂X. In embodiments, R^{17B} is unsubstituted methyl. In embodiments, R^{17B} is unsubstituted ethyl. In embodiments, R^{17B} is unsubstituted propyl. In embodiments, R^{17B} is unsubstituted isopropyl. In embodiments, R^{17B} is unsubstituted butyl. In embodiments, R^{17B} is unsubstituted tert-butyl.

[0206] In embodiments, R^{17C} is hydrogen. In embodiments, R^{17C} is -CX₃. In embodiments, 10 R^{17C} is -CN. In embodiments, R^{17C} is -COOH. In embodiments, R^{17C} is -CONH₂. In

embodiments, R^{17C} is -CHX₂. In embodiments, R^{17C} is -CH₂X. In embodiments, R^{17C} is unsubstituted methyl. In embodiments, R^{17C} is unsubstituted ethyl. In embodiments, R^{17C} is unsubstituted propyl. In embodiments, R^{17C} is unsubstituted isopropyl. In embodiments, R^{17C} is 15 unsubstituted butyl. In embodiments, R^{17C} is unsubstituted tert-butyl.

[0207] In embodiments, R^{17D} is hydrogen. In embodiments, R^{17D} is -CX₃. In embodiments, 5 R^{17D} is -CN. In embodiments, R^{17D} is -COOH. In embodiments, R^{17D} is -CONH₂. In

embodiments, R^{17D} is -CHX₂. In embodiments, R^{17D} is -CH₂X. In embodiments, R^{17D} is unsubstituted methyl. In embodiments, R^{17D} is unsubstituted ethyl. In embodiments, R^{17D} is 20 unsubstituted propyl. In embodiments, R^{17D} is unsubstituted isopropyl. In embodiments, R^{17D} is unsubstituted butyl. In embodiments, R^{17D} is unsubstituted tert-butyl.

[0208] In embodiments, R¹⁸ is hydrogen. In embodiments, R¹⁸ is halogen. In embodiments, 5 R¹⁸ is CX¹⁸₃. In embodiments, R¹⁸ is -CHX¹⁸₂. In embodiments, R¹⁸ is -CH₂X¹⁸. In

embodiments, R¹⁸ is -CN. In embodiments, R¹⁸ is -SO_{n18}R^{18D}. In embodiments, R¹⁸ 25 is -SO_{v18}NR^{18A}R^{18B}. In embodiments, R¹⁸ is -NHR^{18A}R^{18B}. In embodiments, R¹⁸ is -ONR^{18A}R^{18B}. In embodiments, R¹⁸ is -NHC=(O)NHNR^{18A}R^{18B}. In embodiments, R¹⁸ is -NHC(O)NR^{18A}R^{18B}. In embodiments, R¹⁸ is -N(O)_{m18}. In embodiments, R¹⁸ is -NR^{18A}R^{18B}. In embodiments, R¹⁸ is -C(O)R^{18C}. In embodiments, R¹⁸ is -C(O)-OR^{18C}. In embodiments, R¹⁸ is -C(O)NR^{18A}R^{18B}. In embodiments, R¹⁸ is -OR^{18D}. In embodiments, R¹⁸ is -NR^{18A}SO₂R^{18D}. In 30 embodiments, R¹⁸ is -NR^{18A}C(O)R^{18C}. In embodiments, R¹⁸ is -NR^{18A}C(O)OR^{18C}. In embodiments, R¹⁸ is -NR^{18A}OR^{18C}. In embodiments, R¹⁸ is -OCX¹⁸₃. In embodiments, R¹⁸ is -OCHX¹⁸₂. In embodiments, R¹⁸ is substituted or unsubstituted alkyl. In embodiments, R¹⁸ is

substituted or unsubstituted heteroalkyl. In embodiments, R¹⁸ is substituted or unsubstituted cycloalkyl. In embodiments, R¹⁸ is substituted or unsubstituted heterocycloalkyl. In embodiments, R¹⁸ is substituted or unsubstituted aryl. In embodiments, R¹⁸ is substituted or unsubstituted heteroaryl. In embodiments, R¹⁸ is substituted alkyl. In embodiments, R¹⁸ is substituted heteroalkyl. In embodiments, R¹⁸ is substituted cycloalkyl. In embodiments, R¹⁸ is substituted heterocycloalkyl. In embodiments, R¹⁸ is substituted aryl. In embodiments, R¹⁸ is substituted heteroaryl. In embodiments, R¹⁸ is unsubstituted alkyl. In embodiments, R¹⁸ is unsubstituted heteroalkyl. In embodiments, R¹⁸ is unsubstituted cycloalkyl. In embodiments, R¹⁸ is unsubstituted heterocycloalkyl. In embodiments, R¹⁸ is unsubstituted aryl. In

5 embodiments, R¹⁸ is unsubstituted heteroaryl. In embodiments, R¹⁸ is unsubstituted methyl. In

10 embodiments, R¹⁸ is unsubstituted ethyl. In embodiments, R¹⁸ is unsubstituted propyl. In

15 embodiments, R¹⁸ is unsubstituted isopropyl. In embodiments, R¹⁸ is unsubstituted butyl. In

20 embodiments, R¹⁸ is unsubstituted tert-butyl. In embodiments, R¹⁸ is -CH₂Ph.

[0209] In embodiments, R^{18A} is hydrogen. In embodiments, R^{18A} is -CX₃. In embodiments, R^{18A} is -CN. In embodiments, R^{18A} is -COOH. In embodiments, R^{18A} is -CONH₂. In

15 embodiments, R^{18A} is -CHX₂. In embodiments, R^{18A} is -CH₂X. In embodiments, R^{18A} is

20 unsubstituted methyl. In embodiments, R^{18A} is unsubstituted ethyl. In embodiments, R^{18A} is

25 unsubstituted propyl. In embodiments, R^{18A} is unsubstituted isopropyl. In embodiments, R^{18A} is

30 unsubstituted butyl. In embodiments, R^{18A} is unsubstituted tert-butyl.

[0210] In embodiments, R^{18B} is hydrogen. In embodiments, R^{18B} is -CX₃. In embodiments, R^{18B} is -CN. In embodiments, R^{18B} is -COOH. In embodiments, R^{18B} is -CONH₂. In

15 embodiments, R^{18B} is -CHX₂. In embodiments, R^{18B} is -CH₂X. In embodiments, R^{18B} is

20 unsubstituted methyl. In embodiments, R^{18B} is unsubstituted ethyl. In embodiments, R^{18B} is

25 unsubstituted propyl. In embodiments, R^{18B} is unsubstituted isopropyl. In embodiments, R^{18B} is

30 unsubstituted butyl. In embodiments, R^{18B} is unsubstituted tert-butyl.

[0211] In embodiments, R^{18C} is hydrogen. In embodiments, R^{18C} is -CX₃. In embodiments, R^{18C} is -CN. In embodiments, R^{18C} is -COOH. In embodiments, R^{18C} is -CONH₂. In

15 embodiments, R^{18C} is -CHX₂. In embodiments, R^{18C} is -CH₂X. In embodiments, R^{18C} is

20 unsubstituted methyl. In embodiments, R^{18C} is unsubstituted ethyl. In embodiments, R^{18C} is

25 unsubstituted propyl. In embodiments, R^{18C} is unsubstituted isopropyl. In embodiments, R^{18C} is

30 unsubstituted butyl. In embodiments, R^{18C} is unsubstituted tert-butyl.

[0212] In embodiments, R^{18D} is hydrogen. In embodiments, R^{18D} is -CX₃. In embodiments, R^{18D} is -CN. In embodiments, R^{18D} is -COOH. In embodiments, R^{18D} is -CONH₂. In embodiments, R^{18D} is -CHX₂. In embodiments, R^{18D} is -CH₂X. In embodiments, R^{18D} is unsubstituted methyl. In embodiments, R^{18D} is unsubstituted ethyl. In embodiments, R^{18D} is 5 unsubstituted propyl. In embodiments, R^{18D} is unsubstituted isopropyl. In embodiments, R^{18D} is unsubstituted butyl. In embodiments, R^{18D} is unsubstituted tert-butyl.

[0213] In embodiments, R¹⁹ is hydrogen. In embodiments, R¹⁹ is halogen. In embodiments, R¹⁹ is CX¹⁹₃. In embodiments, R¹⁹ is -CHX¹⁹₂. In embodiments, R¹⁹ is -CH₂X¹⁹. In embodiments, R¹⁹ is -CN. In embodiments, R¹⁹ is -SO_{n19}R^{19D}. In embodiments, R¹⁹ is 10 -SO_{v19}NR^{19A}R^{19B}. In embodiments, R¹⁹ is -NHNR^{19A}R^{19B}. In embodiments, R¹⁹ is -ONR^{19A}R^{19B}. In embodiments, R¹⁹ is -NHC=(O)NHNR^{19A}R^{19B}. In embodiments, R¹⁹ is -NHC(O)NR^{19A}R^{19B}. In embodiments, R¹⁹ is -N(O)_{m19}. In embodiments, R¹⁹ is -NR^{19A}R^{19B}. In embodiments, R¹⁹ is -C(O)R^{19C}. In embodiments, R¹⁹ is -C(O)-OR^{19C}. In embodiments, R¹⁹ is 15 -C(O)NR^{19A}R^{19B}. In embodiments, R¹⁹ is -OR^{19D}. In embodiments, R¹⁹ is -NR^{19A}SO₂R^{19D}. In embodiments, R¹⁹ is -NR^{19A}C(O)R^{19C}. In embodiments, R¹⁹ is -NR^{19A}C(O)OR^{19C}. In embodiments, R¹⁹ is 20 -NR^{19A}OR^{19C}. In embodiments, R¹⁹ is -OCX¹⁹₃. In embodiments, R¹⁹ is -OCHX¹⁹₂. In embodiments, R¹⁹ is substituted or unsubstituted alkyl. In embodiments, R¹⁹ is substituted or unsubstituted heteroalkyl. In embodiments, R¹⁹ is substituted or unsubstituted cycloalkyl. In embodiments, R¹⁹ is substituted or unsubstituted heterocycloalkyl. In embodiments, R¹⁹ is substituted or unsubstituted aryl. In embodiments, R¹⁹ is substituted or 25 unsubstituted heteroaryl. In embodiments, R¹⁹ is substituted alkyl. In embodiments, R¹⁹ is substituted heteroalkyl. In embodiments, R¹⁹ is substituted cycloalkyl. In embodiments, R¹⁹ is substituted heterocycloalkyl. In embodiments, R¹⁹ is substituted aryl. In embodiments, R¹⁹ is substituted heteroaryl. In embodiments, R¹⁹ is unsubstituted alkyl. In embodiments, R¹⁹ is 30 unsubstituted heteroalkyl. In embodiments, R¹⁹ is unsubstituted cycloalkyl. In embodiments, R¹⁹ is unsubstituted heterocycloalkyl. In embodiments, R¹⁹ is unsubstituted aryl. In embodiments, R¹⁹ is unsubstituted heteroaryl. In embodiments, R¹⁹ is unsubstituted methyl. In embodiments, R¹⁹ is unsubstituted ethyl. In embodiments, R¹⁹ is unsubstituted propyl. In embodiments, R¹⁹ is unsubstituted isopropyl. In embodiments, R¹⁹ is unsubstituted butyl. In embodiments, R¹⁹ is unsubstituted tert-butyl. In embodiments, R¹⁹ is -CH₂Ph.

[0214] In embodiments, R^{19A} is hydrogen. In embodiments, R^{19A} is -CX₃. In embodiments, R^{19A} is -CN. In embodiments, R^{19A} is -COOH. In embodiments, R^{19A} is -CONH₂. In embodiments, R^{19A} is -CHX₂. In embodiments, R^{19A} is -CH₂X. In embodiments, R^{19A} is

unsubstituted methyl. In embodiments, R^{19A} is unsubstituted ethyl. In embodiments, R^{19A} is unsubstituted propyl. In embodiments, R^{19A} is unsubstituted isopropyl. In embodiments, R^{19A} is unsubstituted butyl. In embodiments, R^{19A} is unsubstituted tert-butyl.

[0215] In embodiments, R^{19B} is hydrogen. In embodiments, R^{19B} is $-CX_3$. In embodiments,

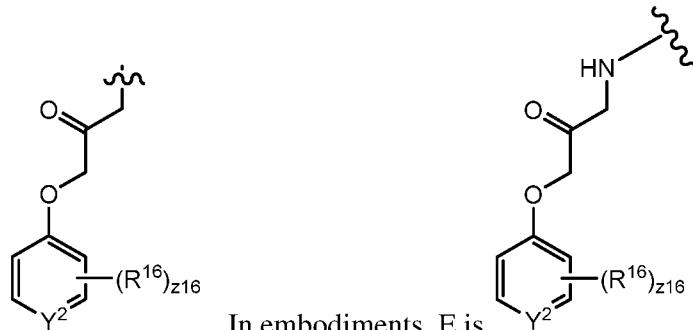
5 R^{19B} is $-CN$. In embodiments, R^{19B} is $-COOH$. In embodiments, R^{19B} is $-CONH_2$. In embodiments, R^{19B} is $-CHX_2$. In embodiments, R^{19B} is $-CH_2X$. In embodiments, R^{19B} is unsubstituted methyl. In embodiments, R^{19B} is unsubstituted ethyl. In embodiments, R^{19B} is unsubstituted propyl. In embodiments, R^{19B} is unsubstituted isopropyl. In embodiments, R^{19B} is unsubstituted butyl. In embodiments, R^{19B} is unsubstituted tert-butyl.

10 [0216] In embodiments, R^{19C} is hydrogen. In embodiments, R^{19C} is $-CX_3$. In embodiments,

R^{19C} is $-CN$. In embodiments, R^{19C} is $-COOH$. In embodiments, R^{19C} is $-CONH_2$. In embodiments, R^{19C} is $-CHX_2$. In embodiments, R^{19C} is $-CH_2X$. In embodiments, R^{19C} is unsubstituted methyl. In embodiments, R^{19C} is unsubstituted ethyl. In embodiments, R^{19C} is unsubstituted propyl. In embodiments, R^{19C} is unsubstituted isopropyl. In embodiments, R^{19C} is unsubstituted butyl. In embodiments, R^{19C} is unsubstituted tert-butyl.

[0217] In embodiments, R^{19D} is hydrogen. In embodiments, R^{19D} is $-CX_3$. In embodiments,

R^{19D} is $-CN$. In embodiments, R^{19D} is $-COOH$. In embodiments, R^{19D} is $-CONH_2$. In embodiments, R^{19D} is $-CHX_2$. In embodiments, R^{19D} is $-CH_2X$. In embodiments, R^{19D} is unsubstituted methyl. In embodiments, R^{19D} is unsubstituted ethyl. In embodiments, R^{19D} is unsubstituted propyl. In embodiments, R^{19D} is unsubstituted isopropyl. In embodiments, R^{19D} is unsubstituted butyl. In embodiments, R^{19D} is unsubstituted tert-butyl.



[0218] In embodiments, E is

. In embodiments, E is

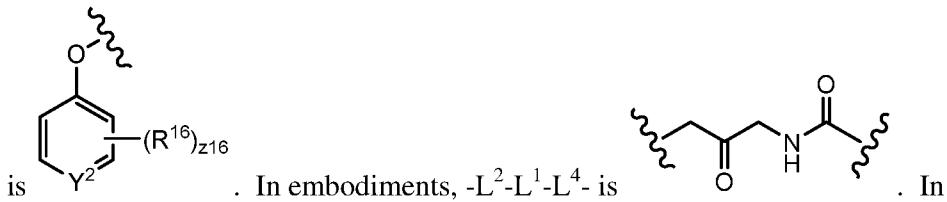
. In



embodiments, E is

. In embodiments, E is

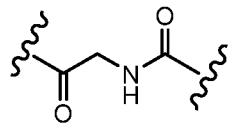
. In embodiments, E



is

. In embodiments, -L²-L¹-L⁴- is

. In



embodiments, -L²-L¹-L⁴- is

. In embodiments, -L²-L¹-L⁴- is -CH₂NHC(O)-.

- 5 [0219] In embodiments, R¹⁶ is independently halogen, CX¹⁶₃, -CHX¹⁶₂, -CH₂X¹⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX¹⁶₃, -OCHX¹⁶₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. In embodiments, R¹⁶ is independently halogen. In embodiments, R¹⁶ is independently -F.
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heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. In embodiments, R¹⁶ is independently halogen. In embodiments, R¹⁶ is independently -F.

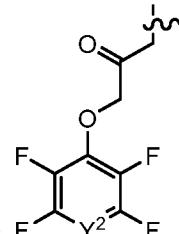
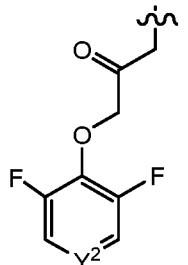
[0220] Y² is N or CH. In embodiments, Y² is CH. In embodiments, Y² is N.

[0221] The symbol z16 is an integer from 0 to 4. Each X¹⁶ is independently -F, -Cl, -Br, or -I.

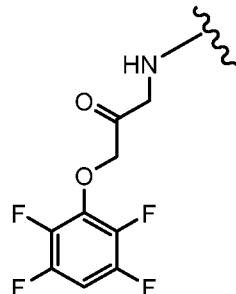
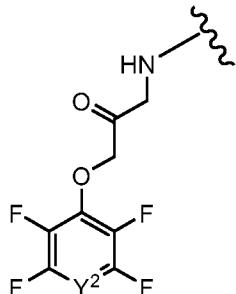
[0222] In embodiments, z16 is 4. In embodiments, z16 is 2. In embodiments, z16 is 1. In

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embodiments, z16 is 0. In embodiments, z16 is 3.



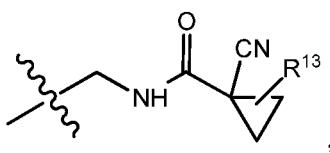
[0223] In embodiments, E is: . In embodiments, E is: F . In



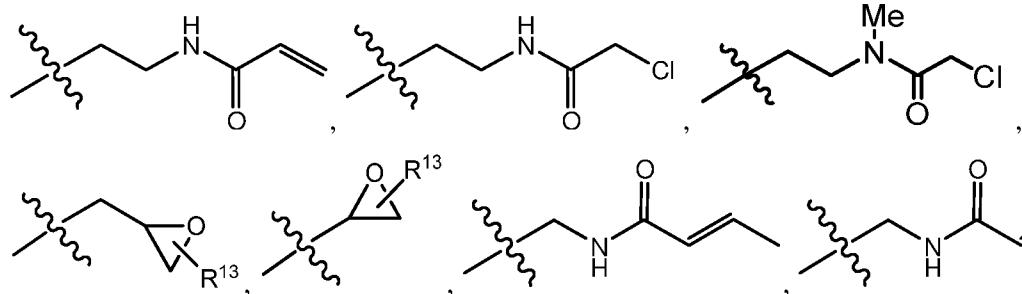
embodiments, E is: F . In embodiments, E is: F .

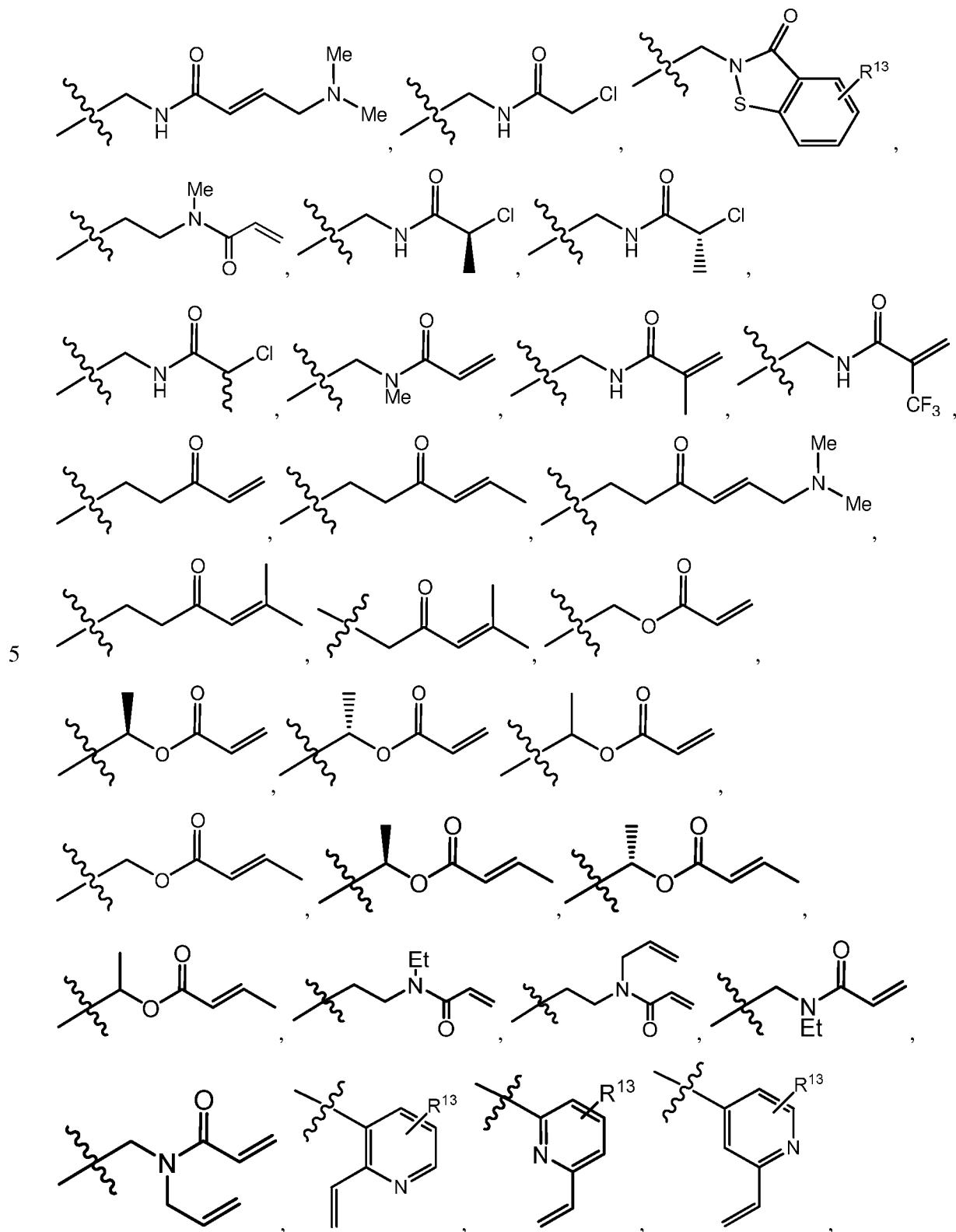
[0224] In embodiments, E comprises a substituted or unsubstituted vinyl sulfone moiety, substituted or unsubstituted vinyl sulfonamide moiety, substituted or unsubstituted fluoro(C₁-

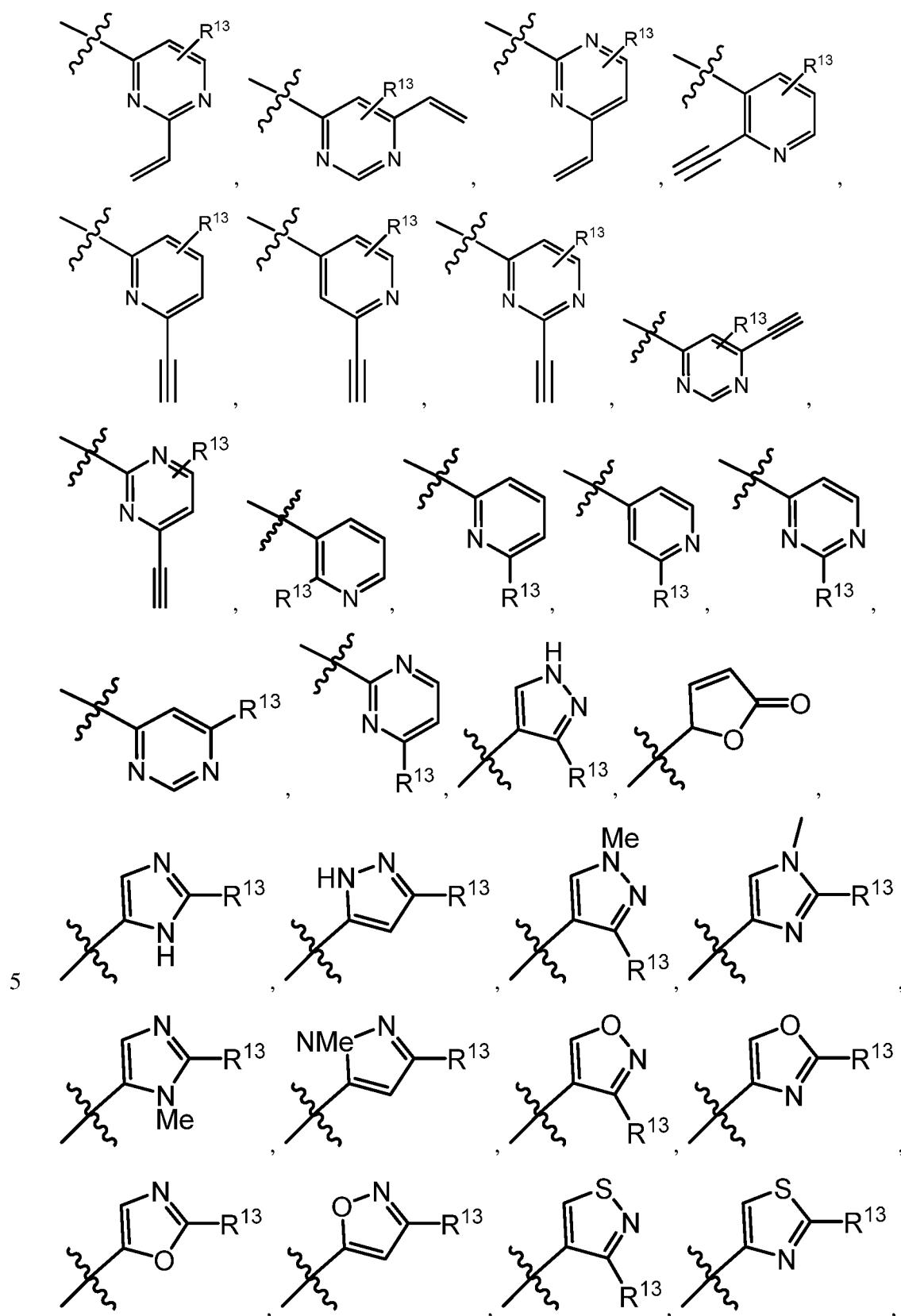
- 5 C₄)alkylketone moiety, substituted or unsubstituted chloro(C₁-C₄)alkylketone moiety, substituted or unsubstituted acrylamide moiety, substituted or unsubstituted disulfide moiety, substituted or unsubstituted thiol moiety, substituted or unsubstituted phosphonate moiety, substituted or unsubstituted aldehyde moiety, substituted or unsubstituted enone moiety, substituted or unsubstituted diazomethylketone moiety, substituted or unsubstituted diazomethylamide moiety,
- 10 substituted or unsubstituted cyanocyclopropyl carboxamide moiety, substituted or unsubstituted epoxide moiety, substituted or unsubstituted epoxyketone moiety, substituted or unsubstituted epoxyamide moiety, substituted or unsubstituted aryl aldehyde moiety, substituted or unsubstituted aryl dialdehyde moiety, substituted or unsubstituted dialdehyde moiety, substituted or unsubstituted nitrogen mustard moiety, substituted or unsubstituted propargyl moiety,

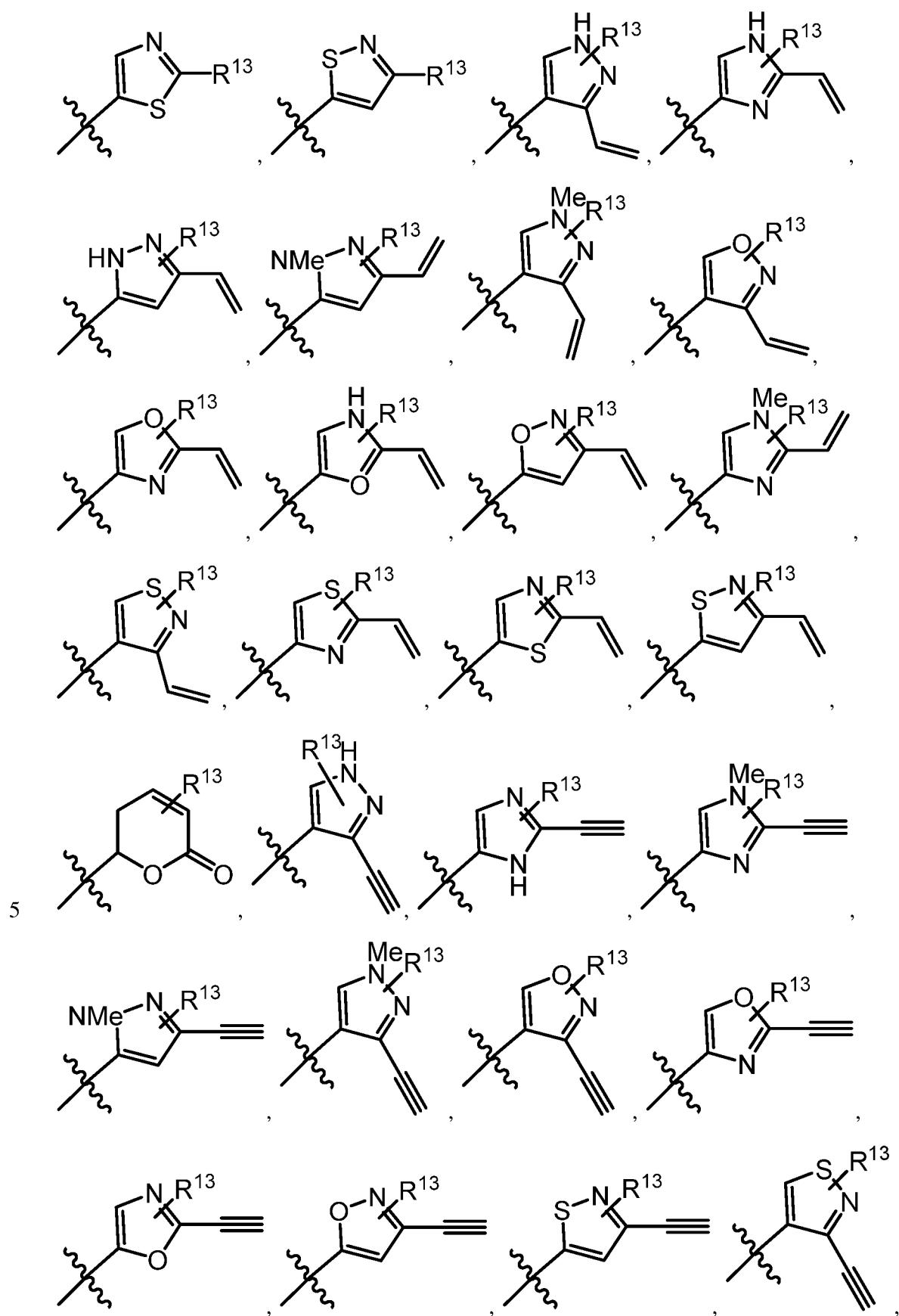


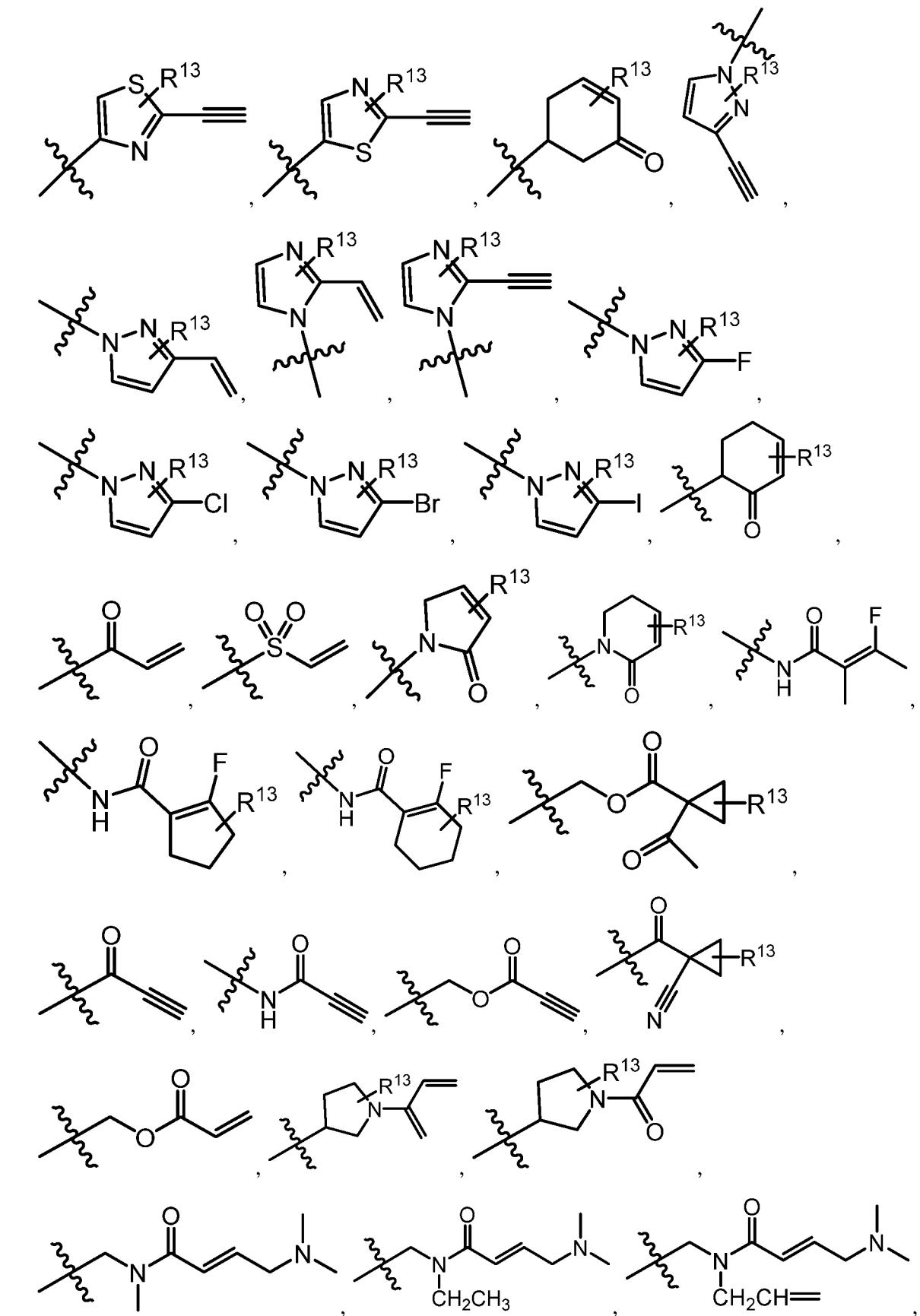
- 15 substituted or unsubstituted propargylamide moiety,

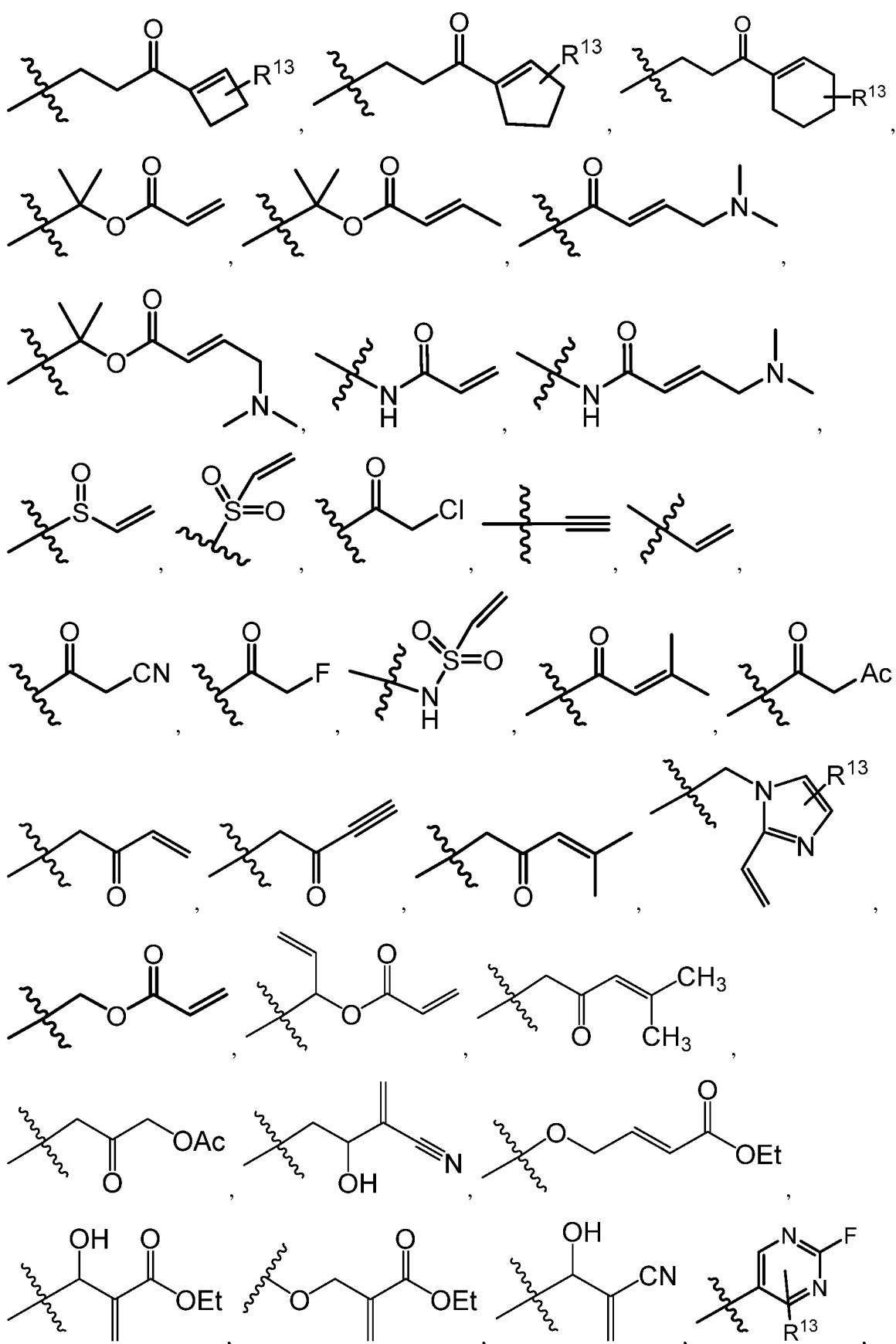


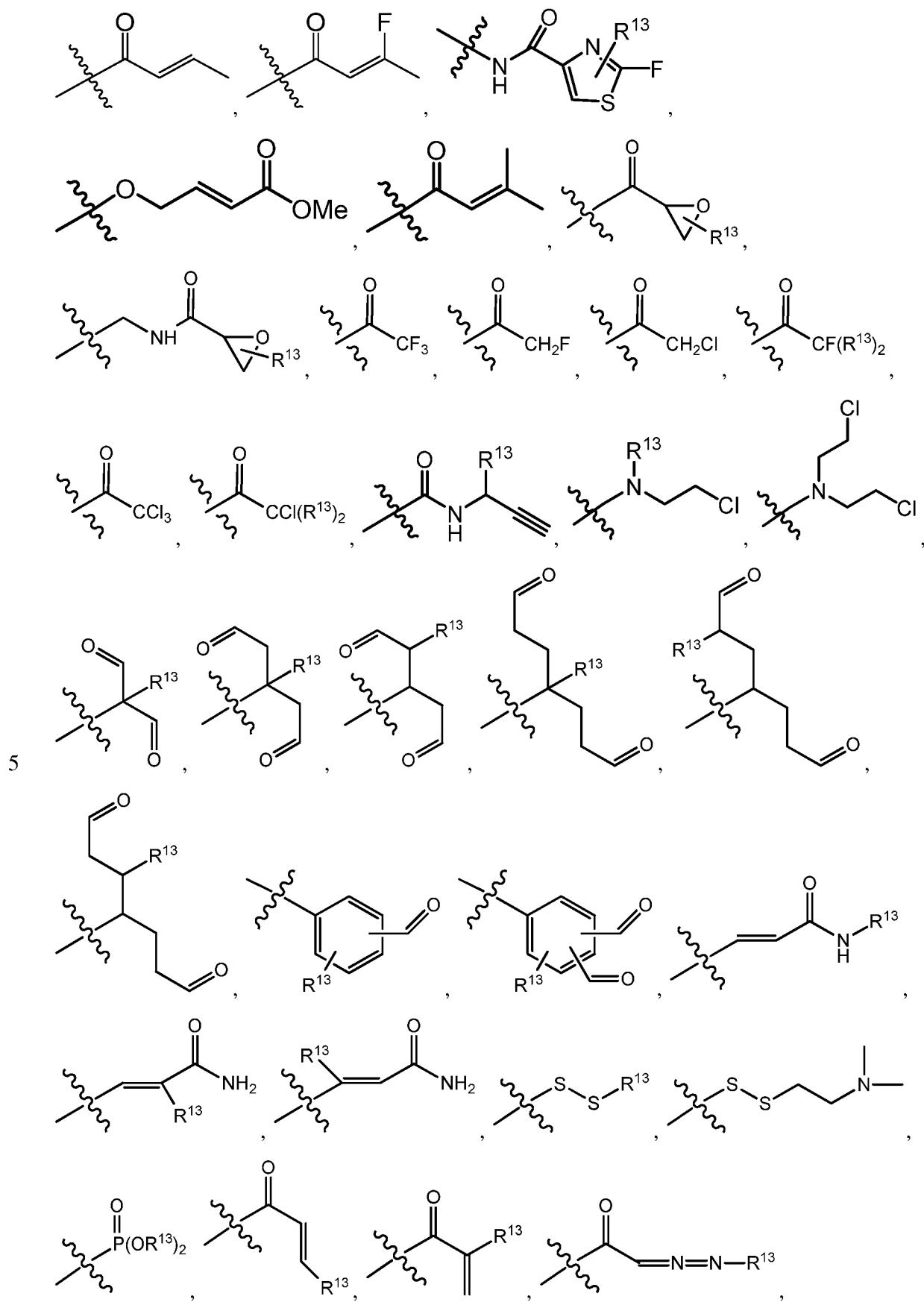


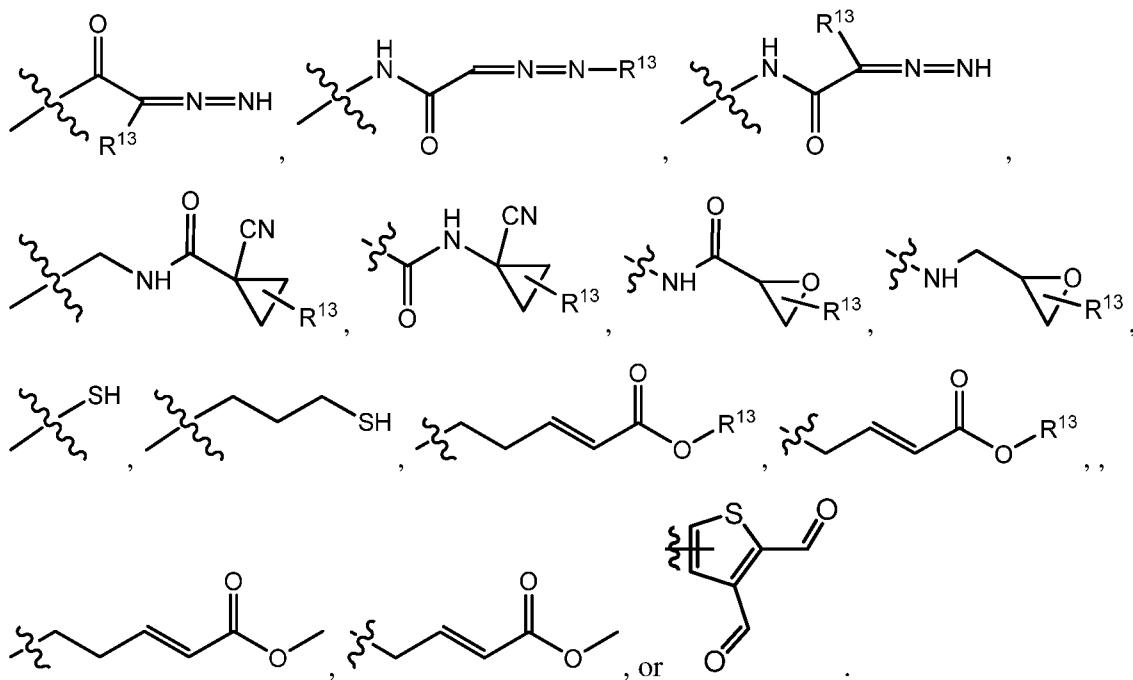




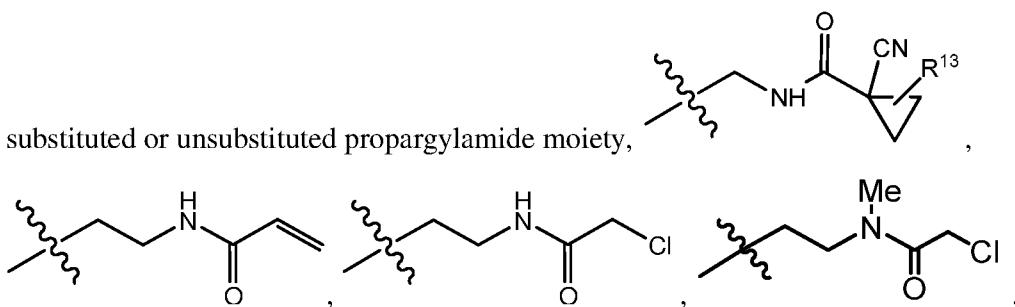


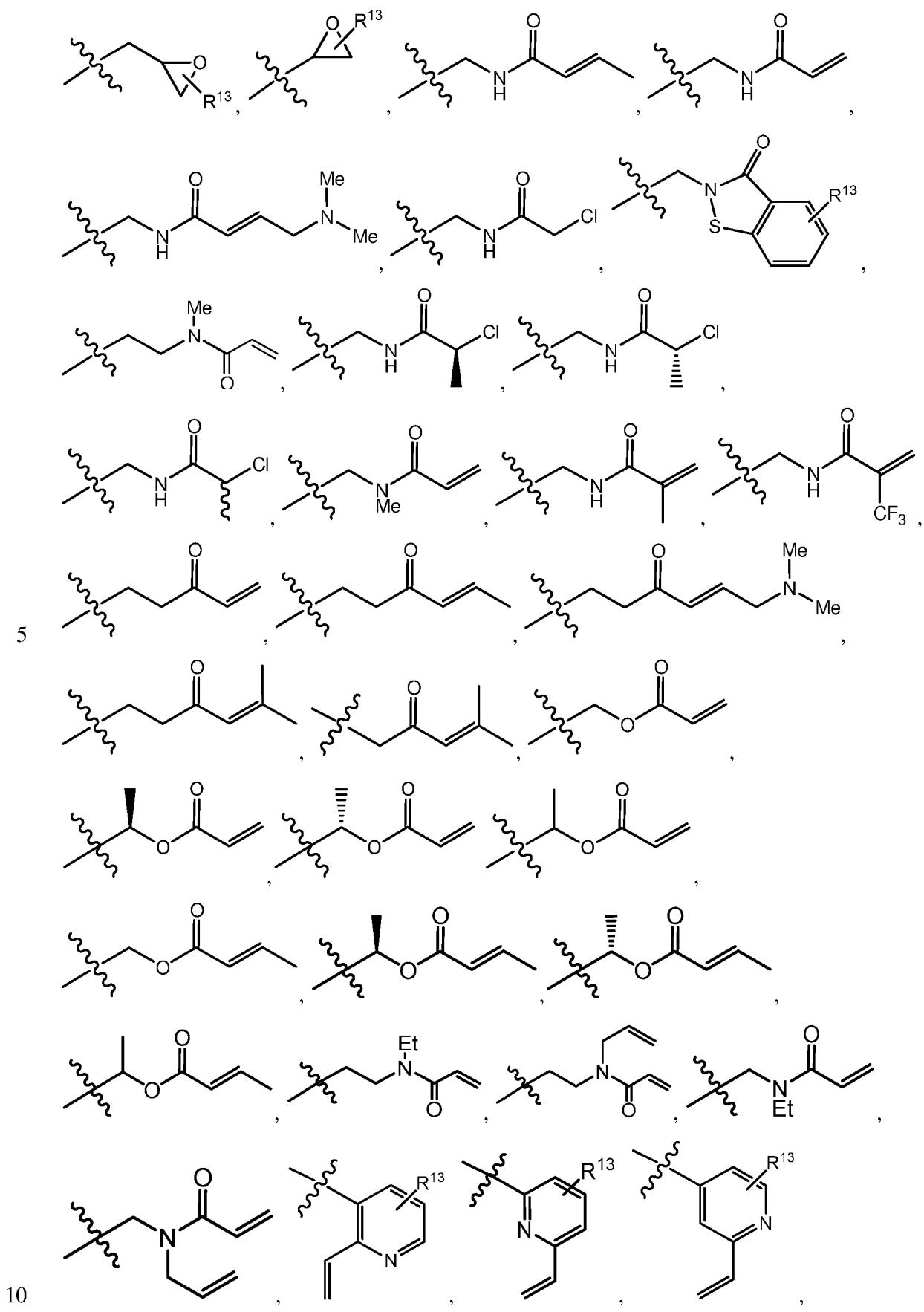


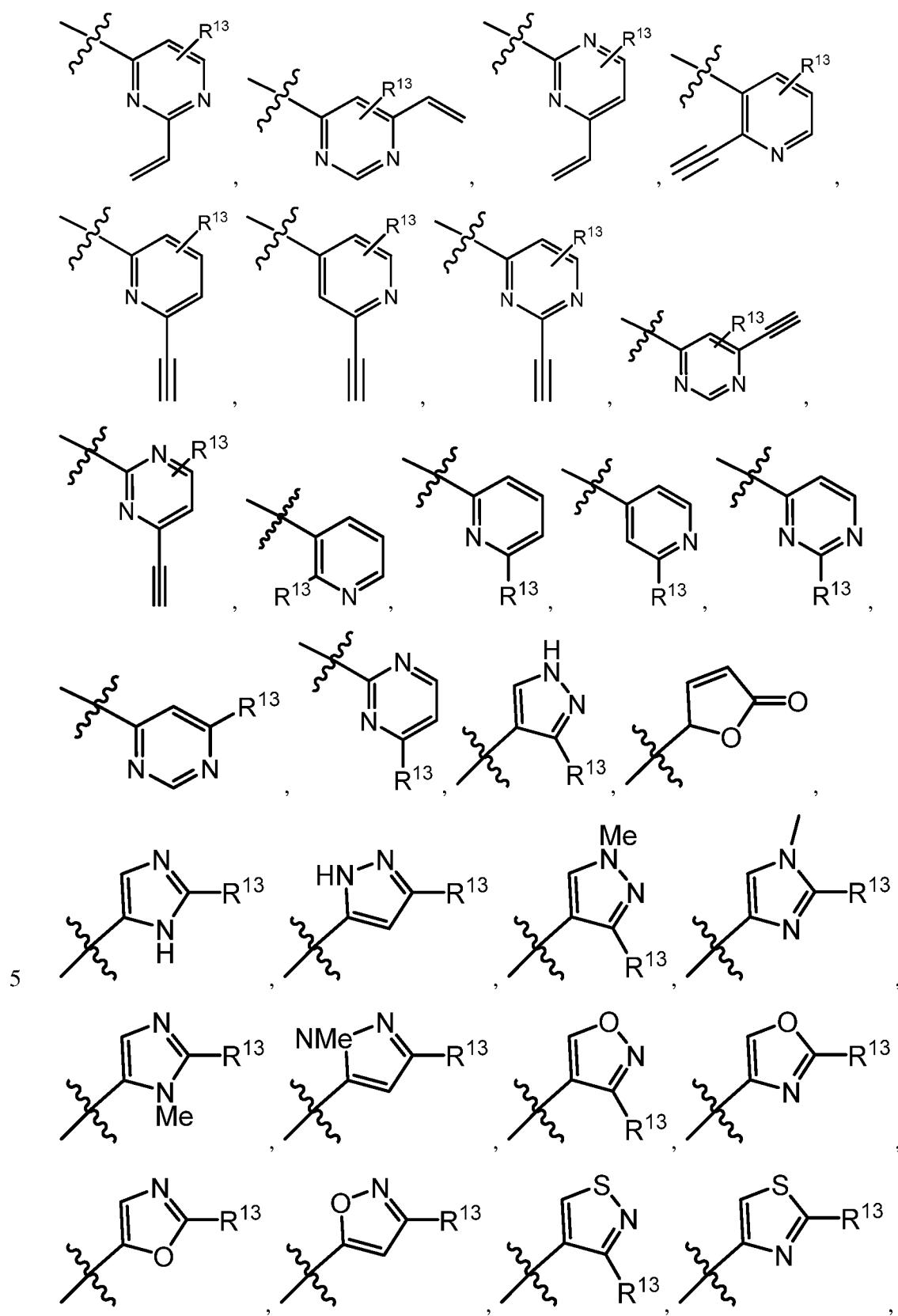


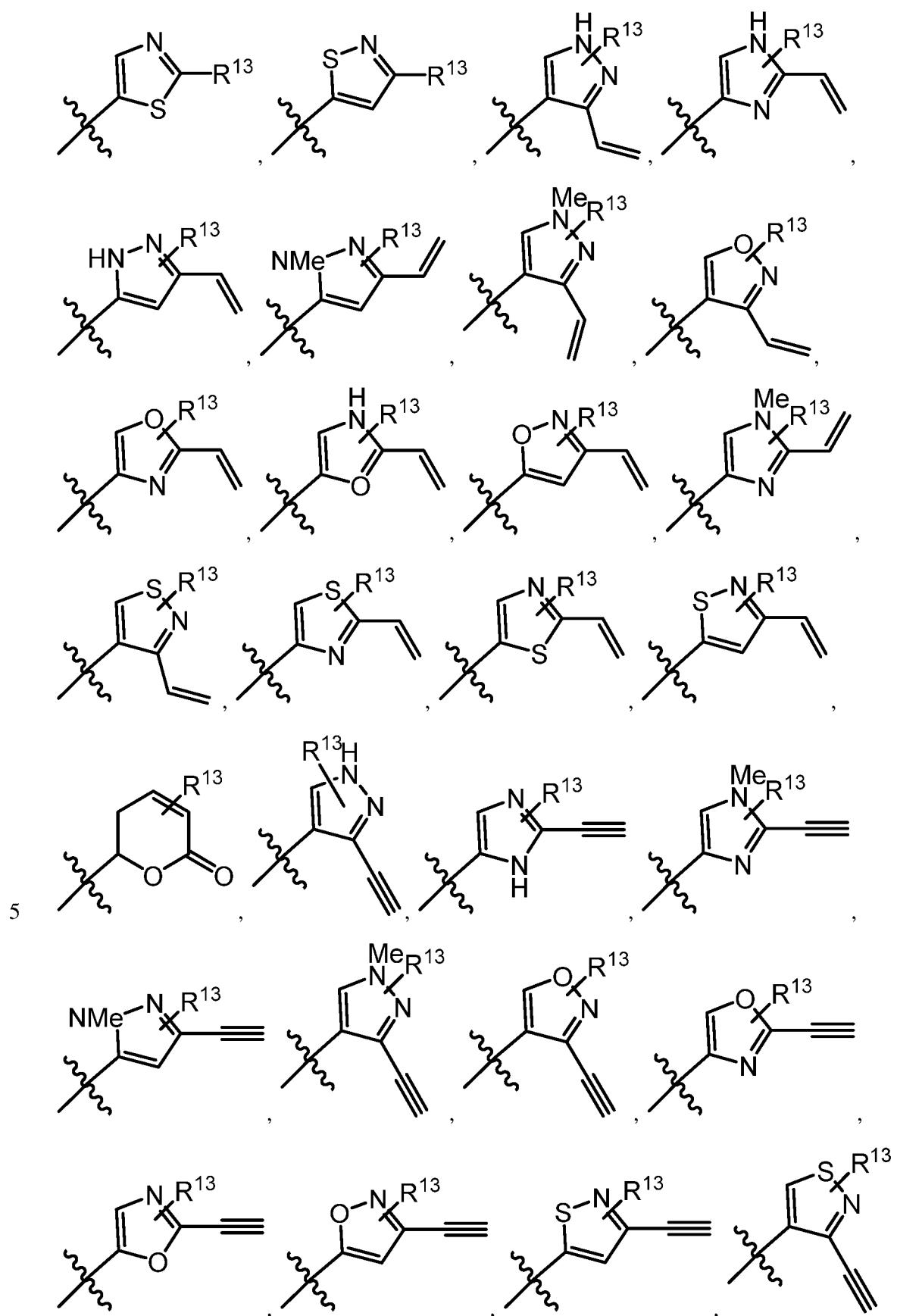


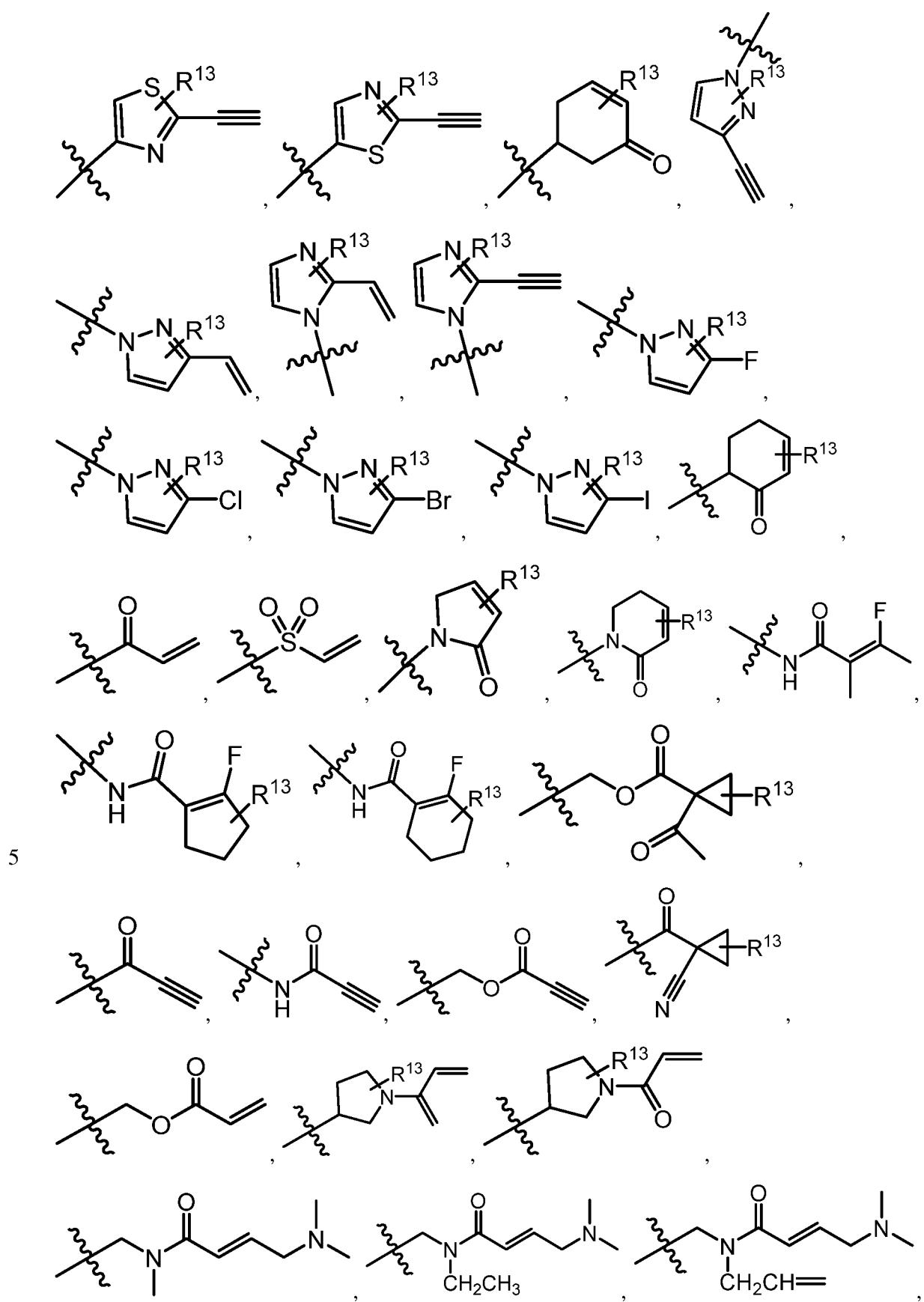
- 5 [0225] In embodiments, E is a substituted or unsubstituted vinyl sulfone moiety, substituted or unsubstituted vinyl sulfonamide moiety, substituted or unsubstituted fluoro(C₁-C₄)alkylketone moiety, substituted or unsubstituted chloro(C₁-C₄)alkylketone moiety, substituted or unsubstituted acrylamide moiety, substituted or unsubstituted disulfide moiety, substituted or unsubstituted thiol moiety, substituted or unsubstituted phosphonate moiety, substituted or unsubstituted aldehyde moiety, substituted or unsubstituted enone moiety, substituted or unsubstituted diazomethylketone moiety, substituted or unsubstituted diazomethylamide moiety, substituted or unsubstituted cyanocyclopropyl carboxamide moiety, substituted or unsubstituted epoxide moiety, substituted or unsubstituted epoxyketone moiety, substituted or unsubstituted epoxyamide moiety, substituted or unsubstituted aryl aldehyde moiety, substituted or unsubstituted aryl dialdehyde moiety, substituted or unsubstituted dialdehyde moiety, substituted or unsubstituted nitrogen mustard moiety, substituted or unsubstituted propargyl moiety,
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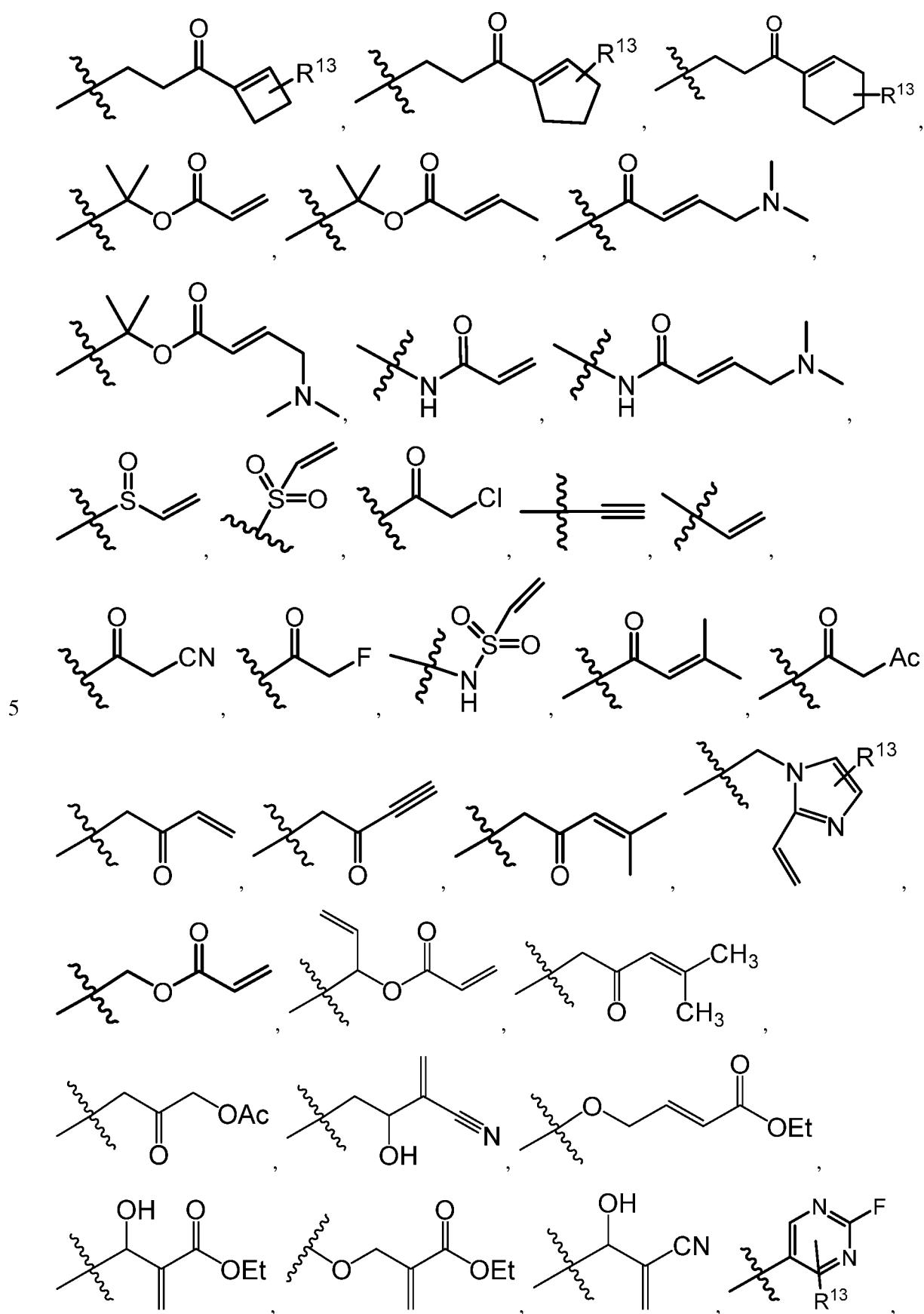


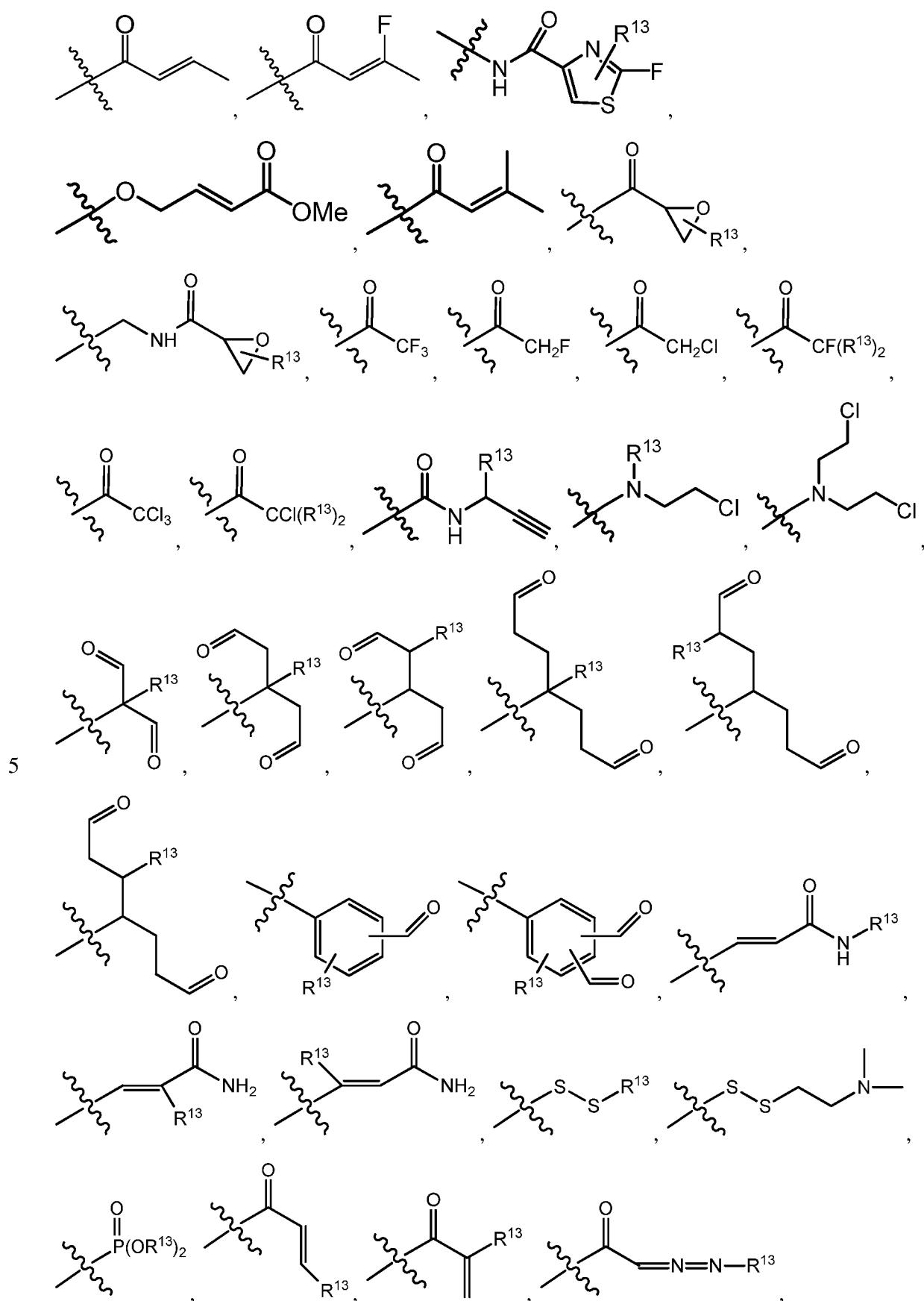


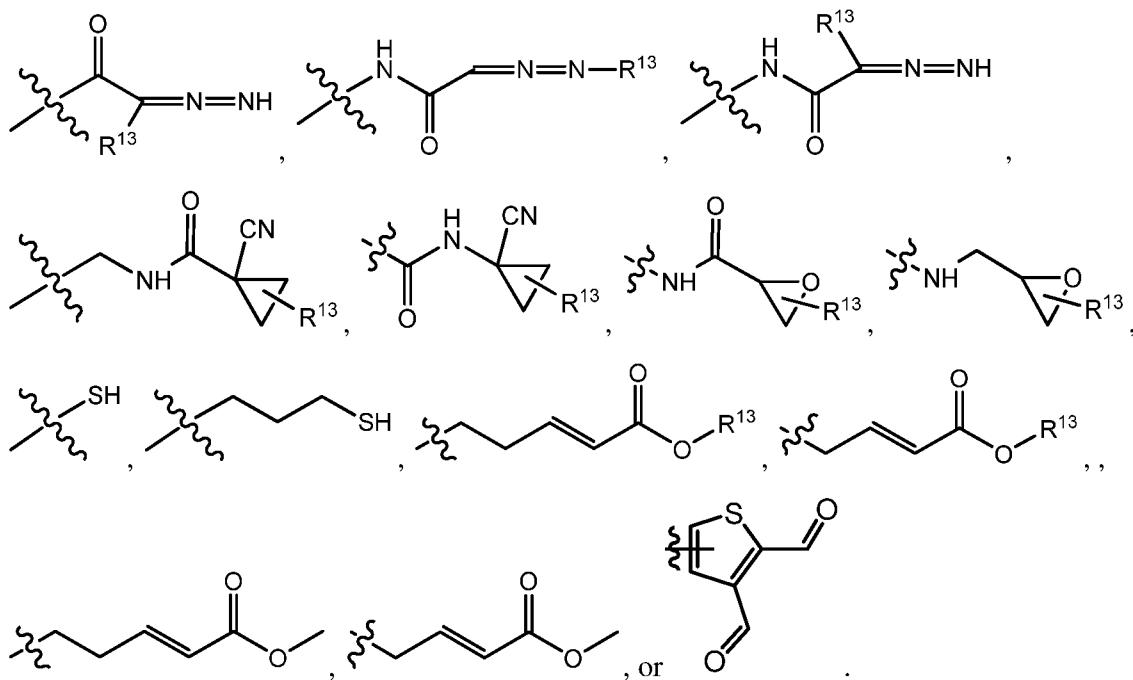












- 5 [0226] In embodiments, E is an unsubstituted vinyl sulfone moiety, unsubstituted vinyl sulfonamide moiety, unsubstituted fluoro(C₁-C₄)alkylketone moiety, unsubstituted chloro(C₁-C₄)alkylketone moiety, unsubstituted acrylamide moiety, unsubstituted disulfide moiety, unsubstituted thiol moiety, unsubstituted phosphonate moiety, unsubstituted aldehyde moiety, unsubstituted enone moiety, unsubstituted diazomethylketone moiety, unsubstituted diazomethylamide moiety, unsubstituted cyanocyclopropyl carboxamide moiety, unsubstituted epoxide moiety, unsubstituted epoxyketone moiety, unsubstituted epoxyamide moiety, unsubstituted aryl aldehyde moiety, unsubstituted aryl dialdehyde moiety, unsubstituted dialdehyde moiety, unsubstituted nitrogen mustard moiety, unsubstituted propargyl moiety, or unsubstituted propargylamide moiety.
- 10 [0227] R¹³ is independently hydrogen, oxo, halogen, CX¹³₃, -CHX¹³₂, -CH₂X¹³, -CN, -SO_{n13}R²², -SO_{v13}NR²⁰R²¹, -NHNR²⁰R²¹, -ONR²⁰R²¹, -NHC=(O)NHNR²⁰R²¹, -NHC(O)NR²⁰R²¹, -N(O)_{m13}, -NR²⁰R²¹, -C(O)R²², -C(O)-OR²², -C(O)NR²⁰R²¹, -OR²³, -NR²⁰SO₂R²³, -NR²⁰C(O)R²², -NR²⁰C(O)OR²², -NR²⁰OR²², -OCX¹³₃, -OCHX¹³₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; an R²⁰ and R²¹ substituent bonded to the same atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. In embodiments, R¹³ is independently hydrogen. In embodiments, R¹³ is independently substituted or unsubstituted alkyl. In embodiments, R¹³ is independently oxo,

- 15 [0227] R¹³ is independently hydrogen, oxo, halogen, CX¹³₃, -CHX¹³₂, -CH₂X¹³, -CN, -SO_{n13}R²², -SO_{v13}NR²⁰R²¹, -NHNR²⁰R²¹, -ONR²⁰R²¹, -NHC=(O)NHNR²⁰R²¹, -NHC(O)NR²⁰R²¹, -N(O)_{m13}, -NR²⁰R²¹, -C(O)R²², -C(O)-OR²², -C(O)NR²⁰R²¹, -OR²³, -NR²⁰SO₂R²³, -NR²⁰C(O)R²², -NR²⁰C(O)OR²², -NR²⁰OR²², -OCX¹³₃, -OCHX¹³₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; an R²⁰ and R²¹ substituent bonded to the same atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. In embodiments, R¹³ is independently hydrogen. In embodiments, R¹³ is independently substituted or unsubstituted alkyl. In embodiments, R¹³ is independently oxo,
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halogen, CX^{13}_3 , $-\text{CHX}^{13}_2$, $-\text{CH}_2\text{X}^{13}$, -CN, $-\text{SO}_{n13}\text{R}^{22}$, $-\text{SO}_{v13}\text{NR}^{20}\text{R}^{21}$, $-\text{NHNR}^{20}\text{R}^{21}$, $-\text{ONR}^{20}\text{R}^{21}$, $-\text{NHC}=(\text{O})\text{NHNR}^{20}\text{R}^{21}$,

$-\text{NHC(O)NR}^{20}\text{R}^{21}$, $-\text{N(O)}_{m13}$, $-\text{NR}^{20}\text{R}^{21}$, $-\text{C(O)R}^{22}$, $-\text{C(O)-OR}^{22}$, $-\text{C(O)NR}^{20}\text{R}^{21}$, $-\text{OR}^{23}$,

$-\text{NR}^{20}\text{SO}_2\text{R}^{23}$, $-\text{NR}^{20}\text{C(O)R}^{22}$, $-\text{NR}^{20}\text{C(O)OR}^{22}$, $-\text{NR}^{20}\text{OR}^{22}$, $-\text{OCX}^{13}_3$, $-\text{OCHX}^{13}_2$, substituted or

5 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. In embodiments, R^{13} is independently substituted or unsubstituted heteroalkyl. In embodiments, R^{13} is independently substituted or unsubstituted cycloalkyl. In embodiments, R^{13} is independently substituted or unsubstituted heterocycloalkyl.

10 In embodiments, R^{13} is independently substituted or unsubstituted aryl. In embodiments, R^{13} is independently substituted or unsubstituted heteroaryl. In embodiments, R^{13} is independently halogen, $-\text{CX}^{13}_3$, $-\text{CHX}^{13}_2$, $-\text{CH}_2\text{X}^{13}$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, $-\text{OCX}^{13}_3$, $-\text{OCHX}^{13}_2$, substituted or unsubstituted C₁-C₆ alkyl,

15 substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{13} is independently halogen, $-\text{CX}^{13}_3$, $-\text{CHX}^{13}_2$, $-\text{CH}_2\text{X}^{13}$, -OH, -SH, -COOH, $-\text{OCX}^{13}_3$, $-\text{OCHX}^{13}_2$, -CH₃, -CH₂CH₃, -

20 OCH₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R^{13} is independently halogen or -OCH₃. In embodiments, R^{13} is substituted or unsubstituted C₁-C₆ alkyl. In embodiments, R^{13} is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^{13} is substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{13} is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{13} is substituted or unsubstituted C₆ aryl. In

25 embodiments, R^{13} is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{13} is independently halogen. In embodiments, R^{13} is independently -CX₃. In embodiments, R^{13} is independently -CHX₂. In embodiments, R^{13} is independently -CH₂X¹³. In embodiments, R^{13} is independently -OH. In embodiments, R^{13} is independently -SH. In embodiments, R^{13} is independently -COOH. In embodiments, R^{13} is independently -OCX₃. In embodiments, R^{13} is independently -OCHX₂.

30 In embodiments, R^{13} is independently -CH₃. In embodiments, R^{13} is independently -CH₂CH₃. In embodiments, R^{13} is independently -OCH₃. In embodiments, R^{13} is independently -OCH₂CH₃. In embodiments, R^{13} is independently -SCH₃. In embodiments, R^{13} is independently -SCH₂CH₃. In embodiments, R^{13} is independently -Cl or -OCH₃. In embodiments, R^{13} is independently

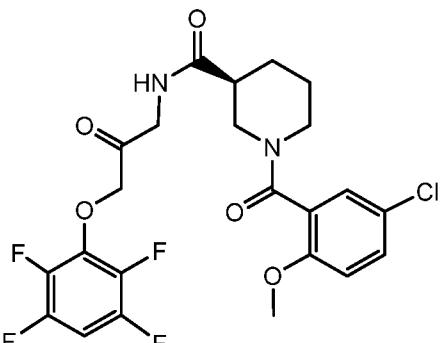
halogen, -CX¹³₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -OCX¹³₃, -OCHX¹³₂, -CHX¹³₂, -CH₂X¹³, substituted or unsubstituted C₁-C₈ alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or 5 unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹³ is independently halogen, -CX¹³₃, -CN, unsubstituted C₁-C₄ alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R¹³ is independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or unsubstituted tert-butyl. In embodiments, R¹³ is independently unsubstituted methyl. In embodiments, R¹³ is independently unsubstituted ethyl. In embodiments, R¹³ is 10 independently unsubstituted propyl. In embodiments, R¹³ is independently unsubstituted n-propyl. In embodiments, R¹³ is independently unsubstituted isopropyl. In embodiments, R¹³ is independently unsubstituted butyl. In embodiments, R¹³ is independently unsubstituted n-butyl. In embodiments, R¹³ is independently unsubstituted isobutyl. In embodiments, R¹³ is independently unsubstituted tert-butyl. In embodiments, R¹³ is independently unsubstituted 15 pentyl. In embodiments, R¹³ is independently unsubstituted hexyl. In embodiments, R¹³ is independently unsubstituted heptyl. In embodiments, R¹³ is independently unsubstituted octyl. In embodiments, R¹³ is independently -F. In embodiments, R¹³ is independently -Cl. In embodiments, R¹³ is independently -Br. In embodiments, R¹³ is independently -I. In embodiments, R¹³ is independently unsubstituted methoxy. In embodiments, R¹³ is 20 independently unsubstituted ethoxy. In embodiments, R¹³ is independently -CF₃. In embodiments, R¹³ is independently -CCl₃. In embodiments, R¹³ is an unsubstituted isopropyl. In embodiments, R¹³ is an unsubstituted phenyl. In embodiments, R¹³ is an unsubstituted pyridyl. In embodiments, R¹³ is independently halogen. In embodiments, R¹³ is independently -CX¹³₃. In embodiments, R¹³ is independently -CHX¹³₂. In embodiments, R¹³ is independently -CH₂X¹³. 25 In embodiments, R¹³ is independently -CN. In embodiments, R¹³ is independently -OH. In embodiments, R¹³ is independently -NH₂. In embodiments, R¹³ is independently -COOH. In embodiments, R¹³ is independently -CONH₂. In embodiments, R¹³ is independently -NO₂. In embodiments, R¹³ is independently -SH. In embodiments, R¹³ is independently -SO₂Cl. In embodiments, R¹³ is independently -SO₃H. In embodiments, R¹³ is independently -SO₄H. In 30 embodiments, R¹³ is independently -SO₂NH₂. In embodiments, R¹³ is independently -NHNH₂. In embodiments, R¹³ is independently -ONH₂. In embodiments, R¹³ is independently -NHC(O)NHNH₂. In embodiments, R¹³ is independently -NHC(O)NH₂. In embodiments, R¹³ is independently -NHSO₂H. In embodiments, R¹³ is independently -NHC(O)H. In embodiments, R¹³ is independently -NHC(O)OH. In embodiments, R¹³ is

independently -NHOH. In embodiments, R¹³ is independently -OCX¹³₃. In embodiments, R¹³ is independently -OCHX¹³₂. In embodiments, R¹³ is independently substituted or unsubstituted alkyl. In embodiments, R¹³ is independently substituted or unsubstituted heteroalkyl. In embodiments, R¹³ is independently substituted or unsubstituted cycloalkyl. In embodiments, R¹³ is independently substituted or unsubstituted heterocycloalkyl. In embodiments, R¹³ is independently substituted or unsubstituted aryl. In embodiments, R¹³ is independently substituted or unsubstituted heteroaryl. In embodiments, R¹³ is independently substituted alkyl. In embodiments, R¹³ is independently substituted heteroalkyl. In embodiments, R¹³ is independently substituted cycloalkyl. In embodiments, R¹³ is independently substituted heterocycloalkyl. In embodiments, R¹³ is independently substituted aryl. In embodiments, R¹³ is independently substituted heteroaryl. In embodiments, R¹³ is independently unsubstituted alkyl. In embodiments, R¹³ is independently unsubstituted heteroalkyl. In embodiments, R¹³ is independently unsubstituted cycloalkyl. In embodiments, R¹³ is independently unsubstituted heterocycloalkyl. In embodiments, R¹³ is independently unsubstituted aryl. In embodiments, R¹³ is independently unsubstituted heteroaryl. In embodiments, R¹³ is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R¹³ is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R¹³ is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹³ is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹³ is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R¹³ is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R¹³ is independently substituted C₁-C₈ alkyl. In embodiments, R¹³ is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R¹³ is independently substituted C₃-C₈ cycloalkyl. In embodiments, R¹³ is independently substituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹³ is independently substituted C₆-C₁₀ aryl. In embodiments, R¹³ is independently substituted 5 to 10 membered heteroaryl. In embodiments, R¹³ is independently unsubstituted C₁-C₈ alkyl. In embodiments, R¹³ is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R¹³ is independently unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹³ is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹³ is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R¹³ is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R¹³ is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R¹³ is independently substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R¹³ is independently substituted or unsubstituted C₃-C₆ cycloalkyl. In embodiments, R¹³ is independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments,

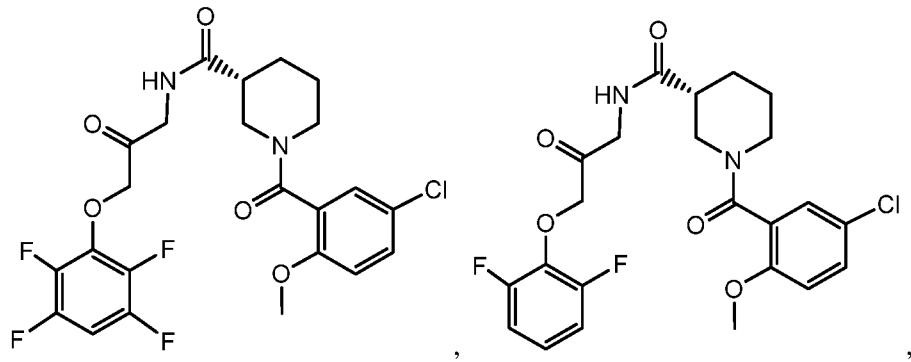
R¹³ is independently substituted or unsubstituted phenyl. In embodiments, R¹³ is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹³ is independently substituted C₁-C₄ alkyl. In embodiments, R¹³ is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R¹³ is independently substituted C₃-C₆ cycloalkyl. In 5 embodiments, R¹³ is independently substituted 3 to 6 membered heterocycloalkyl. In embodiments, R¹³ is independently substituted phenyl. In embodiments, R¹³ is independently substituted 5 to 6 membered heteroaryl. In embodiments, R¹³ is independently unsubstituted C₁-C₄ alkyl. In embodiments, R¹³ is independently unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R¹³ is independently unsubstituted C₃-C₆ cycloalkyl. In embodiments, R¹³ is 10 independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R¹³ is independently unsubstituted phenyl. In embodiments, R¹³ is independently unsubstituted 5 to 6 membered heteroaryl.

[0228] R²⁰, R²¹, R²², and R²³ are independently hydrogen, halogen, -CX^A₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, 15 -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX^A₃, -OCHX^A₂, -CHX^A₂, -CH₂X^A, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R²⁰ and R²¹ substituents bonded to the same nitrogen atom may optionally be joined 20 to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

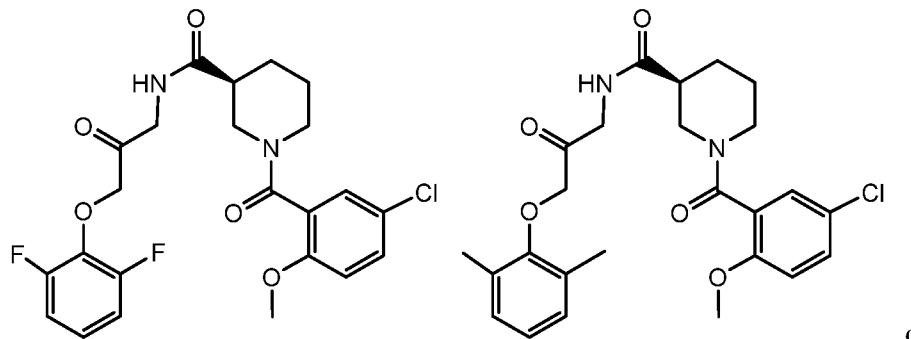
[0229] Each X^A and X¹³ is independently -F, -Cl, -Br, or -I. The symbols n13 and v13 are independently an integer from 0 to 4. The symbol m13 is independently an integer from 1 to 2.



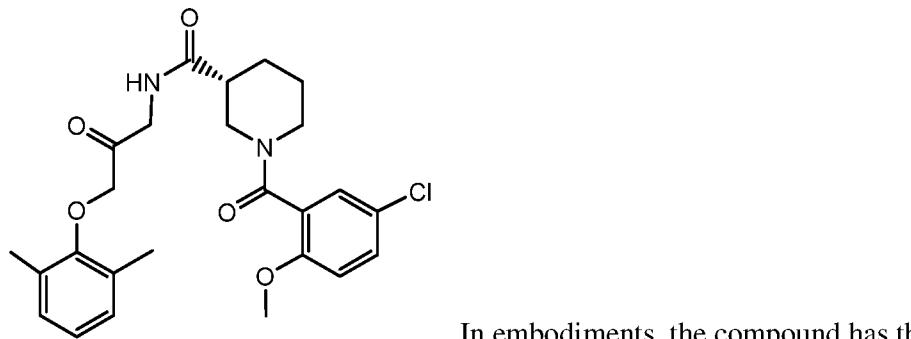
[0230] In embodiments, the compound has the formula: $\text{F}_3\text{C}_6\text{H}_2\text{O-CH}_2\text{CH}_2\text{CH}_2\text{O-}$,



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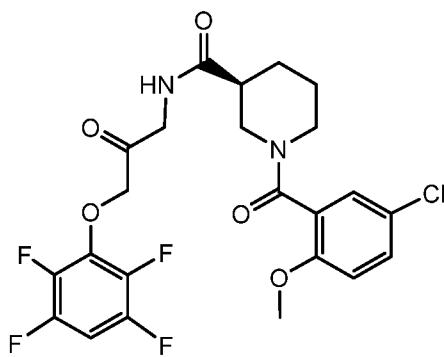


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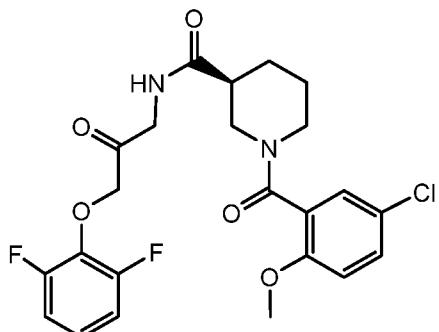


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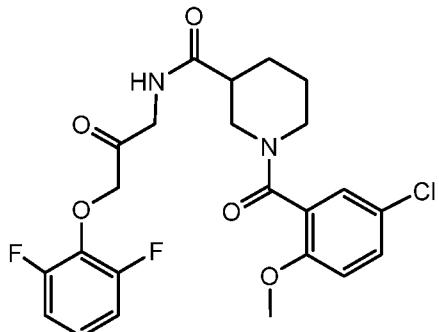
In embodiments, the compound has the formula:



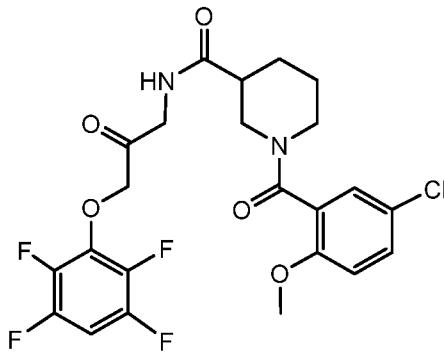
. In embodiments, the compound has the formula:



. In embodiments, the compound has the formula:

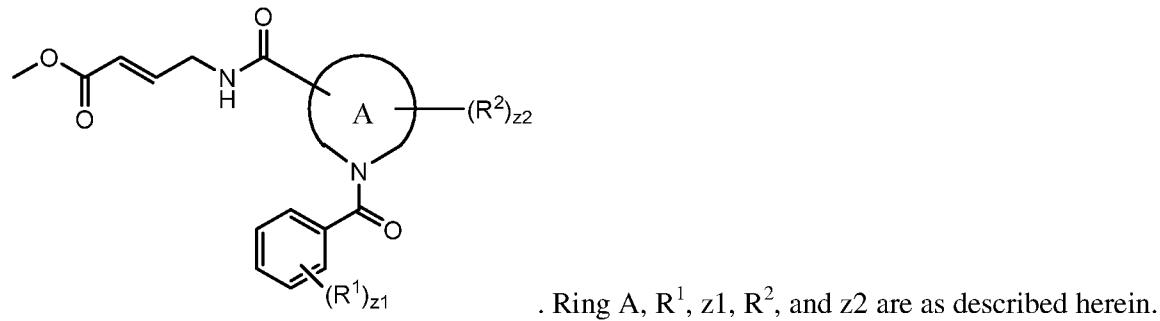


. In embodiments, the compound has the formula:

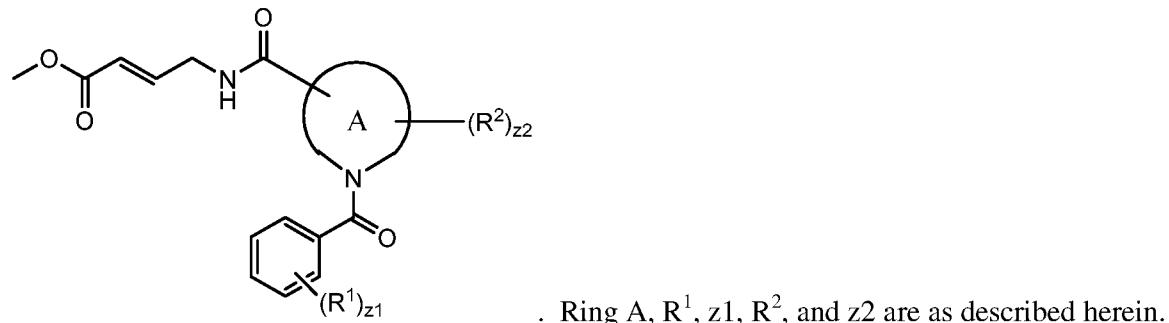


.

[0231] In embodiments, the compound has the formula:

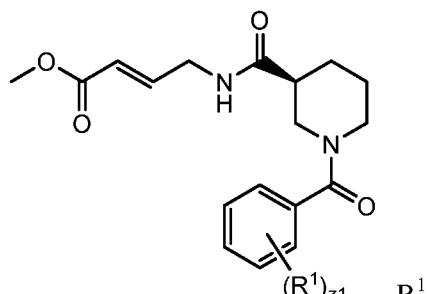


[0232] In embodiments, the compound has the formula:



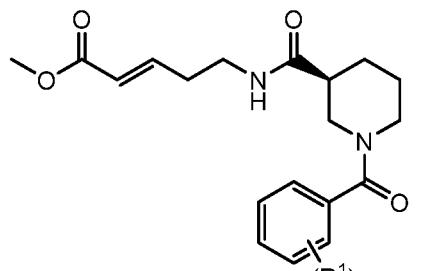
5 **[0233]** In embodiments, the compound has the formula:

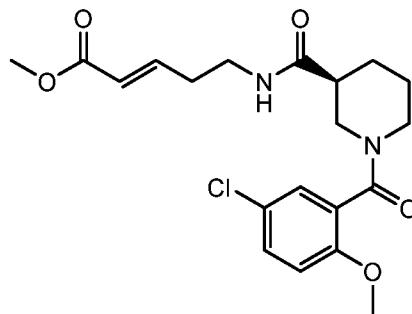
and z1 are as described herein.



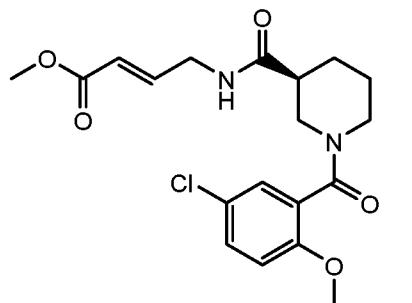
[0234] In embodiments, the compound has the formula:

and z1 are as described herein.

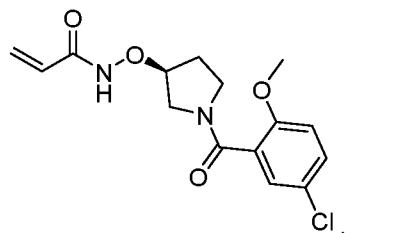




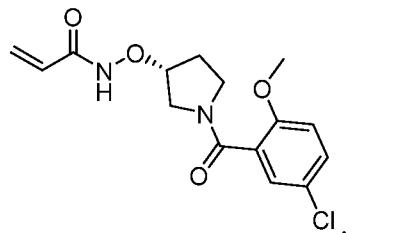
[0235] In embodiments, the compound has the formula:



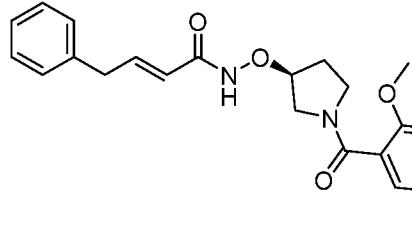
[0236] In embodiments, the compound has the formula:



[0237] In embodiments, the compound has the formula:

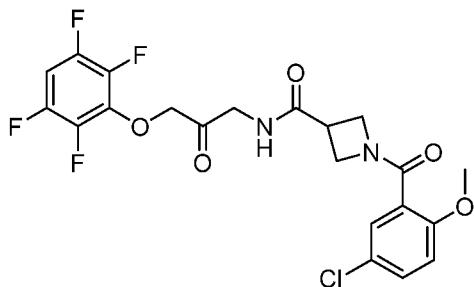


[0238] In embodiments, the compound has the formula:

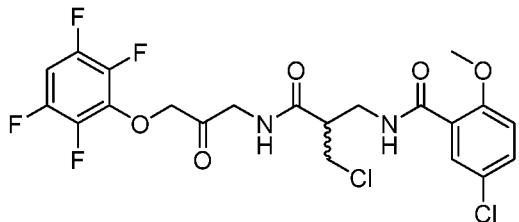


5 [0239] In embodiments, the compound has the formula:

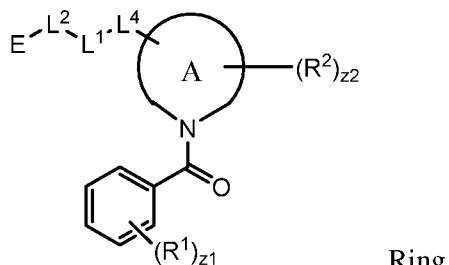
[0240] In embodiments, the compound has the formula:



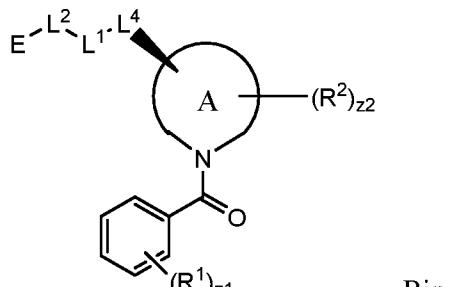
[0241] In embodiments, the compound has the formula:



- 5 **[0242]** In embodiments, the compound has the formula:
 A , R^1 , $z1$, R^2 , $z2$, L^1 , L^2 , L^4 , and E are as described herein.



[0243] In embodiments, the compound has the formula:
 A , R^1 , $z1$, R^2 , $z2$, L^1 , L^2 , L^4 , and E are as described herein.



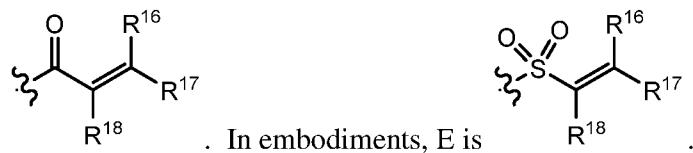
- [0244]** In embodiments, Ring A is a 5 to 7 membered heterocycloalkyl. In embodiments, Ring A is a 3 to 5 membered heterocycloalkyl. In embodiments, Ring A is pyrrolidinyl. In
10 embodiments, Ring A is piperidinyl. In embodiments, Ring A is azetidinyl. In embodiments, Y is N.

[0245] In embodiments, R¹ is independently halogen, CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC(O)NH₂, -N(O)₂, -NH₂, -C(O)H, -C(O)OH, -C(O)NH₂, -OH, -HSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. In embodiments, R¹ is independently halogen, -CF₃, -NH₂, -C(O)H, -C(O)OH, -C(O)NH₂, -OH, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R¹ is independently halogen, -CF₃, -NH₂, -C(O)H, -C(O)OH, -C(O)NH₂, -OH, unsubstituted C₁-C₄ alkyl, or unsubstituted 2 to 4 membered heteroalkyl.

[0246] In embodiments, L¹ is a bond. In embodiments, L¹ is -NH-.

[0247] In embodiments, L² is a bond. In embodiments, L² is -NH-.

[0248] In embodiments, L⁴ is a bond. In embodiments, L⁴ is substituted or unsubstituted C₁-C₃ alkylene. In embodiments, L⁴ is unsubstituted methylene.



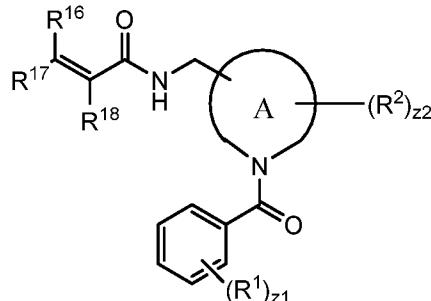
[0249] In embodiments, E is . In embodiments, E is .

[0250] In embodiments, R¹⁶ is unsubstituted methyl. In embodiments, R¹⁷ is unsubstituted methyl. In embodiments, R¹⁸ is unsubstituted methyl. In embodiments, R¹⁸ is hydrogen. In embodiments, R¹⁶ is hydrogen. In embodiments, R¹⁷ is hydrogen. In embodiments, R¹⁶ is -CH₂N(CH₃)₂. In embodiments, R¹⁷ is -CH₂N(CH₃)₂. In embodiments, R¹⁸ is -CH₂N(CH₃)₂. In embodiments, R¹⁶ is -CH₂CH₂N(CH₃)₂. In embodiments, R¹⁷ is -CH₂CH₂N(CH₃)₂. In embodiments, R¹⁸ is -CH₂Ph. In embodiments, R¹⁸ is -CH₂CH₂N(CH₃)₂.

[0251] In embodiments, R² is independently halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC(O)NH₂, -N(O)₂, -NH₂, -C(O)H, -C(O)OH, -C(O)NH₂, -OH, -HSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. In embodiments, R² is independently halogen, -CF₃, -NH₂, -C(O)H, -C(O)OH, -C(O)NH₂, -OH, -C(O)NH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC(O)NH₂, -N(O)₂, -NH₂, -C(O)H, -C(O)OH, -C(O)NH₂, -OH, -HSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl.

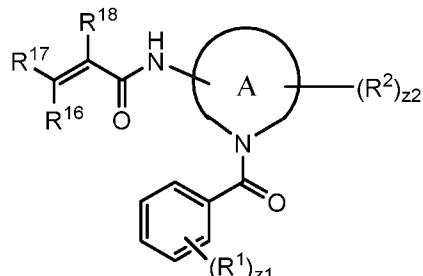
substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently halogen, -CF₃, -NH₂, -C(O)H, -C(O)OH, -C(O)NH₂, -OH, unsubstituted C₁-C₄ alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently -Cl. In 5 embodiments, R² is independently -F. In embodiments, R² is independently -Br. In embodiments, R² is independently -I. In embodiments, R² is independently -OCH₃. In embodiments, R² is independently -OCH₂CH₃.

[0252] In embodiments, z1 is 2. In embodiments, z2 is 0.



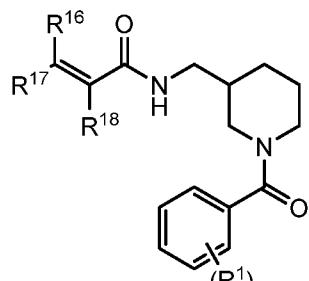
[0253] In embodiments, the compound has the formula:

10 Ring A, R¹, z1, R², z2, R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.

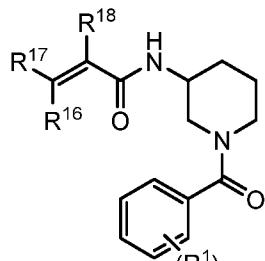


[0254] In embodiments, the compound has the formula:

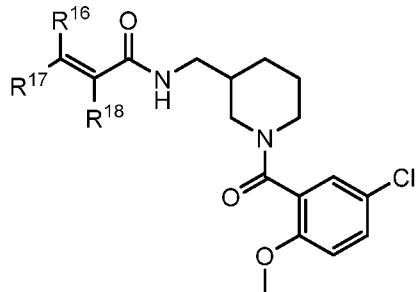
Ring A, R¹, z1, R², z2, R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



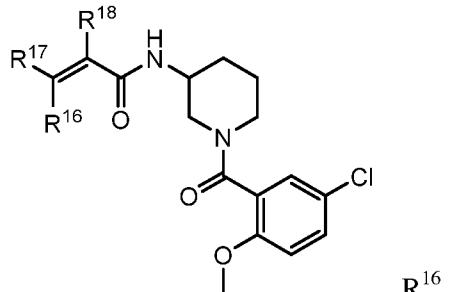
15 [0255] In embodiments, the compound has the formula: . R¹, z1, R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



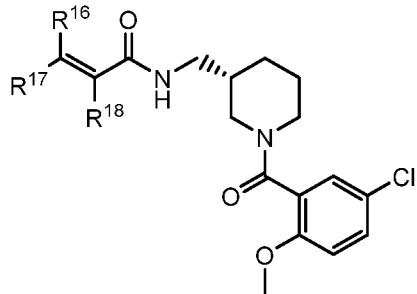
[0256] In embodiments, the compound has the formula: $\text{R}^1, z_1, \text{R}^{16}, \text{R}^{17}, \text{and R}^{18}$ are as described herein. In embodiments, $\text{R}^{16}, \text{R}^{17}$, and R^{18} are hydrogen.



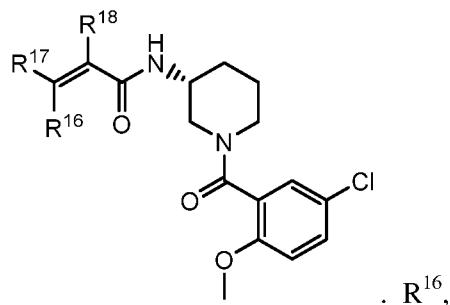
[0257] In embodiments, the compound has the formula: $\text{R}^1, \text{R}^{16}, \text{R}^{17}, \text{and R}^{18}$ are as described herein. In embodiments, $\text{R}^{16}, \text{R}^{17}$, and R^{18} are hydrogen.



5 [0258] In embodiments, the compound has the formula: $\text{R}^1, \text{R}^{16}, \text{R}^{17}, \text{and R}^{18}$ are as described herein. In embodiments, $\text{R}^{16}, \text{R}^{17}$, and R^{18} are hydrogen.

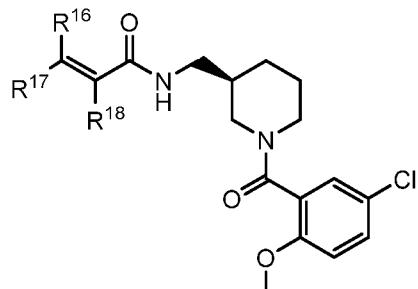


[0259] In embodiments, the compound has the formula: $\text{R}^1, \text{R}^{16}, \text{R}^{17}, \text{and R}^{18}$ are as described herein. In embodiments, $\text{R}^{16}, \text{R}^{17}$, and R^{18} are hydrogen.



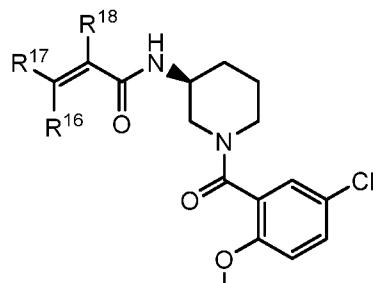
[0260] In embodiments, the compound has the formula:

R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.



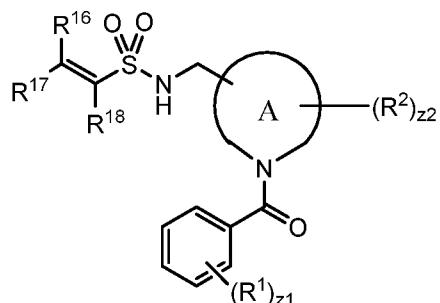
[0261] In embodiments, the compound has the formula:

R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.



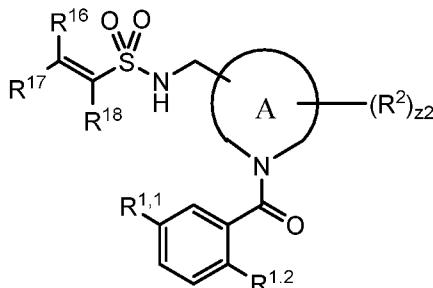
5 [0262] In embodiments, the compound has the formula:

R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.

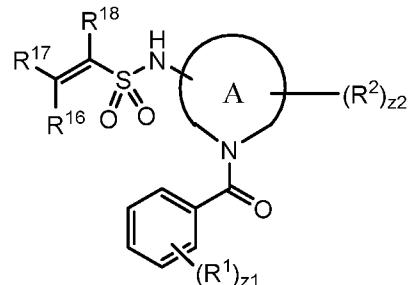


[0263] In embodiments, the compound has the formula:

Ring A, R^1 , $\text{z}1$, R^2 , $\text{z}2$, R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen. In embodiments, the compound has the formula:

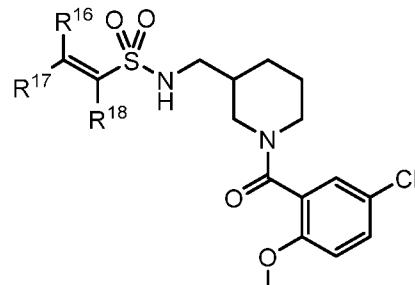


. Ring A, R², z2, R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen. R^{1,1} and R^{1,2} have the values of R¹. R^{1,1} may be halogen. R^{1,1} may be hydrogen. R^{1,1} may be -Cl. R^{1,2} may be hydrogen. R^{1,2} may be unsubstituted 2 to 4 membered heteroalkyl. R^{1,2} may be unsubstituted 2 to 3 membered heteroalkyl. R^{1,2} may be unsubstituted methoxy. R^{1,2} may be unsubstituted ethoxy. R^{1,2} may be unsubstituted propoxy.



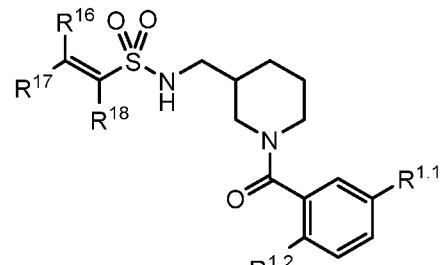
[0264] In embodiments, the compound has the formula:

Ring A, R¹, z1, R², z2, R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



[0265] In embodiments, the compound has the formula:

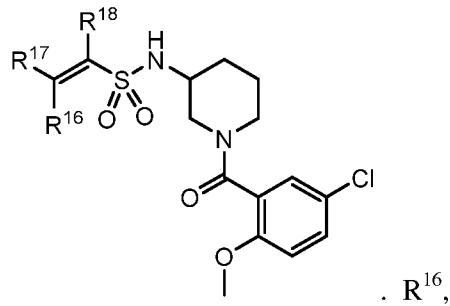
R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen. In



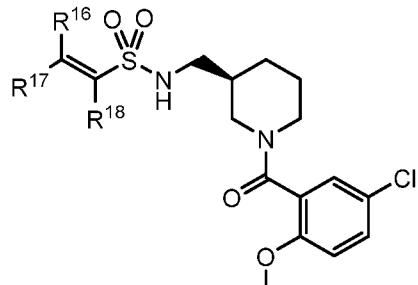
embodiments, the compound has the formula:

R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen. R^{1,1} and R^{1,2} have

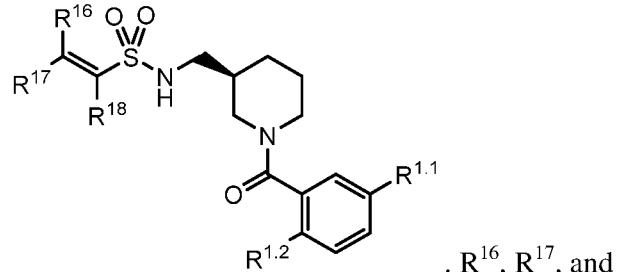
the values of R¹. R^{1.1} may be halogen. R^{1.1} may be hydrogen. R^{1.1} may be -Cl. R^{1.2} may be hydrogen. R^{1.2} may be unsubstituted 2 to 4 membered heteroalkyl. R^{1.2} may be unsubstituted 2 to 3 membered heteroalkyl. R^{1.2} may be unsubstituted methoxy. R^{1.2} may be unsubstituted ethoxy. R^{1.2} may be unsubstituted propoxy.



- 5 [0266] In embodiments, the compound has the formula: . R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.

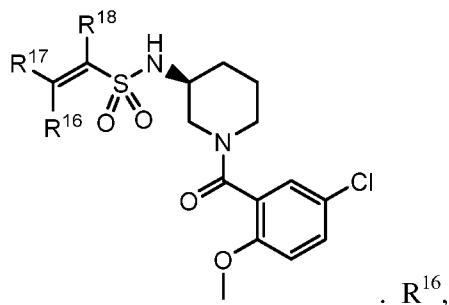


[0267] In embodiments, the compound has the formula: . R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen. In



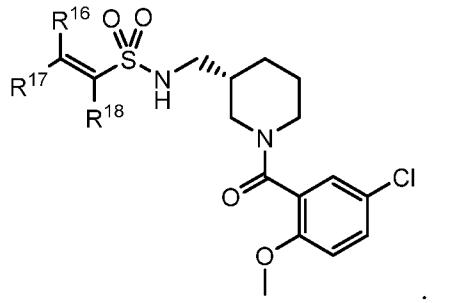
embodiments, the compound has the formula: . R¹⁶, R¹⁷, and

- 10 R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen. R^{1.1} and R^{1.2} have the values of R¹. R^{1.1} may be halogen. R^{1.1} may be hydrogen. R^{1.1} may be -Cl. R^{1.2} may be hydrogen. R^{1.2} may be unsubstituted 2 to 4 membered heteroalkyl. R^{1.2} may be unsubstituted 2 to 3 membered heteroalkyl. R^{1.2} may be unsubstituted methoxy. R^{1.2} may be unsubstituted ethoxy. R^{1.2} may be unsubstituted propoxy.



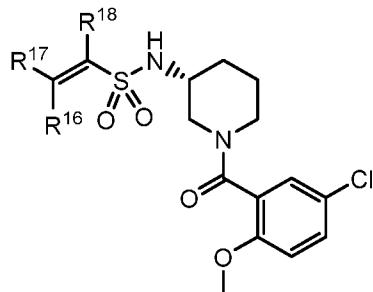
[0268] In embodiments, the compound has the formula:

R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



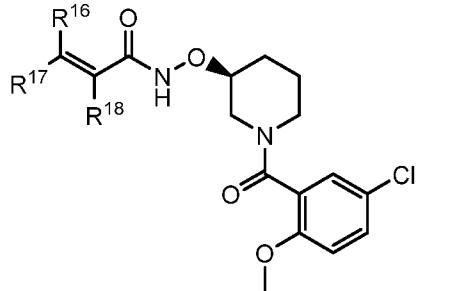
[0269] In embodiments, the compound has the formula:

R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



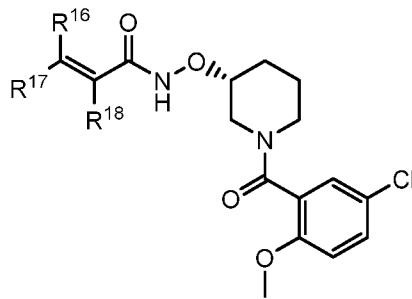
5 In embodiments, the compound has the formula:

R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



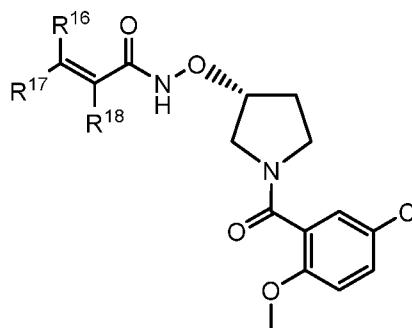
[0270] In embodiments, the compound has the formula:

R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



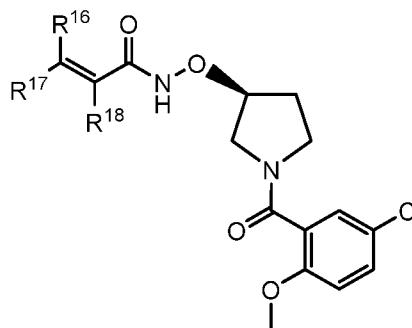
[0271] In embodiments, the compound has the formula:

R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



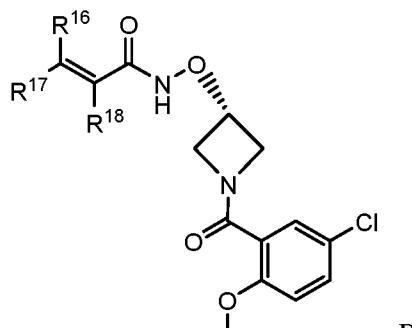
[0272] In embodiments, the compound has the formula:

R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



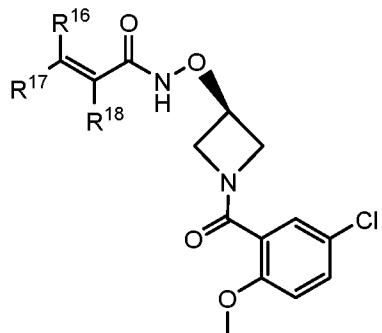
5 [0273] In embodiments, the compound has the formula:

R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen. In embodiments, R¹⁶ and R¹⁸ are hydrogen and R¹⁷ is -CH₂Ph.

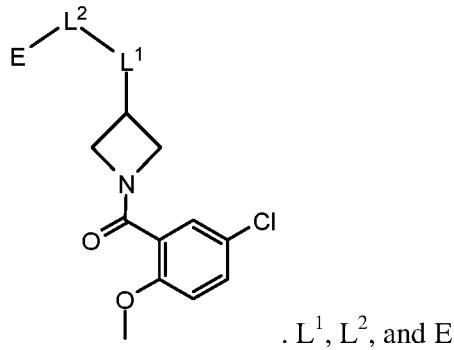


[0274] In embodiments, the compound has the formula:

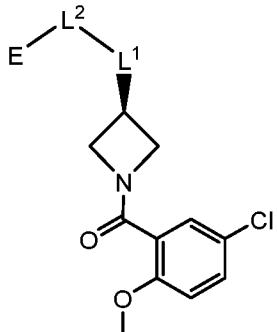
R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



[0275] In embodiments, the compound has the formula: . R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.

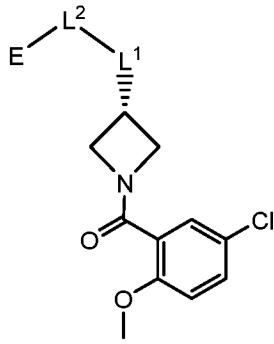


[0276] In embodiments, the compound has the formula: . L^1 , L^2 , and E

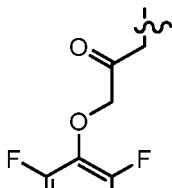


are as described herein. In embodiments, the compound has the formula: .

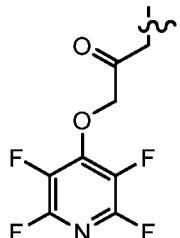
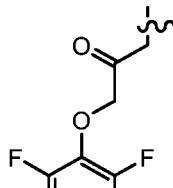
5 L^1 , L^2 , and E are as described herein. In embodiments, the compound has the formula:



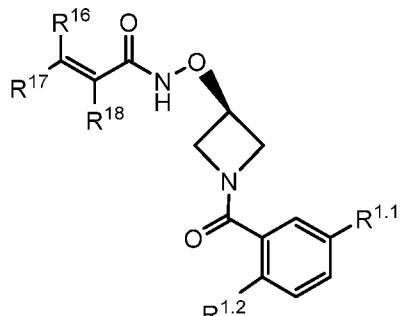
. L^1 , L^2 , and E are as described herein. In embodiments, R^{16} , R^{17} , and R^{18}



are hydrogen. In embodiments, E is: $\text{F}-\text{Y}^2-\text{F}$ and Y^2 is as described herein. In



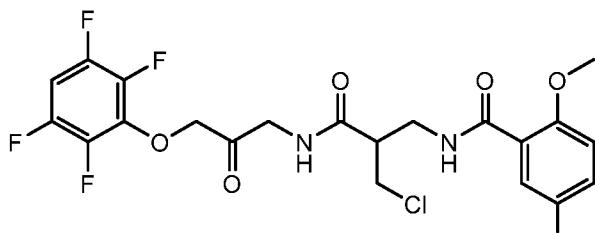
embodiments, E is: $\text{F}-\text{C}_6\text{H}_3-\text{F}$. In embodiments, E is: $\text{F}-\text{C}_5\text{H}_4-\text{F}$. In embodiments, L^1 is $-\text{C}(\text{O})-$. In embodiments, L^2 is $-\text{NH}-$.



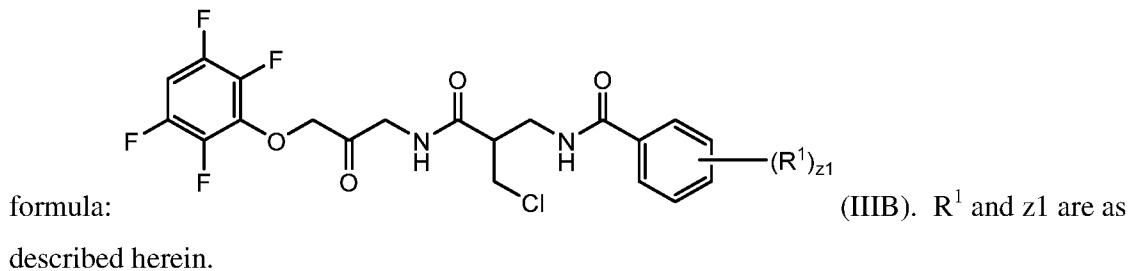
In embodiments, the compound has the formula: . R^{16} , R^{17} , and

- 5 R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen. $\text{R}^{1.1}$ and $\text{R}^{1.2}$ have the values of R^1 . $\text{R}^{1.1}$ may be halogen. $\text{R}^{1.1}$ may be hydrogen. $\text{R}^{1.1}$ may be $-\text{Cl}$. $\text{R}^{1.2}$ may be hydrogen. $\text{R}^{1.2}$ may be unsubstituted 2 to 4 membered heteroalkyl. $\text{R}^{1.2}$ may be unsubstituted 2 to 3 membered heteroalkyl. $\text{R}^{1.2}$ may be unsubstituted methoxy. $\text{R}^{1.2}$ may be unsubstituted ethoxy. $\text{R}^{1.2}$ may be unsubstituted propoxy.

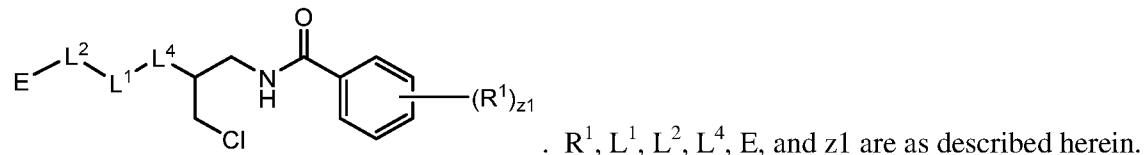
- 10 [0277] In embodiments, the compound has the formula:



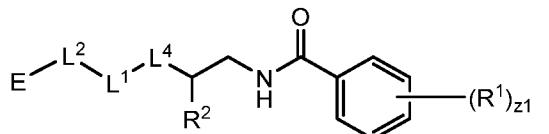
(IIIB). In embodiments, the compound has the



[0278] In embodiments, the compound has the formula:

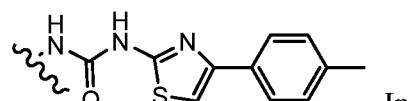


5 In embodiments, the compound has the formula:



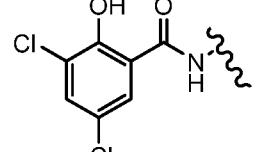
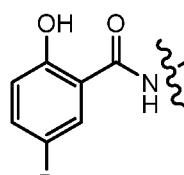
R^1 , R^2 , L^1 , L^2 , L^4 , E, and z_1 are as described herein.

[0279] In embodiments, the compound includes

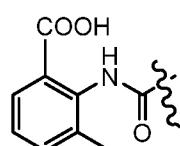


embodiments, the compound includes

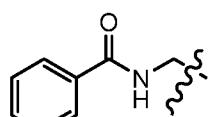
. In embodiments, the compound includes



. In embodiments, the compound includes

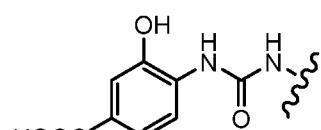


. In embodiments,



10 the compound includes

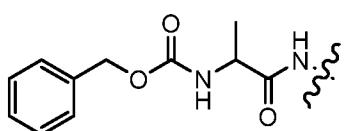
. In embodiments, the compound includes



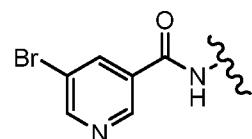
. In embodiments, the compound includes



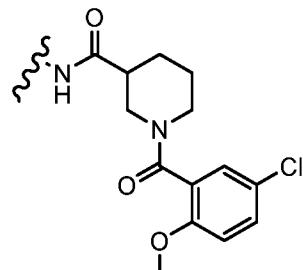
. In embodiments, the compound includes



. In embodiments, the compound includes

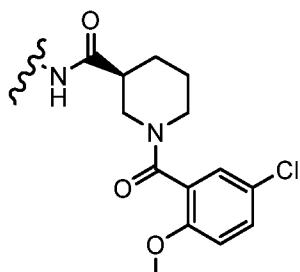


. In

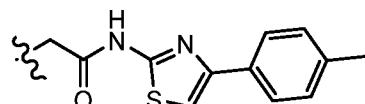


embodiments, the compound includes

. In embodiments, the compound

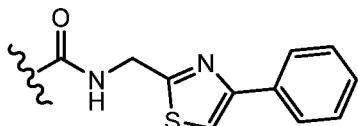


includes . In embodiments, the compound is a compound described herein, including in an example, figures, or table.

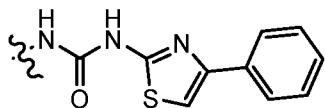


5 In embodiments, the compound includes

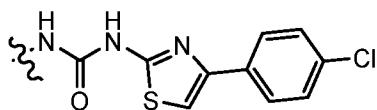
. In embodiments, the



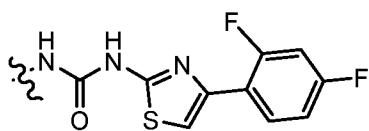
compound includes . In embodiments, the compound includes



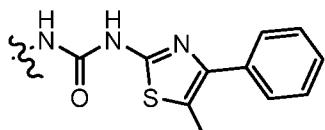
. In embodiments, the compound includes



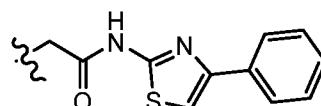
. In embodiments, the compound includes



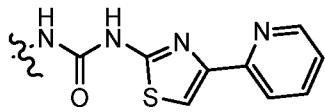
. In embodiments, the compound includes



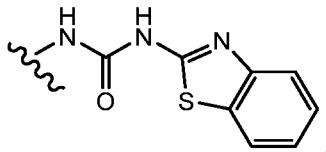
. In embodiments, the compound includes



10

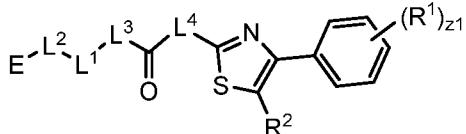


. In embodiments, the compound includes



compound includes

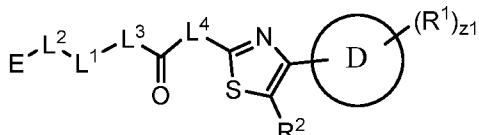
[0280] In an aspect is provided a compound having the formula:



(IV). R^1 , R^2 , R^4 , R^5 , L^1 , L^2 , L^3 , L^4 , E , and $z1$ are as

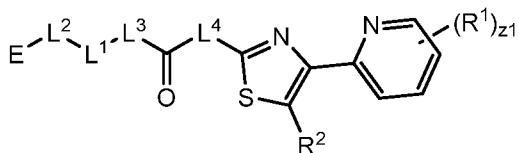
5 described herein (e.g., for formulae I, II, III, and embodiments thereof or in examples, figures, tables, or claims). L^4 may be $-N(R^4)$. L^4 may be $-CH_2N(R^4)$. L^3 may be $-N(R^5)$. L^3 may be a bond. L^4 may be a bond. R^4 and R^5 may be hydrogen. L^3 may be unsubstituted methylene. L^3 may be unsubstituted ethylene. L^3 may be unsubstituted n-propylene. L^3 may be unsubstituted n-butylene. R^2 may be unsubstituted methyl. R^2 may be hydrogen.

10 **[0281]** In an aspect is provided a compound having the formula:



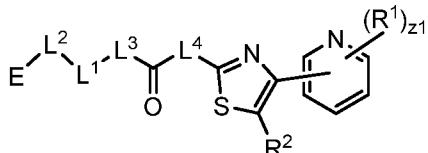
(V). R^1 , R^2 , R^4 , R^5 , L^1 , L^2 , L^3 , L^4 , E , and $z1$ are as

described herein (e.g., for formulae I, II, III, VI, and embodiments thereof or in examples, figures, tables, or claims). L^4 may be $-N(R^4)$. L^4 may be $-N(H)$. L^4 may be $-CH_2N(R^4)$. L^3 may be $-N(R^5)$. L^3 may be $-N(H)$. L^3 may be a bond. L^4 may be a bond. R^4 and R^5 may be 15 hydrogen. L^3 may be unsubstituted methylene. L^3 may be unsubstituted ethylene. L^3 may be unsubstituted n-propylene. L^3 may be unsubstituted n-butylene. R^2 may be unsubstituted methyl. R^2 may be hydrogen. Ring D is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In embodiments, Ring D is C₃-C₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₆-C₁₀ aryl, or 5 to 10 membered heteroaryl. In embodiments, Ring D is C₃-C₈ cycloalkyl. In embodiments, Ring D is 20 3 to 8 membered heterocycloalkyl. In embodiments, Ring D is C₆-C₁₀ aryl. In embodiments, Ring D is 5 to 10 membered heteroaryl. In embodiments, Ring D is phenyl. In embodiments, Ring D is 5 to 9 membered heteroaryl. In embodiments, Ring D is 5 to 6 membered heteroaryl. In embodiments, Ring D is 5 membered heteroaryl. In embodiments, Ring D is 6 membered heteroaryl. In embodiments, Ring D is pyridyl. In embodiments, the compound is



. R¹, R², R⁴, R⁵, L¹, L², L³, L⁴, E, and z1 are as

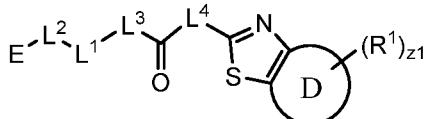
described herein (e.g., for formulae I, II, III, VI, and embodiments thereof or in examples, figures, tables, or claims). In embodiments, z1 is 0. In embodiments, the compound is



. R¹, R², R⁴, R⁵, L¹, L², L³, L⁴, E, and z1 are as described

- 5 herein (e.g., for formulae I, II, III, VI, and embodiments thereof or in examples, figures, tables, or claims).

[0282] In an aspect is provided a compound having the formula:



(VI). R¹, R², R⁴, R⁵, L¹, L², L³, L⁴, E, and z1 are as described

herein (e.g., for formulae I, II, III, IV, V, and embodiments thereof or in examples, figures,

- 10 tables, or claims). L⁴ may be -N(R⁴)-. L⁴ may be -N(H)-. L⁴ may be -CH₂N(R⁴)-. L³ may be -N(R⁵)-. L³ may be -N(H)-. L³ may be a bond. L⁴ may be a bond. R⁴ and R⁵ may be hydrogen. L³ may be unsubstituted methylene. L³ may be unsubstituted ethylene. L³ may be unsubstituted n-propylene. L³ may be unsubstituted n-butylene. R² may be unsubstituted methyl. R² may be hydrogen. Ring D is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In embodiments, Ring D is C₃-C₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₆-C₁₀ aryl, or 5 to 10 membered heteroaryl. In embodiments, Ring D is C₃-C₈ cycloalkyl. In embodiments, Ring D is 3 to 8 membered heterocycloalkyl. In embodiments, Ring D is C₆-C₁₀ aryl. In embodiments, Ring D is 5 to 10 membered heteroaryl. In embodiments, Ring D is phenyl. In embodiments, Ring D is 5 to 9 membered heteroaryl. In embodiments, Ring D is 5 to 6 membered heteroaryl. In
15 embodiments, Ring D is 5 membered heteroaryl. In embodiments, Ring D is 6 membered heteroaryl. In embodiments, Ring D is pyridyl.
- 20

- In embodiments, Ring D is 5 membered heteroaryl. In embodiments, Ring D is 6 membered heteroaryl. In embodiments, Ring D is pyridyl.
- [0283]** In embodiments, R¹ is independently hydrogen, oxo, halogen, -CX¹₃, -CHX¹₂, -OCH₂X¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹₃, -OCHX¹₂, R³⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, or 2 to 4 membered), R³⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9

5 membered, or 5 to 6 membered). In embodiments, R¹ is independently oxo, halogen, -CX¹₃, -CHX¹₂, -OCH₂X¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹₃, -OCHX¹₂, R³⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8

10 membered, 2 to 6 membered, or 2 to 4 membered), R³⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹ is halogen. In embodiments, X¹ is F.

15 [0284] R³⁰ is independently oxo, halogen, -CX³⁰₃, -CHX³⁰₂, -OCH₂X³⁰, -OCHX³⁰₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³⁰₃, -OCHX³⁰₂, R³¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³⁰ is halogen. In embodiments, X³⁰ is F.

25 [0285] R³¹ is independently oxo, halogen, -CX³¹₃, -CHX³¹₂, -OCH₂X³¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³¹₃, -OCHX³¹₂, R³²-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³²-substituted or unsubstituted aryl (e.g., C₆-

C_{10} , C_{10} , or phenyl), or R^{32} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{31} is halogen. In embodiments, X^{31} is F.

[0286] In embodiments, R^2 is independently oxo, halogen, $-CX_3^2$, $-CHX_2^2$, $-OCH_2X^2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, -

- 5 SO_4H , $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -
 $NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX_3^2$, $-OCHX_2^2$, R^{33} -substituted or unsubstituted alkyl
(e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{33} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R^{33} -substituted or unsubstituted cycloalkyl
(e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{33} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R^{33} -substituted or unsubstituted aryl (e.g., C_6-
 C_{10} , C_{10} , or phenyl), or R^{33} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). In embodiments, R^2 is independently oxo,
- 10 halogen, $-CX_3^2$, $-CHX_2^2$, $-OCH_2X^2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, -
 SO_4H , $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -
- 15 $NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX_3^2$, $-OCHX_2^2$, R^{33} -substituted or unsubstituted alkyl
(e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{33} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R^{33} -substituted or unsubstituted cycloalkyl
(e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{33} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R^{33} -substituted or unsubstituted aryl (e.g., C_6-
 C_{10} , C_{10} , or phenyl), or R^{33} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X^2 is halogen. In embodiments, X^2 is F.

[0287] R^{33} is independently oxo,

halogen, $-CX_3^{33}$, $-CHX_2^{33}$, $-OCH_2X^{33}$, $-OCHX_2^{33}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, -S
 H , $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, -

- 25 $NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX_3^{33}$, $-OCHX_2^{33}$, R^{34} -substituted or
unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{34} -substituted or unsubstituted heteroalkyl
(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{34} -substituted or unsubstituted
cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{34} -substituted or unsubstituted heterocycloalkyl (e.g.,
3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{34} -substituted or unsubstituted aryl
(e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{34} -substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X^{33} is halogen. In embodiments, X^{33} is F.
- 30

[0288] R^{34} is independently oxo,

halogen, $-CX_3^{34}$, $-CHX_2^{34}$, $-OCH_2X^{34}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, -

SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³⁴₃, -OCHX³⁴₂, R³⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³⁴ is halogen. In embodiments, X³⁴ is F.

[0289] In embodiments, R³ is independently hydrogen, oxo,

halogen, -CX³₃, -CHX³₂, -OCH₂X³, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³₃, -OCHX³₂, R³⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³⁶-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁶-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³ is halogen. In embodiments, X³ is F.

[0290] R³⁶ is independently oxo,

halogen, -CX³⁶₃, -CHX³⁶₂, -OCH₂X³⁶, -OCHX³⁶₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³⁶₃, -OCHX³⁶₂, R³⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³⁶ is halogen. In embodiments, X³⁶ is F.

[0291] R³⁷ is independently oxo,

halogen, -CX³⁷₃, -CHX³⁷₂, -OCH₂X³⁷, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³⁷₃, -OCHX³⁷₂, R³⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, or 2 to 4 membered), R³⁸-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³⁷ is halogen. In embodiments, X³⁷ is F.

5 [0292] In embodiments, R⁴ is independently hydrogen, oxo, halogen, -CX⁴₃, -CHX⁴₂, -OCH₂X⁴, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴₃, -OCHX⁴₂, R³⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁴ is halogen. In embodiments, X⁴ is F.

10 [0293] R³⁹ is independently oxo, halogen, -CX³⁹₃, -CHX³⁹₂, -OCH₂X³⁹, -OCHX³⁹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³⁹₃, -OCHX³⁹₂, R⁴⁰-substituted or 15 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³⁹ is halogen. In embodiments, X³⁹ is F.

20 [0294] R⁴⁰ is independently oxo, halogen, -CX⁴⁰₃, -CHX⁴⁰₂, -OCH₂X⁴⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴⁰₃, -OCHX⁴⁰₂, R⁴¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀,

C₁₀, C₁₀, or phenyl), or R⁴¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁴⁰ is halogen. In embodiments, X⁴⁰ is F.

[0295] In embodiments, R⁵ is independently hydrogen, oxo, halogen, -CX⁵₃, -CHX⁵₂, -OCH₂X⁵, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

5 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵₃, -OCHX⁵₂, R⁴²-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁴²-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
10 membered, 3 to 6 membered, or 5 to 6 membered), R⁴²-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁴²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁵ is halogen. In embodiments, X⁵ is F.

[0296] R⁴² is independently oxo, halogen, -CX⁴²₃, -CHX⁴²₂, -OCH₂X⁴², -OCHX⁴²₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

15 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴²₃, -OCHX⁴²₂, R⁴³-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴³-substituted or unsubstituted heteroalkyl
(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴³-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴³-substituted or unsubstituted heterocycloalkyl (e.g.,
20 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴³-substituted or unsubstituted aryl
(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴³-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X⁴² is halogen. In embodiments, X⁴² is F.

[0297] R⁴³ is independently oxo,

halogen, -CX⁴³₃, -CHX⁴³₂, -OCH₂X⁴³, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

25 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴³₃, -OCHX⁴³₂, R⁴⁴-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁴-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁴-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁴-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
30 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁴-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁴⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁴³ is halogen. In embodiments, X⁴³ is F.

[0298] In embodiments, R⁶ is independently hydrogen, oxo, halogen, -CX⁶₃, -CHX⁶₂, -OCH₂X⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶₃, -OCHX⁶₂, R⁴⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁶ is halogen. In embodiments, X⁶ is F.

[0299] R⁴⁵ is independently oxo, halogen, -CX⁴⁵₃, -CHX⁴⁵₂, -OCH₂X⁴⁵, -OCHX⁴⁵₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴⁵₃, -OCHX⁴⁵₂, R⁴⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁶-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁶-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁴⁵ is halogen. In embodiments, X⁴⁵ is F.

[0300] R⁴⁶ is independently oxo, halogen, -CX⁴⁶₃, -CHX⁴⁶₂, -OCH₂X⁴⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴⁶₃, -OCHX⁴⁶₂, R⁴⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁴⁶ is halogen. In embodiments, X⁴⁶ is F.

[0301] In embodiments, R⁷ is independently hydrogen, oxo, halogen, -CX⁷₃, -CHX⁷₂, -OCH₂X⁷, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷₃, -OCHX⁷₂, R⁴⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁸-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷ is halogen. In embodiments, X⁷ is F.

[0302] R⁴⁸ is independently oxo,

halogen, -CX⁴⁸₃, -CHX⁴⁸₂, -OCH₂X⁴⁸, -OCHX⁴⁸₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴⁸₃, -OCHX⁴⁸₂, R⁴⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁴⁸ is halogen. In embodiments, X⁴⁸ is F.

[0303] R⁴⁹ is independently oxo,

halogen, -CX⁴⁹₃, -CHX⁴⁹₂, -OCH₂X⁴⁹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴⁹₃, -OCHX⁴⁹₂, R⁵⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁴⁹ is halogen. In embodiments, X⁴⁹ is F.

[0304] In embodiments, R⁸ is independently hydrogen, oxo,

halogen, -CX⁸₃, -CHX⁸₂, -OCH₂X⁸, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸₃, -OCHX⁸₂, R⁵¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵¹-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁸ is halogen. In embodiments, X⁸ is F.

- 5 [0305] R⁵¹ is independently oxo, halogen, -CX⁵¹₃, -CHX⁵¹₂, -OCH₂X⁵¹, -OCHX⁵¹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵¹₃, -OCHX⁵¹₂, R⁵²-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵²-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵¹ is halogen. In embodiments, X⁵¹ is F.
- 10 [0306] R⁵² is independently oxo, halogen, -CX⁵²₃, -CHX⁵²₂, -OCH₂X⁵², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵²₃, -OCHX⁵²₂, R⁵³-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵³-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵² is halogen. In embodiments, X⁵² is F.
- 15 [0307] In embodiments, R⁹ is independently hydrogen, oxo, halogen, -CX⁹₃, -CHX⁹₂, -OCH₂X⁹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹₃, -OCHX⁹₂, R⁵⁴-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁴-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁴-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁴-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁴-substituted or unsubstituted aryl (e.g., C₆-

C₁₀, C₁₀, or phenyl), or R⁵⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹ is halogen. In embodiments, X⁹ is F.

[0308] R⁵⁴ is independently oxo,

halogen, -CX⁵⁴₃, -CHX⁵⁴₂, -OCH₂X⁵⁴, -OCHX⁵⁴₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

5 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵⁴₃, -OCHX⁵⁴₂, R⁵⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁵-substituted or unsubstituted heterocycloalkyl (e.g., 10 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵⁴ is halogen. In embodiments, X⁵⁴ is F.

[0309] R⁵⁵ is independently oxo,

halogen, -CX⁵⁵₃, -CHX⁵⁵₂, -OCH₂X⁵⁵, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

15 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵⁵₃, -OCHX⁵⁵₂, R⁵⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁶-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁶-substituted or unsubstituted heterocycloalkyl (e.g., 20 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵⁵ is halogen. In embodiments, X⁵⁵ is F.

[0310] In embodiments, R¹⁰ is independently hydrogen, oxo,

halogen, -CX¹⁰₃, -CHX¹⁰₂, -OCH₂X¹⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

25 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁰₃, -OCHX¹⁰₂, R⁵⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁷-substituted or unsubstituted heterocycloalkyl (e.g., 30 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁰ is halogen. In embodiments, X¹⁰ is F.

[0311] R⁵⁷ is independently oxo,
 halogen, -CX⁵⁷₃, -CHX⁵⁷₂, -OCH₂X⁵⁷, -OCHX⁵⁷₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S
 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵⁷₃, -OCHX⁵⁷₂, R⁵⁸-substituted or

5 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁸-substituted or unsubstituted heteroalkyl
 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁸-substituted or unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁸-substituted or unsubstituted heterocycloalkyl (e.g.,
 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁸-substituted or unsubstituted aryl
 (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10
 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵⁷ is halogen. In embodiments, X⁵⁷ is F.

[0312] R⁵⁸ is independently oxo,
 halogen, -CX⁵⁸₃, -CHX⁵⁸₂, -OCH₂X⁵⁸, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵⁸₃, -OCHX⁵⁸₂, R⁵⁹-substituted or unsubstituted alkyl

15 (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁹-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁹-substituted or unsubstituted aryl (e.g., C₆-
 C₁₀, C₁₀, or phenyl), or R⁵⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
 20 membered, or 5 to 6 membered). X⁵⁸ is halogen. In embodiments, X⁵⁸ is F.

[0313] In embodiments, R^{7A} is independently hydrogen, oxo,
 halogen, -CX^{7A}₃, -CHX^{7A}₂, -OCH₂X^{7A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{7A}₃, -OCHX^{7A}₂, R^{48A}-substituted or unsubstituted

25 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{48A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R^{48A}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{48A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R^{48A}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{48A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5

30 to 9 membered, or 5 to 6 membered). In embodiments, R^{7A} is independently oxo,
 halogen, -CX^{7A}₃, -CHX^{7A}₂, -OCH₂X^{7A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{7A}₃, -OCHX^{7A}₂, R^{48A}-substituted or unsubstituted

alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{48A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{48A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{48A}-substituted or unsubstituted aryl (e.g., 5 C₆-C₁₀, C₁₀, or phenyl), or R^{48A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{7A} is halogen. In embodiments, X^{7A} is F.

[0314] R^{48A} is independently oxo,

halogen, -CX^{48A}₃, -CHX^{48A}₂, -OCH₂X^{48A}, -OCHX^{48A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂

, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -

10 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{48A}₃, -OCHX^{48A}₂, R^{49A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{49A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{49A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{49A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{49A}-substituted or unsubstituted aryl (e.g., 15 C₆-C₁₀, C₁₀, or phenyl), or R^{49A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{48A} is halogen. In embodiments, X^{48A} is F.

[0315] R^{49A} is independently oxo,

halogen, -CX^{49A}₃, -CHX^{49A}₂, -OCH₂X^{49A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

20 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{49A}₃, -OCHX^{49A}₂, R^{50A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{50A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{50A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{50A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{50A}-substituted or unsubstituted aryl (e.g., 25 C₆-C₁₀, C₁₀, or phenyl), or R^{50A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{49A} is halogen. In embodiments, X^{49A} is F.

[0316] In embodiments, R^{8A} is independently hydrogen, oxo,

halogen, -CX^{8A}₃, -CHX^{8A}₂, -OCH₂X^{8A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

30 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{8A}₃, -OCHX^{8A}₂, R^{51A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{51A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{51A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{51A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

membered, 3 to 6 membered, or 5 to 6 membered), R^{51A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{51A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{8A} is halogen. In embodiments, X^{8A} is F.

[0317] R^{51A} is independently oxo,

5 halogen, -CX^{51A}₃, -CHX^{51A}₂, -OCH₂X^{51A}, -OCHX^{51A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{51A}₃, -OCHX^{51A}₂, R^{52A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{52A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{52A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{52A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{52A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{52A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{51A} is halogen. In embodiments, X^{51A} is F.

[0318] R^{52A} is independently oxo,

15 halogen, -CX^{52A}₃, -CHX^{52A}₂, -OCH₂X^{52A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{52A}₃, -OCHX^{52A}₂, R^{53A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{53A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{53A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{53A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{53A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{53A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{52A} is halogen. In embodiments, X^{52A} is F.

[0319] In embodiments, R^{9A} is independently hydrogen, oxo,

25 halogen, -CX^{9A}₃, -CHX^{9A}₂, -OCH₂X^{9A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{9A}₃, -OCHX^{9A}₂, R^{54A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{54A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{54A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{54A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{54A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{54A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{9A} is halogen. In embodiments, X^{9A} is F.

[0320] R^{54A} is independently oxo, halogen, -CX^{54A}₃, -CHX^{54A}₂, -OCH₂X^{54A}, -OCHX^{54A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{54A}₃, -OCHX^{54A}₂, R^{55A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{55A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{55A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{55A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{55A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{55A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{54A} is halogen. In embodiments, X^{54A} is F.

[0321] R^{55A} is independently oxo, halogen, -CX^{55A}₃, -CHX^{55A}₂, -OCH₂X^{55A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{55A}₃, -OCHX^{55A}₂, R^{56A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{56A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{56A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{56A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{56A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{56A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{55A} is halogen. In embodiments, X^{55A} is F.

[0322] In embodiments, R^{10A} is independently hydrogen, oxo, halogen, -CX^{10A}₃, -CHX^{10A}₂, -OCH₂X^{10A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{10A}₃, -OCHX^{10A}₂, R^{57A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{57A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{57A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{57A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{57A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{57A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{10A} is halogen. In embodiments, X^{10A} is F.

[0323] R^{57A} is independently oxo, halogen, -CX^{57A}₃, -CHX^{57A}₂, -OCH₂X^{57A}, -OCHX^{57A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂,

NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{57A}₃, -OCHX^{57A}₂, R^{58A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{58A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{58A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{58A}-substituted or unsubstituted heterocycloalkyl (e.g., 5

3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{58A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{58A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{57A} is halogen. In embodiments, X^{57A} is F.

[0324] R^{58A} is independently oxo,

halogen, -CX^{58A}₃, -CHX^{58A}₂, -OCH₂X^{58A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{58A}₃, -OCHX^{58A}₂, R^{59A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{59A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{59A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{59A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{59A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{59A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{58A} is halogen. In embodiments, X^{58A} is F.

[0325] In embodiments, R^{7B} is independently hydrogen, oxo,

halogen, -CX^{7B}₃, -CHX^{7B}₂, -OCH₂X^{7B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{7B}₃, -OCHX^{7B}₂, R^{48B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{48B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{48B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{48B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{48B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7B} is independently oxo, halogen, -CX^{7B}₃, -CHX^{7B}₂, -OCH₂X^{7B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{7B}₃, -OCHX^{7B}₂, R^{48B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{48B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{48B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

membered, 3 to 6 membered, or 5 to 6 membered), R^{48B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{48B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{7B} is halogen. In embodiments, X^{7B} is F.

[0326] R^{48B} is independently oxo,

halogen, -CX^{48B}₃, -CHX^{48B}₂, -OCH₂X^{48B}, -OCHX^{48B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{48B}₃, -OCHX^{48B}₂, R^{49B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{49B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{49B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{49B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{49B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{49B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{48B} is halogen. In embodiments, X^{48B} is F.

[0327] R^{49B} is independently oxo,

halogen, -CX^{49B}₃, -CHX^{49B}₂, -OCH₂X^{49B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{49B}₃, -OCHX^{49B}₂, R^{50B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{50B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{50B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{50B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{50B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{50B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{49B} is halogen. In embodiments, X^{49B} is F.

[0328] In embodiments, R^{8B} is independently hydrogen, oxo,

halogen, -CX^{8B}₃, -CHX^{8B}₂, -OCH₂X^{8B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{8B}₃, -OCHX^{8B}₂, R^{51B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{51B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{51B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{51B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{51B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{51B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{8B} is halogen. In embodiments, X^{8B} is F.

[0329] R^{51B} is independently oxo,
 halogen, -CX^{51B}₃, -CHX^{51B}₂, -OCH₂X^{51B}, -OCHX^{51B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂
 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{51B}₃, -OCHX^{51B}₂, R^{52B}-substituted or

5 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{52B}-substituted or unsubstituted heteroalkyl
 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{52B}-substituted or unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{52B}-substituted or unsubstituted heterocycloalkyl (e.g.,
 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{52B}-substituted or unsubstituted aryl
 (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{52B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10
 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{51B} is halogen. In embodiments, X^{51B} is F.

[0330] R^{52B} is independently oxo,
 halogen, -CX^{52B}₃, -CHX^{52B}₂, -OCH₂X^{52B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{52B}₃, -OCHX^{52B}₂, R^{53B}-substituted or unsubstituted

15 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{53B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R^{53B}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{53B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R^{53B}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{53B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
 20 to 9 membered, or 5 to 6 membered). X^{52B} is halogen. In embodiments, X^{52B} is F.

[0331] In embodiments, R^{9B} is independently hydrogen, oxo,
 halogen, -CX^{9B}₃, -CHX^{9B}₂, -OCH₂X^{9B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{9B}₃, -OCHX^{9B}₂, R^{54B}-substituted or unsubstituted

25 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{54B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R^{54B}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{54B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R^{54B}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{54B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
 30 to 9 membered, or 5 to 6 membered). X^{9B} is halogen. In embodiments, X^{9B} is F.

[0332] R^{54B} is independently oxo,
 halogen, -CX^{54B}₃, -CHX^{54B}₂, -OCH₂X^{54B}, -OCHX^{54B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂
 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -

NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{54B}₃, -OCHX^{54B}₂, R^{55B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{55B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{55B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{55B}-substituted or unsubstituted heterocycloalkyl (e.g., 5

5 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{55B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{55B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{54B} is halogen. In embodiments, X^{54B} is F.

[0333] R^{55B} is independently oxo,

halogen, -CX^{55B}₃, -CHX^{55B}₂, -OCH₂X^{55B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

10 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{55B}₃, -OCHX^{55B}₂, R^{56B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{56B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{56B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{56B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{56B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{56B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{55B} is halogen. In embodiments, X^{55B} is F.

[0334] In embodiments, R^{10B} is independently hydrogen, oxo,

halogen, -CX^{10B}₃, -CHX^{10B}₂, -OCH₂X^{10B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

20 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{10B}₃, -OCHX^{10B}₂, R^{57B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{57B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{57B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{57B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{57B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{57B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{10B} is halogen. In embodiments, X^{10B} is F.

[0335] R^{57B} is independently oxo,

halogen, -CX^{57B}₃, -CHX^{57B}₂, -OCH₂X^{57B}, -OCHX^{57B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂,

30 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{57B}₃, -OCHX^{57B}₂, R^{58B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{58B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{58B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{58B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{58B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{57B} is halogen. In embodiments, X^{57B} is F.

cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{58B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{58B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{58B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{57B} is halogen. In embodiments, X^{57B} is F.

- 5 [0336] R^{58B} is independently oxo, halogen, -CX^{58B}₃, -CHX^{58B}₂, -OCH₂X^{58B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{58B}₃, -OCHX^{58B}₂, R^{59B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{59B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{59B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{59B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{59B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{59B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{58B} is halogen. In embodiments, X^{58B} is F.
- 10 [0337] In embodiments, R¹¹ is independently hydrogen, oxo, halogen, -CX¹¹₃, -CHX¹¹₂, -OCH₂X¹¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹¹₃, -OCHX¹¹₂, R⁶⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹¹ is halogen. In embodiments, X¹¹ is F.
- 15 [0338] R⁶⁰ is independently oxo, halogen, -CX⁶⁰₃, -CHX⁶⁰₂, -OCH₂X⁶⁰, -OCHX⁶⁰₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶⁰₃, -OCHX⁶⁰₂, R⁶¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶¹-substituted or unsubstituted aryl

(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁶⁰ is halogen. In embodiments, X⁶⁰ is F.

[0339] R⁶¹ is independently oxo,

halogen, -CX⁶¹₃, -CHX⁶¹₂, -OCH₂X⁶¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

- 5 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶¹₃, -OCHX⁶¹₂, R⁶²-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁶²-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R⁶²-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁶²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁶¹ is halogen. In embodiments, X⁶¹ is F.

[0340] In embodiments, R¹² is independently hydrogen, oxo,

halogen, -CX¹²₃, -CHX¹²₂, -OCH₂X¹², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

- 15 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹²₃, -OCHX¹²₂, R⁶³-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁶³-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R⁶³-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁶³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X¹² is halogen. In embodiments, X¹² is F.

[0341] R⁶³ is independently oxo,

halogen, -CX⁶³₃, -CHX⁶³₂, -OCH₂X⁶³, -OCHX⁶³₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

- 25 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶³₃, -OCHX⁶³₂, R⁶⁴-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁴-substituted or unsubstituted heteroalkyl
(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁴-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁴-substituted or unsubstituted heterocycloalkyl (e.g.,
3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁴-substituted or unsubstituted aryl
(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X⁶³ is halogen. In embodiments, X⁶³ is F.

[0342] R⁶⁴ is independently oxo, halogen, -CX⁶⁴₃, -CHX⁶⁴₂, -OCH₂X⁶⁴, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶⁴₃, -OCHX⁶⁴₂, R⁶⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁶⁴ is halogen. In embodiments, X⁶⁴ is F.

[0343] In embodiments, R¹³ is independently hydrogen, oxo, halogen, -CX¹³₃, -CHX¹³₂, -OCH₂X¹³, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹³₃, -OCHX¹³₂, R⁶⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁶-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁶-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹³ is halogen. In embodiments, X¹³ is F.

[0344] R⁶⁶ is independently oxo, halogen, -CX⁶⁶₃, -CHX⁶⁶₂, -OCH₂X⁶⁶, -OCHX⁶⁶₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶⁶₃, -OCHX⁶⁶₂, R⁶⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁶⁶ is halogen. In embodiments, X⁶⁶ is F.

[0345] R⁶⁷ is independently oxo, halogen, -CX⁶⁷₃, -CHX⁶⁷₂, -OCH₂X⁶⁷, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶⁷₃, -OCHX⁶⁷₂, R⁶⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁸-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁶⁷ is halogen. In embodiments, X⁶⁷ is F.

[0346] In embodiments, R¹⁴ is independently hydrogen, oxo, halogen, -CX¹⁴₃, -CHX¹⁴₂, -OCH₂X¹⁴, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁴₃, -OCHX¹⁴₂, R⁶⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁴ is halogen. In embodiments, X¹⁴ is F.

[0347] R⁶⁹ is independently oxo, halogen, -CX⁶⁹₃, -CHX⁶⁹₂, -OCH₂X⁶⁹, -OCHX⁶⁹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶⁹₃, -OCHX⁶⁹₂, R⁷⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁶⁹ is halogen. In embodiments, X⁶⁹ is F.

[0348] R⁷⁰ is independently oxo, halogen, -CX⁷⁰₃, -CHX⁷⁰₂, -OCH₂X⁷⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷⁰₃, -OCHX⁷⁰₂, R⁷¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷¹-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷⁰ is halogen. In embodiments, X⁷⁰ is F.

- 5 [0349] In embodiments, R¹⁵ is independently hydrogen, oxo, halogen, -CX¹⁵₃, -CHX¹⁵₂, -OCH₂X¹⁵, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁵₃, -OCHX¹⁵₂, R⁷²-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷²-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁵ is halogen. In embodiments, X¹⁵ is F.
- 10 [0350] R⁷² is independently oxo, halogen, -CX⁷²₃, -CHX⁷²₂, -OCH₂X⁷², -OCHX⁷²₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷²₃, -OCHX⁷²₂, R⁷³-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷³-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷² is halogen. In embodiments, X⁷² is F.
- 15 [0351] R⁷³ is independently oxo, halogen, -CX⁷³₃, -CHX⁷³₂, -OCH₂X⁷³, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷³₃, -OCHX⁷³₂, R⁷⁴-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁴-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁴-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁴-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁴-substituted or unsubstituted aryl (e.g., C₆-

C₁₀, C₁₀, or phenyl), or R⁷⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷³ is halogen. In embodiments, X⁷³ is F.

[0352] In embodiments, R¹⁶ is independently hydrogen, oxo, halogen, -CX¹⁶₃, -CHX¹⁶₂, -OCH₂X¹⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

5 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, - NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁶₃, -OCHX¹⁶₂, R⁷⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁶ is halogen. In embodiments, X¹⁶ is F.

[0353] R⁷⁵ is independently oxo,

halogen, -CX⁷⁵₃, -CHX⁷⁵₂, -OCH₂X⁷⁵, -OCHX⁷⁵₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

15 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, - NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷⁵₃, -OCHX⁷⁵₂, R⁷⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁶-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁶-substituted or unsubstituted heterocycloalkyl (e.g., 20 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷⁵ is halogen. In embodiments, X⁷⁵ is F.

[0354] R⁷⁶ is independently oxo,

halogen, -CX⁷⁶₃, -CHX⁷⁶₂, -OCH₂X⁷⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

25 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, - NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷⁶₃, -OCHX⁷⁶₂, R⁷⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷⁶ is halogen. In embodiments, X⁷⁶ is F.

[0355] In embodiments, R¹⁷ is independently hydrogen, oxo, halogen, -CX¹⁷₃, -CHX¹⁷₂, -OCH₂X¹⁷, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁷₃, -OCHX¹⁷₂, R⁷⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁸-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁷ is halogen. In embodiments, X¹⁷ is F.

[0356] R⁷⁸ is independently oxo, halogen, -CX⁷⁸₃, -CHX⁷⁸₂, -OCH₂X⁷⁸, -OCHX⁷⁸₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷⁸₃, -OCHX⁷⁸₂, R⁷⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷⁸ is halogen. In embodiments, X⁷⁸ is F.

[0357] R⁷⁹ is independently oxo, halogen, -CX⁷⁹₃, -CHX⁷⁹₂, -OCH₂X⁷⁹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷⁹₃, -OCHX⁷⁹₂, R⁸⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷⁹ is halogen. In embodiments, X⁷⁹ is F.

[0358] In embodiments, R¹⁸ is independently hydrogen, oxo, halogen, -CX¹⁸₃, -CHX¹⁸₂, -OCH₂X¹⁸, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁸₃, -OCHX¹⁸₂, R⁸¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁸ is halogen. In embodiments, X¹⁸ is F.

[0359] R⁸¹ is independently oxo,

halogen, -CX⁸¹₃, -CHX⁸¹₂, -OCH₂X⁸¹, -OCHX⁸¹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸¹₃, -OCHX⁸¹₂, R⁸²-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸²-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁸¹ is halogen. In embodiments, X⁸¹ is F.

[0360] R⁸² is independently oxo,

halogen, -CX⁸²₃, -CHX⁸²₂, -OCH₂X⁸², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸²₃, -OCHX⁸²₂, R⁸³-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸³-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁸² is halogen. In embodiments, X⁸² is F.

[0361] In embodiments, R¹⁹ is independently hydrogen, oxo,

halogen, -CX¹⁹₃, -CHX¹⁹₂, -OCH₂X¹⁹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁹₃, -OCHX¹⁹₂, R⁸⁴-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁴-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁴-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁴-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁴-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁹ is halogen. In embodiments, X¹⁹ is F.

- 5 [0362] R⁸⁴ is independently oxo,
halogen, -CX⁸⁴₃, -CHX⁸⁴₂, -OCH₂X⁸⁴, -OCHX⁸⁴₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S
H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸⁴₃, -OCHX⁸⁴₂, R⁸⁵-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁵-substituted or unsubstituted heteroalkyl
10 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁵-substituted or unsubstituted heterocycloalkyl (e.g.,
3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁵-substituted or unsubstituted aryl
(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X⁸⁴ is halogen. In embodiments, X⁸⁴ is F.
- 15 [0363] R⁸⁵ is independently oxo,
halogen, -CX⁸⁵₃, -CHX⁸⁵₂, -OCH₂X⁸⁵, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸⁵₃, -OCHX⁸⁵₂, R⁸⁶-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
20 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁶-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁶-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁶-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁸⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁸⁵ is halogen. In embodiments, X⁸⁵ is F.
- 25 [0364] In embodiments, R^{16A} is independently hydrogen, oxo,
halogen, -CX^{16A}₃, -CHX^{16A}₂, -OCH₂X^{16A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{16A}₃, -OCHX^{16A}₂, R^{75A}-substituted or unsubstituted
alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{75A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
30 membered, 2 to 6 membered, or 2 to 4 membered), R^{75A}-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{75A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R^{75A}-substituted or unsubstituted aryl (e.g.,

C_6-C_{10} , C_{10} , or phenyl), or R^{75A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{16A} is halogen. In embodiments, X^{16A} is F.

[0365] R^{75A} is independently oxo,

halogen, $-CX^{75A}_3$, $-CHX^{75A}_2$, $-OCH_2X^{75A}$, $-OCHX^{75A}_2$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂

- 5 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{75A}₃, $-OCHX^{75A}_2$, R^{76A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{76A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{76A} -substituted or unsubstituted heterocycloalkyl (e.g., 10 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{76A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{76A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{75A} is halogen. In embodiments, X^{75A} is F.

[0366] R^{76A} is independently oxo,

halogen, $-CX^{76A}_3$, $-CHX^{76A}_2$, $-OCH_2X^{76A}$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

- 15 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{76A}₃, $-OCHX^{76A}_2$, R^{77A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{77A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{77A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{77A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 20 membered, 3 to 6 membered, or 5 to 6 membered), R^{77A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{77A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{76A} is halogen. In embodiments, X^{76A} is F.

[0367] In embodiments, R^{17A} is independently hydrogen, oxo,

halogen, $-CX^{17A}_3$, $-CHX^{17A}_2$, $-OCH_2X^{17A}$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

- 25 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{17A}₃, $-OCHX^{17A}_2$, R^{78A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{78A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{78A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{78A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 30 membered, 3 to 6 membered, or 5 to 6 membered), R^{78A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{78A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{17A} is halogen. In embodiments, X^{17A} is F.

[0368] R^{78A} is independently oxo, halogen, -CX^{78A}₃, -CHX^{78A}₂, -OCH₂X^{78A}, -OCHX^{78A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{78A}₃, -OCHX^{78A}₂, R^{79A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{79A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{79A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{79A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{78A} is halogen. In embodiments, X^{78A} is F.

[0369] R^{79A} is independently oxo, halogen, -CX^{79A}₃, -CHX^{79A}₂, -OCH₂X^{79A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{79A}₃, -OCHX^{79A}₂, R^{80A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{80A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{80A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{80A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79A} is halogen. In embodiments, X^{79A} is F.

[0370] In embodiments, R^{18A} is independently hydrogen, oxo, halogen, -CX^{18A}₃, -CHX^{18A}₂, -OCH₂X^{18A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{18A}₃, -OCHX^{18A}₂, R^{81A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{81A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{81A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{81A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{81A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{81A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18A} is halogen. In embodiments, X^{18A} is F.

[0371] R^{81A} is independently oxo, halogen, -CX^{81A}₃, -CHX^{81A}₂, -OCH₂X^{81A}, -OCHX^{81A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂,

NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{81A}₃, -OCHX^{81A}₂, R^{82A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{82A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{82A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{82A}-substituted or unsubstituted heterocycloalkyl (e.g., 5 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{82A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81A} is halogen. In embodiments, X^{81A} is F.

[0372] R^{82A} is independently oxo,

halogen, -CX^{82A}₃, -CHX^{82A}₂, -OCH₂X^{82A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{82A}₃, -OCHX^{82A}₂, R^{83A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{83A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{83A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{83A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{83A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{83A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{82A} is halogen. In embodiments, X^{82A} is F.

[0373] In embodiments, R^{19A} is independently hydrogen, oxo,

halogen, -CX^{19A}₃, -CHX^{19A}₂, -OCH₂X^{19A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{19A}₃, -OCHX^{19A}₂, R^{84A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{84A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{84A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{84A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{84A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{84A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{19A} is halogen. In embodiments, X^{19A} is F.

[0374] R^{84A} is independently oxo,

halogen, -CX^{84A}₃, -CHX^{84A}₂, -OCH₂X^{84A}, -OCHX^{84A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂,

, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{84A}₃, -OCHX^{84A}₂, R^{85A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{85A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{85A}-substituted or unsubstituted heterocycloalkyl

cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{85A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{85A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{85A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{84A} is halogen. In embodiments, X^{84A} is F.

- 5 [0375] R^{85A} is independently oxo,
 halogen, -CX^{85A}₃, -CHX^{85A}₂, -OCH₂X^{85A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{85A}₃, -OCHX^{85A}₂, R^{86A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{86A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{86A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{86A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{86A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{86A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{85A} is halogen. In embodiments, X^{85A} is F.

- 10 [0376] In embodiments, R^{16B} is independently hydrogen, oxo,
 halogen, -CX^{16B}₃, -CHX^{16B}₂, -OCH₂X^{16B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{16B}₃, -OCHX^{16B}₂, R^{75B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{75B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{75B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{75B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{75B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{75B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{16B} is halogen. In embodiments, X^{16B} is F.

- 20 [0377] R^{75B} is independently oxo,
 halogen, -CX^{75B}₃, -CHX^{75B}₂, -OCH₂X^{75B}, -OCHX^{75B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{75B}₃, -OCHX^{75B}₂, R^{76B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{76B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{76B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{76B}-substituted or unsubstituted aryl

(e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{76B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{75B} is halogen. In embodiments, X^{75B} is F.

[0378] R^{76B} is independently oxo,

halogen, -CX^{76B}₃, -CHX^{76B}₂, -OCH₂X^{76B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

5 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{76B}₃, -OCHX^{76B}₂, R^{77B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{77B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{77B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{77B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{77B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{77B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{76B} is halogen. In embodiments, X^{76B} is F.

[0379] In embodiments, R^{17B} is independently hydrogen, oxo,

halogen, -CX^{17B}₃, -CHX^{17B}₂, -OCH₂X^{17B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

15 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{17B}₃, -OCHX^{17B}₂, R^{78B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{78B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{78B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{78B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{78B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{78B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{17B} is halogen. In embodiments, X^{17B} is F.

[0380] R^{78B} is independently oxo,

halogen, -CX^{78B}₃, -CHX^{78B}₂, -OCH₂X^{78B}, -OCHX^{78B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂

25 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{78B}₃, -OCHX^{78B}₂, R^{79B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{79B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{79B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{79B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{78B} is halogen. In embodiments, X^{78B} is F.

[0381] R^{79B} is independently oxo,
halogen, -CX^{79B}₃, -CHX^{79B}₂, -OCH₂X^{79B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{79B}₃, -OCHX^{79B}₂, R^{80B}-substituted or unsubstituted
5 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{80B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{80B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{80B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79B} is halogen. In embodiments, X^{79B} is F.

[0382] In embodiments, R^{18B} is independently hydrogen, oxo,
halogen, -CX^{18B}₃, -CHX^{18B}₂, -OCH₂X^{18B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{18B}₃, -OCHX^{18B}₂, R^{81B}-substituted or unsubstituted
15 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{81B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{81B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{81B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{81B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{81B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18B} is halogen. In embodiments, X^{18B} is F.

[0383] R^{81B} is independently oxo,
halogen, -CX^{81B}₃, -CHX^{81B}₂, -OCH₂X^{81B}, -OCHX^{81B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{81B}₃, -OCHX^{81B}₂, R^{82B}-substituted or
25 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{82B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{82B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{82B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{82B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81B} is halogen. In embodiments, X^{81B} is F.

[0384] R^{82B} is independently oxo,
halogen, -CX^{82B}₃, -CHX^{82B}₂, -OCH₂X^{82B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{82B}₃, -OCHX^{82B}₂, R^{83B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{83B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{83B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{83B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{83B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{83B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{82B} is halogen. In embodiments, X^{82B} is F.

[0385] In embodiments, R^{19B} is independently hydrogen, oxo, halogen, -CX^{19B}₃, -CHX^{19B}₂, -OCH₂X^{19B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{19B}₃, -OCHX^{19B}₂, R^{84B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{84B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{84B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{84B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{84B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{84B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{19B} is halogen. In embodiments, X^{19B} is F.

[0386] R^{84B} is independently oxo, halogen, -CX^{84B}₃, -CHX^{84B}₂, -OCH₂X^{84B}, -OCHX^{84B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{84B}₃, -OCHX^{84B}₂, R^{85B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{85B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{85B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{85B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{85B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{85B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{84B} is halogen. In embodiments, X^{84B} is F.

[0387] R^{85B} is independently oxo, halogen, -CX^{85B}₃, -CHX^{85B}₂, -OCH₂X^{85B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{85B}₃, -OCHX^{85B}₂, R^{86B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{86B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{86B}-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{86B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{86B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{86B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{85B} is halogen. In embodiments, X^{85B} is F.

- 5 [0388] In embodiments, R^{16C} is independently hydrogen, oxo, halogen, -CX^{16C}₃, -CHX^{16C}₂, -OCH₂X^{16C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{16C}₃, -OCHX^{16C}₂, R^{75C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{75C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{75C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{75C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{75C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{75C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{16C} is halogen. In embodiments, X^{16C} is F.
- 10 [0389] R^{75C} is independently oxo, halogen, -CX^{75C}₃, -CHX^{75C}₂, -OCH₂X^{75C}, -OCHX^{75C}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{75C}₃, -OCHX^{75C}₂, R^{76C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{76C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{76C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{76C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{76C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{75C} is halogen. In embodiments, X^{75C} is F.
- 15 [0390] R^{76C} is independently oxo, halogen, -CX^{76C}₃, -CHX^{76C}₂, -OCH₂X^{76C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{76C}₃, -OCHX^{76C}₂, R^{77C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{77C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{77C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{77C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{77C}-substituted or unsubstituted aryl (e.g.,
- 20
- 25
- 30

C₆-C₁₀, C₁₀, or phenyl), or R^{77C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{76C} is halogen. In embodiments, X^{76C} is F.

[0391] In embodiments, R^{17C} is independently hydrogen, oxo,

halogen, -CX^{17C}₃, -CHX^{17C}₂, -OCH₂X^{17C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

5 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{17C}₃, -OCHX^{17C}₂, R^{78C}-substituted or unsubstituted
alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{78C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R^{78C}-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{78C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
10 membered, 3 to 6 membered, or 5 to 6 membered), R^{78C}-substituted or unsubstituted aryl (e.g.,
C₆-C₁₀, C₁₀, or phenyl), or R^{78C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
to 9 membered, or 5 to 6 membered). X^{17C} is halogen. In embodiments, X^{17C} is F.

[0392] R^{78C} is independently oxo,

halogen, -CX^{78C}₃, -CHX^{78C}₂, -OCH₂X^{78C}, -OCHX^{78C}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂

15 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{78C}₃, -OCHX^{78C}₂, R^{79C}-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{79C}-substituted or unsubstituted heteroalkyl
(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79C}-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{79C}-substituted or unsubstituted heterocycloalkyl (e.g.,
20 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79C}-substituted or unsubstituted aryl
(e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{79C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X^{78C} is halogen. In embodiments, X^{78C} is F.

[0393] R^{79C} is independently oxo,

halogen, -CX^{79C}₃, -CHX^{79C}₂, -OCH₂X^{79C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

25 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{79C}₃, -OCHX^{79C}₂, R^{80C}-substituted or unsubstituted
alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{80C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R^{80C}-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{80C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
30 membered, 3 to 6 membered, or 5 to 6 membered), R^{80C}-substituted or unsubstituted aryl (e.g.,
C₆-C₁₀, C₁₀, or phenyl), or R^{80C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
to 9 membered, or 5 to 6 membered). X^{79C} is halogen. In embodiments, X^{79C} is F.

[0394] In embodiments, R^{18C} is independently hydrogen, oxo, halogen, -CX^{18C}₃, -CHX^{18C}₂, -OCH₂X^{18C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{18C}₃, -OCHX^{18C}₂, R^{81C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{81C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{81C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{81C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{81C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{81C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18C} is halogen. In embodiments, X^{18C} is F.

[0395] R^{81C} is independently oxo, halogen, -CX^{81C}₃, -CHX^{81C}₂, -OCH₂X^{81C}, -OCHX^{81C}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{81C}₃, -OCHX^{81C}₂, R^{82C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{82C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{82C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{82C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{82C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81C} is halogen. In embodiments, X^{81C} is F.

[0396] R^{82C} is independently oxo, halogen, -CX^{82C}₃, -CHX^{82C}₂, -OCH₂X^{82C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{82C}₃, -OCHX^{82C}₂, R^{83C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{83C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{83C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{83C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{83C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{83C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{82C} is halogen. In embodiments, X^{82C} is F.

[0397] In embodiments, R^{19C} is independently hydrogen, oxo, halogen, -CX^{19C}₃, -CHX^{19C}₂, -OCH₂X^{19C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{19C}₃, -OCHX^{19C}₂, R^{84C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{84C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{84C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{84C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{84C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{84C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{19C} is halogen. In embodiments, X^{19C} is F.

[0398] R^{84C} is independently oxo,

halogen, -CX^{84C}₃, -CHX^{84C}₂, -OCH₂X^{84C}, -OCHX^{84C}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{84C}₃, -OCHX^{84C}₂, R^{85C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{85C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{85C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{85C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{85C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{85C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{84C} is halogen. In embodiments, X^{84C} is F.

[0399] R^{85C} is independently oxo,

halogen, -CX^{85C}₃, -CHX^{85C}₂, -OCH₂X^{85C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{85C}₃, -OCHX^{85C}₂, R^{86C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{86C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{86C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{86C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{86C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{86C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{85C} is halogen. In embodiments, X^{85C} is F.

[0400] In embodiments, R^{16D} is independently hydrogen, oxo,

halogen, -CX^{16D}₃, -CHX^{16D}₂, -OCH₂X^{16D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{16D}₃, -OCHX^{16D}₂, R^{75D}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{75D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{75D}-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{75D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{75D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{75D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{16D} is halogen. In embodiments, X^{16D} is F.

- 5 [0401] R^{75D} is independently oxo,
halogen, -CX^{75D}₃, -CHX^{75D}₂, -OCH₂X^{75D}, -OCHX^{75D}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂,
, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{75D}₃, -OCHX^{75D}₂, R^{76D}-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{76D}-substituted or unsubstituted heteroalkyl
10 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76D}-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{76D}-substituted or unsubstituted heterocycloalkyl (e.g.,
3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{76D}-substituted or unsubstituted aryl
(e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{76D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X^{75D} is halogen. In embodiments, X^{75D} is F.
- 15 [0402] R^{76D} is independently oxo,
halogen, -CX^{76D}₃, -CHX^{76D}₂, -OCH₂X^{76D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{76D}₃, -OCHX^{76D}₂, R^{77D}-substituted or unsubstituted
alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{77D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
20 membered, 2 to 6 membered, or 2 to 4 membered), R^{77D}-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{77D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R^{77D}-substituted or unsubstituted aryl (e.g.,
C₆-C₁₀, C₁₀, or phenyl), or R^{77D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
to 9 membered, or 5 to 6 membered). X^{76D} is halogen. In embodiments, X^{76D} is F.
- 25 [0403] In embodiments, R^{17D} is independently hydrogen, oxo,
halogen, -CX^{17D}₃, -CHX^{17D}₂, -OCH₂X^{17D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{17D}₃, -OCHX^{17D}₂, R^{78D}-substituted or unsubstituted
alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{78D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
30 membered, 2 to 6 membered, or 2 to 4 membered), R^{78D}-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{78D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R^{78D}-substituted or unsubstituted aryl (e.g.,

C_6-C_{10} , C_{10} , or phenyl), or R^{78D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{17D} is halogen. In embodiments, X^{17D} is F.

[0404] R^{78D} is independently oxo,

halogen, $-CX^{78D}_3$, $-CHX^{78D}_2$, $-OCH_2X^{78D}$, $-OCHX^{78D}_2$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂

5 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{78D}₃, $-OCHX^{78D}_2$, R^{79D} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{79D} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79D} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{79D} -substituted or unsubstituted heterocycloalkyl (e.g., 10 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79D} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{79D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{78D} is halogen. In embodiments, X^{78D} is F.

[0405] R^{79D} is independently oxo,

halogen, $-CX^{79D}_3$, $-CHX^{79D}_2$, $-OCH_2X^{79D}$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

15 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{79D}₃, $-OCHX^{79D}_2$, R^{80D} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{80D} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80D} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{80D} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 20 membered, 3 to 6 membered, or 5 to 6 membered), R^{80D} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{80D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79D} is halogen. In embodiments, X^{79D} is F.

[0406] In embodiments, R^{18D} is independently hydrogen, oxo,

halogen, $-CX^{18D}_3$, $-CHX^{18D}_2$, $-OCH_2X^{18D}$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

25 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{18D}₃, $-OCHX^{18D}_2$, R^{81D} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{81D} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{81D} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{81D} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 30 membered, 3 to 6 membered, or 5 to 6 membered), R^{81D} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{81D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18D} is halogen. In embodiments, X^{18D} is F.

[0407] R^{81D} is independently oxo,
 halogen, -CX^{81D}₃, -CHX^{81D}₂, -OCH₂X^{81D}, -OCHX^{81D}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂
 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{81D}₃, -OCHX^{81D}₂, R^{82D}-substituted or
 5 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{82D}-substituted or unsubstituted heteroalkyl
 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{82D}-substituted or unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{82D}-substituted or unsubstituted heterocycloalkyl (e.g.,
 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82D}-substituted or unsubstituted aryl
 (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{82D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10
 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81D} is halogen. In embodiments, X^{81D} is F.

[0408] R^{82D} is independently oxo,
 halogen, -CX^{82D}₃, -CHX^{82D}₂, -OCH₂X^{82D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{82D}₃, -OCHX^{82D}₂, R^{83D}-substituted or unsubstituted
 15 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{83D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R^{83D}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{83D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R^{83D}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{83D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
 20 to 9 membered, or 5 to 6 membered). X^{82D} is halogen. In embodiments, X^{82D} is F.

[0409] In embodiments, R^{19D} is independently hydrogen, oxo,
 halogen, -CX^{19D}₃, -CHX^{19D}₂, -OCH₂X^{19D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{19D}₃, -OCHX^{19D}₂, R^{84D}-substituted or unsubstituted
 25 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{84D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R^{84D}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{84D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R^{84D}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{84D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
 30 to 9 membered, or 5 to 6 membered). X^{19D} is halogen. In embodiments, X^{19D} is F.

[0410] R^{84D} is independently oxo,
 halogen, -CX^{84D}₃, -CHX^{84D}₂, -OCH₂X^{84D}, -OCHX^{84D}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂
 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -

NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{84D}₃, -OCHX^{84D}₂, R^{85D}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{85D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{85D}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{85D}-substituted or unsubstituted heterocycloalkyl (e.g.,

5 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{85D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{85D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{84D} is halogen. In embodiments, X^{84D} is F.

[0411] R^{85D} is independently oxo,

halogen, -CX^{85D}₃, -CHX^{85D}₂, -OCH₂X^{85D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

10 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{85D}₃, -OCHX^{85D}₂, R^{86D}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{86D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{86D}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{86D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

15 membered, 3 to 6 membered, or 5 to 6 membered), R^{86D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{86D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{85D} is halogen. In embodiments, X^{85D} is F.

[0412] In embodiments, R²⁰ is independently hydrogen, oxo,

halogen, -CX²⁰₃, -CHX²⁰₂, -OCH₂X²⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

20 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²⁰₃, -OCHX²⁰₂, R⁸⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

25 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²⁰ is halogen. In embodiments, X²⁰ is F.

[0413] R⁸⁷ is independently oxo,

halogen, -CX⁸⁷₃, -CHX⁸⁷₂, -OCH₂X⁸⁷, -OCHX⁸⁷₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

30 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸⁷₃, -OCHX⁸⁷₂, R⁸⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁸-substituted or unsubstituted

cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁸⁷ is halogen. In embodiments, X⁸⁷ is F.

- 5 [0414] R⁸⁸ is independently oxo,
halogen, -CX⁸⁸₃, -CHX⁸⁸₂, -OCH₂X⁸⁸, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸⁸₃, -OCHX⁸⁸₂, R⁸⁹-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
10 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁹-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁹-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁸⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁸⁸ is halogen. In embodiments, X⁸⁸ is F.
- 15 [0415] In embodiments, R²¹ is independently hydrogen, oxo,
halogen, -CX²¹₃, -CHX²¹₂, -OCH₂X²¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²¹₃, -OCHX²¹₂, R⁹⁰-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
20 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁰-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁰-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁹⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X²¹ is halogen. In embodiments, X²¹ is F.
- 25 [0416] R⁹⁰ is independently oxo,
halogen, -CX⁹⁰₃, -CHX⁹⁰₂, -OCH₂X⁹⁰, -OCHX⁹⁰₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S
H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹⁰₃, -OCHX⁹⁰₂, R⁹¹-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹¹-substituted or unsubstituted heteroalkyl
30 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹¹-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹¹-substituted or unsubstituted heterocycloalkyl (e.g.,
3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹¹-substituted or unsubstituted aryl

(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹⁰ is halogen. In embodiments, X⁹⁰ is F.

[0417] R⁹¹ is independently oxo,

halogen, -CX⁹¹₃, -CHX⁹¹₂, -OCH₂X⁹¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

5 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹¹₃, -OCHX⁹¹₂, R⁹²-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁹²-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
10 membered, 3 to 6 membered, or 5 to 6 membered), R⁹²-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁹²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁹¹ is halogen. In embodiments, X⁹¹ is F.

[0418] In embodiments, R²² is independently hydrogen, oxo,

halogen, -CX²²₃, -CHX²²₂, -OCH₂X²², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

15 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²²₃, -OCHX²²₂, R⁹³-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁹³-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
20 membered, 3 to 6 membered, or 5 to 6 membered), R⁹³-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁹³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X²² is halogen. In embodiments, X²² is F.

[0419] R⁹³ is independently oxo,

halogen, -CX⁹³₃, -CHX⁹³₂, -OCH₂X⁹³, -OCHX⁹³₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

25 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹³₃, -OCHX⁹³₂, R⁹⁴-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁴-substituted or unsubstituted heteroalkyl
(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁴-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁴-substituted or unsubstituted heterocycloalkyl (e.g.,
30 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁴-substituted or unsubstituted aryl
(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X⁹³ is halogen. In embodiments, X⁹³ is F.

[0420] R⁹⁴ is independently oxo, halogen, -CX⁹⁴₃, -CHX⁹⁴₂, -OCH₂X⁹⁴, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹⁴₃, -OCHX⁹⁴₂, R⁹⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹⁴ is halogen. In embodiments, X⁹⁴ is F.

[0421] In embodiments, R²³ is independently hydrogen, oxo, halogen, -CX²³₃, -CHX²³₂, -OCH₂X²³, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²³₃, -OCHX²³₂, R⁹⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁶-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁶-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²³ is halogen. In embodiments, X²³ is F.

[0422] R⁹⁶ is independently oxo, halogen, -CX⁹⁶₃, -CHX⁹⁶₂, -OCH₂X⁹⁶, -OCHX⁹⁶₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹⁶₃, -OCHX⁹⁶₂, R⁹⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹⁶ is halogen. In embodiments, X⁹⁶ is F.

[0423] R⁹⁷ is independently oxo, halogen, -CX⁹⁷₃, -CHX⁹⁷₂, -OCH₂X⁹⁷, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹⁷₃, -OCHX⁹⁷₂, R⁹⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁸-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹⁷ is halogen. In embodiments, X⁹⁷ is F.

[0424] In embodiments, R²⁴ is independently hydrogen, oxo, halogen, -CX²⁴₃, -CHX²⁴₂, -OCH₂X²⁴, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²⁴₃, -OCHX²⁴₂, R⁹⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²⁴ is halogen. In embodiments, X²⁴ is F.

[0425] R⁹⁹ is independently oxo, halogen, -CX⁹⁹₃, -CHX⁹⁹₂, -OCH₂X⁹⁹, -OCHX⁹⁹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹⁹₃, -OCHX⁹⁹₂, R¹⁰⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R¹⁰⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R¹⁰⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R¹⁰⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R¹⁰⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R¹⁰⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹⁹ is halogen. In embodiments, X⁹⁹ is F.

[0426] R¹⁰⁰ is independently oxo, halogen, -CX¹⁰⁰₃, -CHX¹⁰⁰₂, -OCH₂X¹⁰⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁰⁰₃, -OCHX¹⁰⁰₂, R¹⁰¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R¹⁰¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R¹⁰¹-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R¹⁰¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R¹⁰¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R¹⁰¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁰⁰ is halogen. In embodiments, X¹⁰⁰ is F.

- 5 [0427] R³², R³⁵, R³⁸, R⁴¹, R⁴⁴, R⁴⁷, R⁵⁰, R⁵³, R⁵⁶, R⁵⁹, R^{50A}, R^{53A}, R^{56A}, R^{59A}, R^{50B}, R^{53B}, R^{56B}, R^{59B}, R⁶², R⁶⁵, R⁶⁸, R⁷¹, R⁷⁴, R⁷⁷, R⁸⁰, R⁸³, R⁸⁶, R^{77A}, R^{80A}, R^{83A}, R^{86A}, R^{77B}, R^{80B}, R^{83B}, R^{86B}, R^{77C}, R^{80C}, R^{83C}, R^{86C}, R^{77D}, R^{80D}, R^{83D}, R^{86D}, R⁸⁹, R⁹², R⁹⁵, R⁹⁸, and R¹⁰¹ are independently hydrogen, oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). R³², R³⁵, R³⁸, R⁴¹, R⁴⁴, R⁴⁷, R⁵⁰, R⁵³, R⁵⁶, R⁵⁹, R^{50A}, R^{53A}, R^{56A}, R^{59A}, R^{50B}, R^{53B}, R^{56B}, R^{59B}, R⁶², R⁶⁵, R⁶⁸, R⁷¹, R⁷⁴, R⁷⁷, R⁸⁰, R⁸³, R⁸⁶, R^{77A}, R^{80A}, R^{83A}, R^{86A}, R^{77B}, R^{80B}, R^{83B}, R^{86B}, R^{77C}, R^{80C}, R^{83C}, R^{86C}, R^{77D}, R^{80D}, R^{83D}, R^{86D}, R⁸⁹, R⁹², R⁹⁵, R⁹⁸, and R¹⁰¹ are independently oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
- 10 [0428] In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a single stereoisomer. In embodiments, unless otherwise indicated, a compound described herein is a single enantiomer.
- 15 [0429] In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a single stereoisomer. In embodiments, unless otherwise indicated, a compound described herein is a single enantiomer.
- 20 [0430] In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a single stereoisomer. In embodiments, unless otherwise indicated, a compound described herein is a single enantiomer.
- 25 [0431] In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a single stereoisomer. In embodiments, unless otherwise indicated, a compound described herein is a single enantiomer.
- 30 [0432] In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a single stereoisomer. In embodiments, unless otherwise indicated, a compound described herein is a single enantiomer.

[0429] In embodiments, the compound inhibits proliferation of cancer cells under nutrient deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under nutrient deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under nutrient

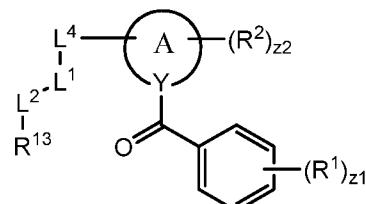
- 5 deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under serum deprivation conditions relative to the absence of the compound. In embodiments, the compound inhibits proliferation of cancer cells under serum deprivation conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under conditions (e.g. local cell environment in a patient)
10 mimicking serum deprivation relative to the absence of the compound. In embodiments, the compound inhibits proliferation of cancer cells under conditions (e.g. local cell environment in a patient) mimicking serum deprivation relative to the absence of the compound.

[0430] In some embodiments, the compound is any one of the compounds described herein (e.g., in an aspect, embodiment, claim, figure, table, or example).

- 15 **[0431]** In some embodiments, a compound as described herein may include multiple instances of R¹, R², R⁷, R⁸, R⁹, R¹⁰, X, X¹, X², m¹, n¹, v¹, m², n², v², and/or other variables. In such embodiments, each variable may optional be different and be appropriately labeled to distinguish each group for greater clarity. For example, where each R¹, R², R⁷, R⁸, R⁹, R¹⁰, X, X¹, X², m¹, n¹, v¹, m², n², and/or v², is different, they may be referred to, for example, as R^{1.1}, R^{1.2}, R^{1.3}, R^{1.4}, R^{1.5}, R^{1.6}, R^{1.7}, R^{2.1}, R^{2.2}, R^{2.3}, R^{2.4}, R^{2.5}, R^{2.6}, R^{2.7}, R^{2.8}, R^{2.9}, R^{2.10}, R^{7.1}, R^{7.2}, R^{7.3}, R^{7.4}, R^{7.5}, R^{7.6}, R^{7.7}, R^{8.1}, R^{8.2}, R^{8.3}, R^{8.4}, R^{8.5}, R^{8.6}, R^{8.7}, R^{9.1}, R^{9.2}, R^{9.3}, R^{9.4}, R^{9.5}, R^{9.6}, R^{9.7}, R^{10.1}, R^{10.2}, R^{10.3}, R^{10.4}, R^{10.5}, R^{10.6}, R^{10.7}, X¹, X², X³, X⁴, X⁵, X⁶, X⁷, X^{1.1}, X^{1.2}, X^{1.3}, X^{1.4}, X^{1.5}, X^{1.6}, X^{2.1}, X^{2.2}, X^{2.3}, X^{2.4}, X^{2.5}, X^{2.6}, X^{2.7}, X^{2.8}, X^{2.9}, X^{2.10}, m¹, m², m³, m⁴, m⁵, m⁶, m⁷, n¹, n², n³, n⁴, n⁵, n⁶, n⁷, v¹, v², v³, v⁴, v⁵, v⁶, v⁷, m^{1.1}, m^{1.2}, m^{1.3}, m^{1.4}, m^{1.5}, m^{1.6}, n^{1.1}, n^{1.2}, n^{1.3}, n^{1.4}, n^{1.5}, n^{1.6}, v^{1.1}, v^{1.2}, v^{1.3}, v^{1.4}, v^{1.5}, v^{1.6}, v^{1.7}, v^{1.8}, v^{1.9}, v^{1.10}, v^{1.11}, v^{1.12}, v^{1.13}, v^{1.14}, v^{1.15}, v^{1.16}, v^{1.17}, v^{1.18}, v^{1.19}, v^{1.20}, v^{1.21}, v^{1.22}, v^{1.23}, v^{1.24}, v^{1.25}, v^{1.26}, v^{1.27}, v^{1.28}, v^{1.29}, v^{1.30}, v^{1.31}, v^{1.32}, v^{1.33}, v^{1.34}, v^{1.35}, v^{1.36}, v^{1.37}, v^{1.38}, v^{1.39}, v^{1.40}, v^{1.41}, v^{1.42}, v^{1.43}, v^{1.44}, v^{1.45}, v^{1.46}, v^{1.47}, v^{1.48}, v^{1.49}, v^{1.50}, v^{1.51}, v^{1.52}, v^{1.53}, v^{1.54}, v^{1.55}, v^{1.56}, v^{1.57}, v^{1.58}, v^{1.59}, v^{1.60}, v^{1.61}, v^{1.62}, v^{1.63}, v^{1.64}, v^{1.65}, v^{1.66}, v^{1.67}, v^{1.68}, v^{1.69}, v^{1.70}, v^{1.71}, v^{1.72}, v^{1.73}, v^{1.74}, v^{1.75}, v^{1.76}, v^{1.77}, v^{1.78}, v^{1.79}, v^{1.80}, v^{1.81}, v^{1.82}, v^{1.83}, v^{1.84}, v^{1.85}, v^{1.86}, v^{1.87}, v^{1.88}, v^{1.89}, v^{1.90}, v^{1.91}, v^{1.92}, v^{1.93}, v^{1.94}, v^{1.95}, v^{1.96}, v^{1.97}, v^{1.98}, v^{1.99}, v^{1.100}, v^{1.101}, v^{1.102}, v^{1.103}, v^{1.104}, v^{1.105}, v^{1.106}, v^{1.107}, v^{1.108}, v^{1.109}, v^{1.110}, v^{1.111}, v^{1.112}, v^{1.113}, v^{1.114}, v^{1.115}, v^{1.116}, v^{1.117}, v^{1.118}, v^{1.119}, v^{1.120}, v^{1.121}, v^{1.122}, v^{1.123}, v^{1.124}, v^{1.125}, v^{1.126}, v^{1.127}, v^{1.128}, v^{1.129}, v^{1.130}, v^{1.131}, v^{1.132}, v^{1.133}, v^{1.134}, v^{1.135}, v^{1.136}, v^{1.137}, v^{1.138}, v^{1.139}, v^{1.140}, v^{1.141}, v^{1.142}, v^{1.143}, v^{1.144}, v^{1.145}, v^{1.146}, v^{1.147}, v^{1.148}, v^{1.149}, v^{1.150}, v^{1.151}, v^{1.152}, v^{1.153}, v^{1.154}, v^{1.155}, v^{1.156}, v^{1.157}, v^{1.158}, v^{1.159}, v^{1.160}, v^{1.161}, v^{1.162}, v^{1.163}, v^{1.164}, v^{1.165}, v^{1.166}, v^{1.167}, v^{1.168}, v^{1.169}, v^{1.170}, v^{1.171}, v^{1.172}, v^{1.173}, v^{1.174}, v^{1.175}, v^{1.176}, v^{1.177}, v^{1.178}, v^{1.179}, v^{1.180}, v^{1.181}, v^{1.182}, v^{1.183}, v^{1.184}, v^{1.185}, v^{1.186}, v^{1.187}, v^{1.188}, v^{1.189}, v^{1.190}, v^{1.191}, v^{1.192}, v^{1.193}, v^{1.194}, v^{1.195}, v^{1.196}, v^{1.197}, v^{1.198}, 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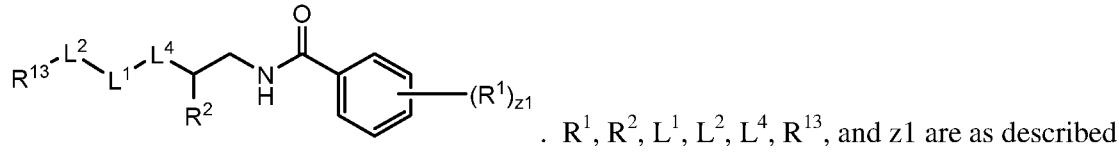
v⁷, the definition of m1 is assumed by m1¹, m1², m1³, m1⁴, m1⁵, m1⁶, the definition of n1 is assumed by n1¹, n1², n1³, n1⁴, n1⁵, n1⁶, the definition of v1 is assumed by v1¹, v1², v1³, v1⁴, v1⁵, v1⁶, the definition of m2 is assumed by m2¹, m2², m2³, m2⁴, m2⁵, m2⁶, m2⁷, m2⁸, m2⁹, m2¹⁰, the definition of n2 is assumed by n2¹, n2², n2³, n2⁴, n2⁵, n2⁶, n2⁷, n2⁸, n2⁹, n2¹⁰, the definition of v2 is assumed by v2¹, v2², v2³, v2⁴, v2⁵, v2⁶, v2⁷, v2⁸, v2⁹, v2¹⁰.

5 [0432] The variables used within a definition of R¹, R², R⁷, R⁸, R⁹, R¹⁰, X, X¹, X², m1, n1, v1, m2, n2, v2, and/or other variables that appear at multiple instances and are different may similarly be appropriately labeled to distinguish each group for greater clarity.



[0433] In an aspect is provided a compound having the formula:
10 (IJ). Ring A, R¹, z1, R², z2, L¹, L², L⁴, and R¹³ are as described herein. In embodiments, R¹³ is hydrogen. In embodiments, R¹³ is unsubstituted methyl. In embodiments, the compound is LB9. In embodiments, the compound is DB9.

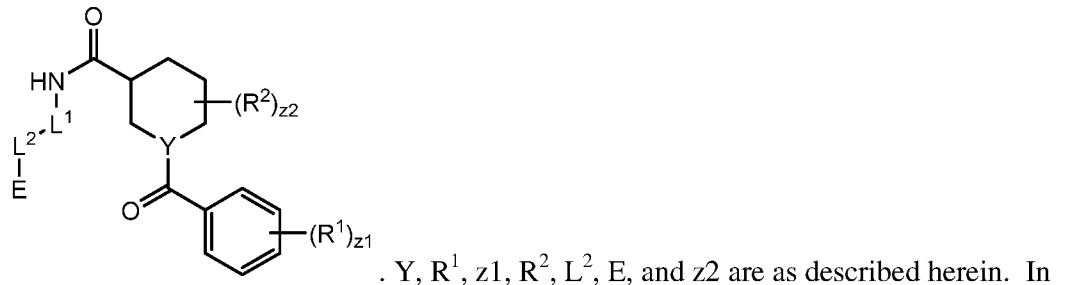
[0434] In an aspect is provided, a compound having the formula:



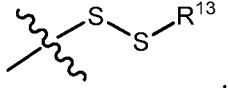
15 . R¹, R², L¹, L², L⁴, R¹³, and z1 are as described

herein. In embodiments, R¹³ is hydrogen. In embodiments, R¹³ is unsubstituted methyl.

[0435] In embodiments, the compound does not have the formula:

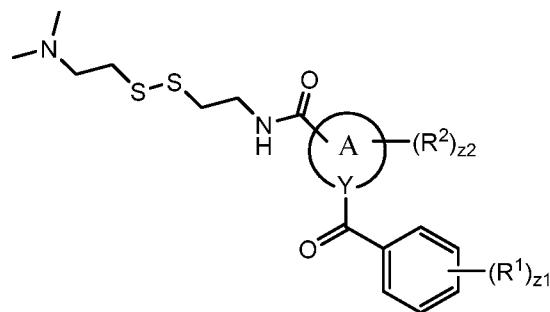


. Y, R¹, z1, R², L², E, and z2 are as described herein. In
embodiments, R¹ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4



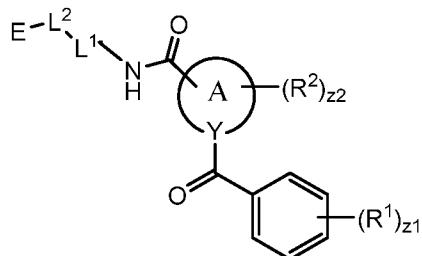
membered unsubstituted heteroalkyl. In embodiments, E is

20 [0436] In embodiments, the compound does not have the formula:

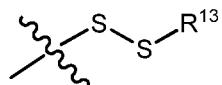


. Ring A, Y, R^1 , $z1$, R^2 , and $z2$ are as described herein. In embodiments, R^1 is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments, R^1 is halogen.

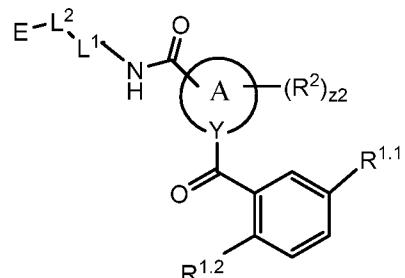
[0437] In embodiments, the compound does not have the formula:



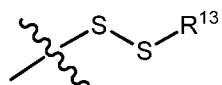
5 . Ring A, Y, R^1 , $z1$, R^2 , $z2$, L^1 , L^2 , and E are as described herein. In embodiments, R^1 is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments, R^1 is halogen. In embodiments, E is



[0438] In embodiments, the compound does not have the formula:

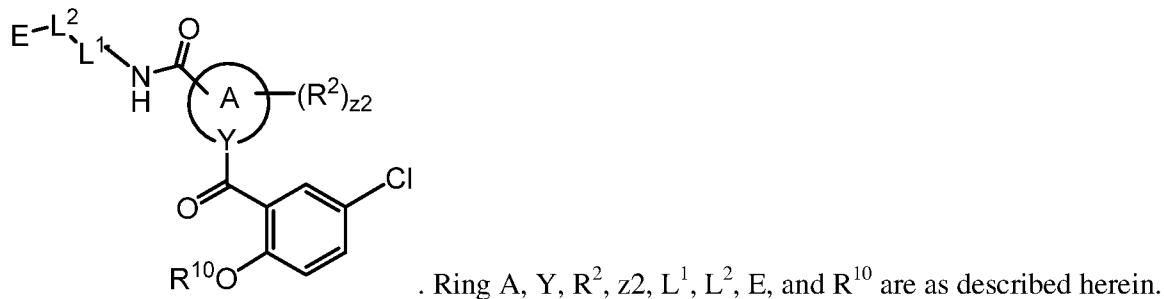


10 . Ring A, Y, $R^{1.1}$, $R^{1.2}$, R^2 , $z2$, L^1 , L^2 and E are as described herein. In embodiments, $R^{1.1}$ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments, $R^{1.2}$ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments, $R^{1.1}$ is halogen. In embodiments, $R^{1.2}$ is halogen. In embodiments, E is

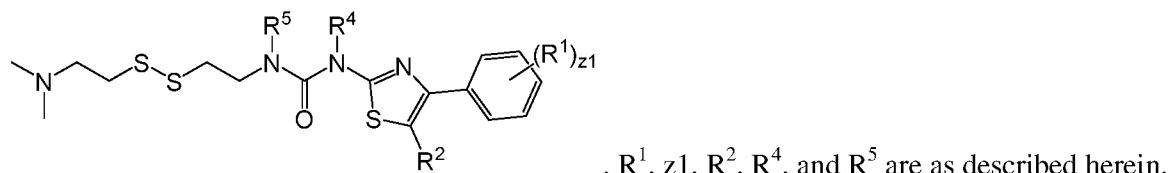


15 .

[0439] In embodiments, the compound does not have the formula:

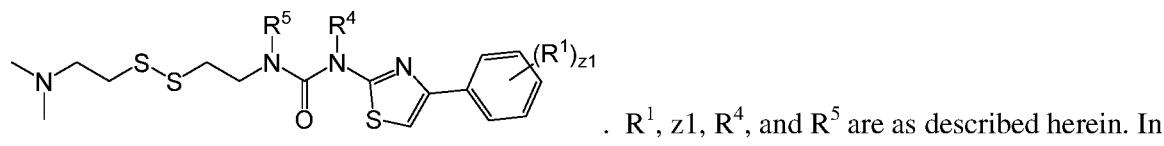


[0440] In embodiments, the compound does not have the formula:



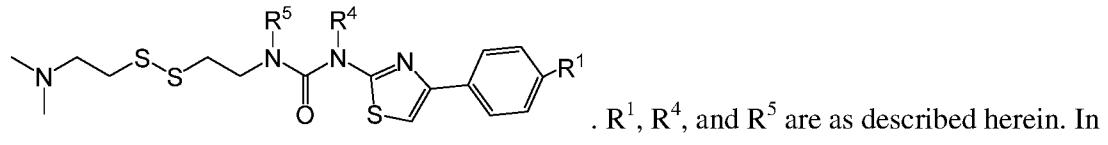
In embodiments, R¹ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

[0441] In embodiments, the compound does not have the formula:



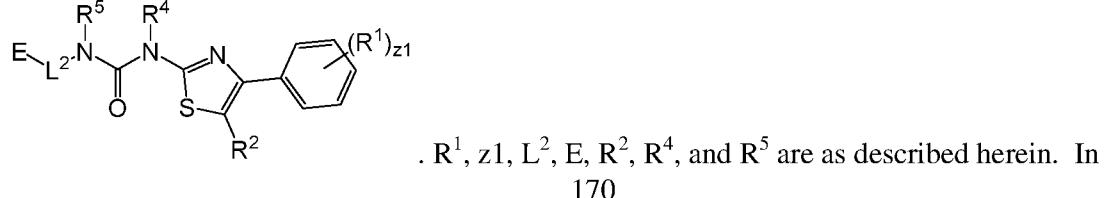
embodiments, R¹ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

[0442] In embodiments, the compound does not have the formula:

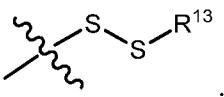


embodiments, R¹ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

[0443] In embodiments, the compound does not have the formula:



embodiments, R¹ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4

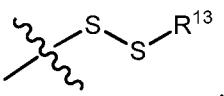


membered unsubstituted heteroalkyl. In embodiments, E is

[0444] In embodiments, the compound does not have the formula:

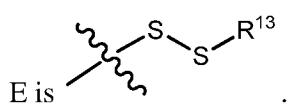
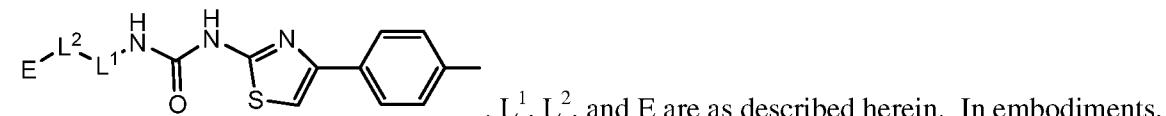


5 embodiments, R¹ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4

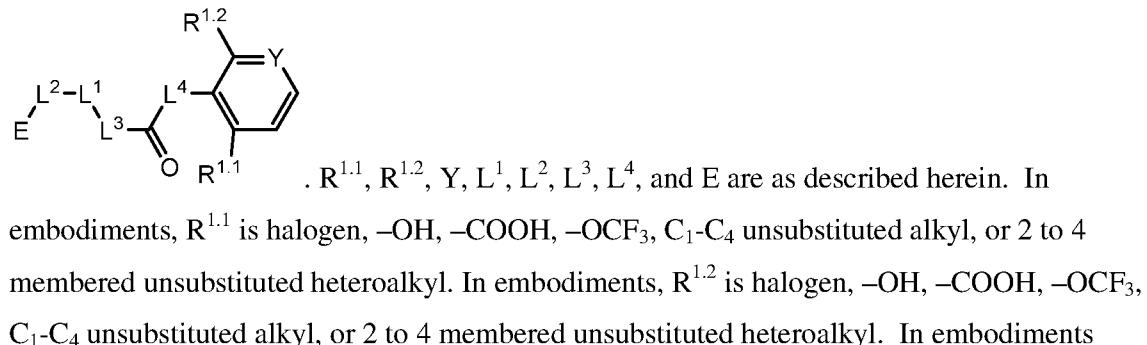


membered unsubstituted heteroalkyl. In embodiments, E is

[0445] In embodiments, the compound does not have the formula:

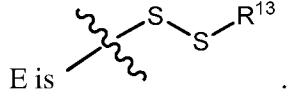


10 **[0446]** In embodiments, the compound does not have the formula:



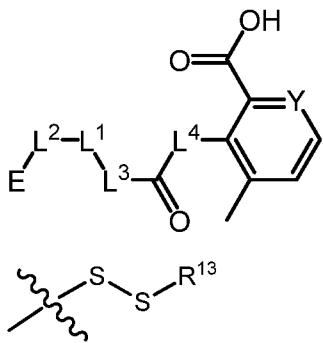
embodiments, R^{1.1} is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4

membered unsubstituted heteroalkyl. In embodiments, R^{1.2} is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments

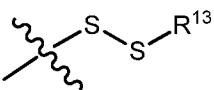


15 E is

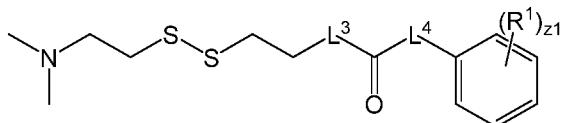
[0447] In embodiments, the compound does not have the formula:



L^1 , L^2 , L^3 , L^4 , and E are as described herein. In embodiments, E is



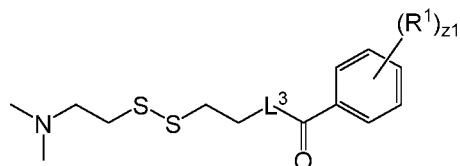
[0448] In embodiments, the compound does not have the formula:



R^1 , $z1$, L^3 , and L^4 are as described herein. In

- 5 embodiments, R^1 is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1-C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

[0449] In embodiments, the compound does not have the formula:

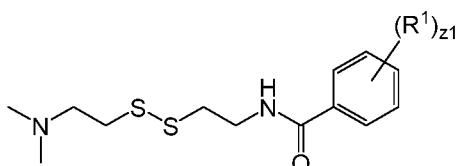


R^1 , $z1$, and L^3 are as described herein. In embodiments,

10 R^1 is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1-C_4 unsubstituted alkyl, or 2 to 4 membered

unsubstituted heteroalkyl.

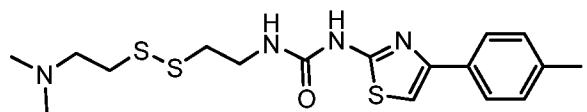
[0450] In embodiments, the compound does not have the formula:



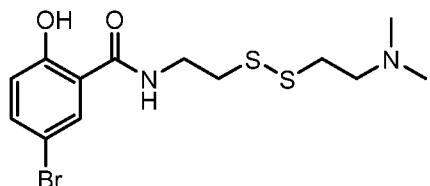
R^1 and $z1$, are as described herein. In embodiments, R^1 is

halogen, $-OH$, $-COOH$, $-OCF_3$, C_1-C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted

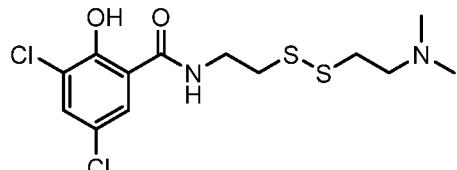
heteroalkyl.



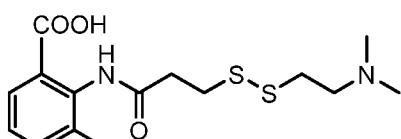
[0451] In embodiments, the compound is not .



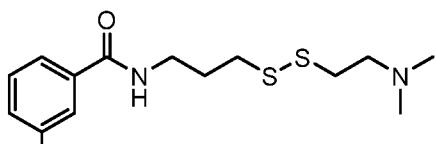
In embodiments, the compound is not . In embodiments, the



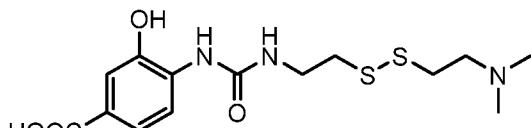
compound is not . In embodiments, the compound is not



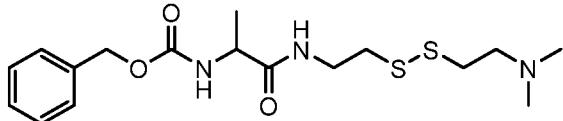
. In embodiments, the compound is not



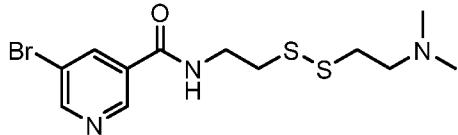
. In embodiments, the compound is not



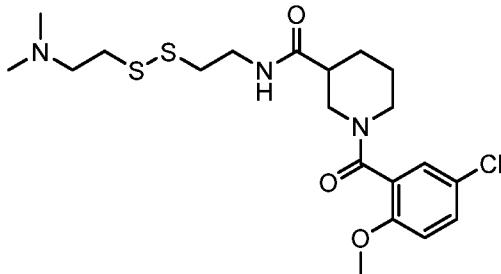
. In embodiments, the compound is not



. In embodiments, the compound is not

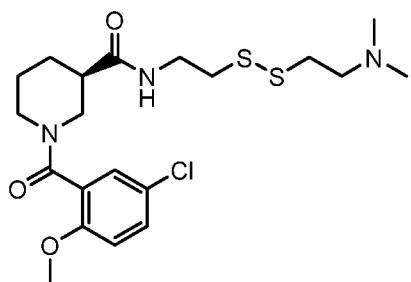


. In embodiments, the compound is not

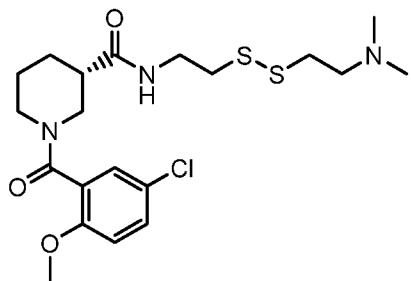


. In embodiments, the compound is not

5

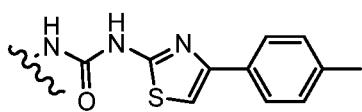


. In embodiments, the compound is not



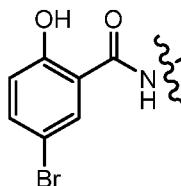
.

[0452] In embodiments, the compound is not a compound described herein, including in an example, figures, or table. In embodiments, the compound does not include

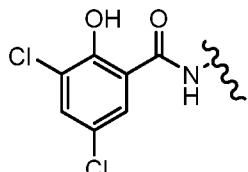


5

. In embodiments, the compound does not include



In embodiments, the compound does not include

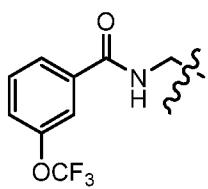


. In embodiments, the

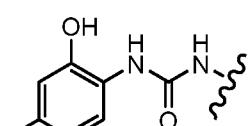
compound does not include



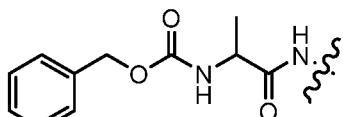
. In embodiments, the compound does not include



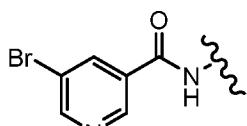
. In embodiments, the compound does not include



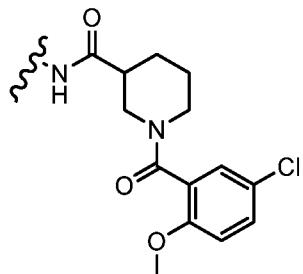
In embodiments, the compound does not include



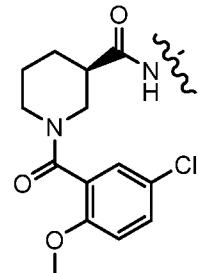
. In embodiments,



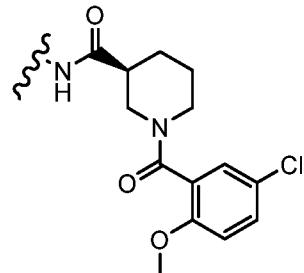
the compound does not include . In embodiments, the compound does not



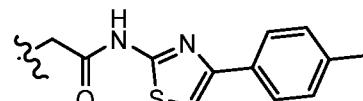
include . In embodiments, the compound does not include



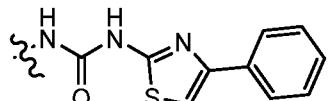
. In embodiments, the compound does not include . In



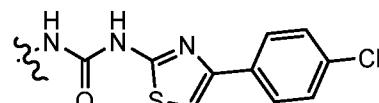
embodiments, the compound does not include . In embodiments,



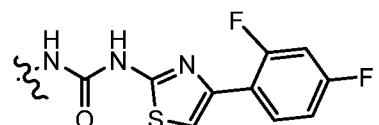
5 the compound does not include . In embodiments, the compound



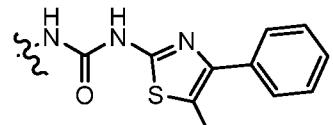
does not include . In embodiments, the compound does not include



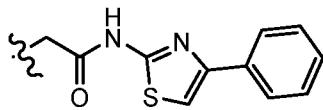
. In embodiments, the compound does not include



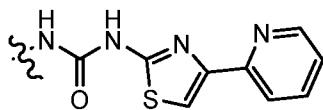
. In embodiments, the compound does not include



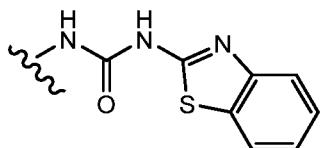
. In embodiments, the compound does not include



. In embodiments, the compound does not include



. In embodiments, the compound does not include



.

III. Pharmaceutical compositions

5 [0453] In an aspect is provided a pharmaceutical composition including a compound described herein and a pharmaceutically acceptable excipient.

[0454] In embodiments, the pharmaceutical composition includes an effective amount of the compound. In embodiments, the pharmaceutical composition includes a therapeutically effective amount of the compound. In embodiments, the pharmaceutical composition includes a second

10 agent (e.g., an anti-cancer agent). In embodiments of the pharmaceutical compositions, the pharmaceutical composition includes a second agent in a therapeutically effective amount. In embodiments, the anti-cancer agent is an EGFR inhibitor (e.g. gefitinib (IressaTM), erlotinib (TarcevaTM), cetuximab (ErbituxTM), lapatinib (TykerbTM), panitumumab (VectibixTM), vandetanib (CaprelsaTM), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-

15 724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, or BMS-599626). In embodiments, the anti-cancer agent is erlotinib. In embodiments, the anti-cancer agent is gefitinib. In embodiments, the anti-cancer agent is lapatinib. In embodiments, the anti-cancer agent is panitumumab. In

20 embodiments, the anti-cancer agent is panitumumab.

[0455] The pharmaceutical compositions may include optical isomers, diastereomers, or pharmaceutically acceptable salts of the modulators disclosed herein. The compound included in the pharmaceutical composition may be covalently attached to a carrier moiety. Alternatively, the compound included in the pharmaceutical composition is not covalently linked to a carrier

25 moiety.

IV. Methods for Treating Diseases

[0456] In another aspect, a method of treating a disease in a subject in need of such treatment (patient) is provided. The method including administering a therapeutically effective amount of a compound described herein (including embodiments, examples, figures, tables) to the patient.

5 In some embodiments, the disease is cancer. In some embodiments, the cancer is lung cancer, colorectal cancer, colon cancer, pancreatic cancer, breast cancer, or leukemia. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is non-small cell lung cancer. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the 10 cancer is leukemia. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is a cancer associated with aberrant K-Ras. In some embodiments, the cancer is a cancer associated with a mutant K-Ras. In some embodiments, the cancer is a cancer associated with K-Ras G12C. In some embodiments, the cancer is a cancer associated with K-Ras G12D. In some embodiments, the cancer is a cancer associated with K-Ras G12V. In some 15 embodiments, the cancer is a cancer associated with K-Ras G12S. In some embodiments, the cancer is a cancer associated with K-Ras G13C. In some embodiments, the cancer is a cancer associated with K-Ras G13D.

[0457] In some embodiments, a method of treating a disorder in a subject in need thereof is provided, comprising a) determining the presence or absence of a mutation in a Ras protein (such 20 as in a K-Ras, N-Ras, or H-Ras protein) in a malignant or neoplastic cell isolated from the subject and b) if the mutation is determined to be present in the subject, administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of the invention. In some embodiments, the disorder is cancer.

[0458] The compounds of the invention (i.e. compounds described herein, including in 25 embodiments, examples, figures, tables) can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation or anti-cancer agents). In embodiments, the anti-cancer agent is an EGFR 30 inhibitor (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788,

pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, or BMS-599626). In embodiments, the anti-cancer agent is erlotinib. In embodiments, the anti-cancer agent is gefitinib. In embodiments, the anti-cancer agent is lapatinib. In embodiments, the anti-cancer agent is panitumumab. In embodiments, the anti-cancer agent is panitumumab.

5 V. Methods of Modulating Activity

[0459] In an aspect is provided a method of reducing the level of activity of a K-Ras protein (e.g., human K-Ras 4B), the method including contacting the K-Ras protein with a compound described herein (including in embodiments, examples, figures, and tables). In some embodiments, the activity of the K-Ras protein is it's GTPase activity, nucleotide exchange, differential GDP or GTP binding, effector protein binding, effector protein activation, guanine exchange factor (GEF) binding, GEF-facilitated nucleotide exchange, phosphate release, nucleotide release, nucleotide binding, K-Ras subcellular localization, K-Ras post-translational processing, K-Ras post-translational modifications, prenylation, or a GTP bound K-Ras signaling pathway. In some embodiments, the activity of the K-Ras protein is its GTPase activity, nucleotide exchange, effector protein binding, effector protein activation, guanine exchange factor (GEF) binding, GEF-facilitated nucleotide exchange, phosphate release, nucleotide release, nucleotide binding, or the activity of a GTP bound K-Ras signaling pathway. In some embodiments, the activity of the K-Ras protein is the activity of a signaling pathway activated by GTP bound K-Ras. In some embodiments, the modulating is increasing the activity of said K-Ras protein. In some embodiments, the modulating is reducing the activity of said K-Ras protein. In some embodiments, the K-Ras protein is a human K-Ras protein. In some embodiments, the human K-Ras protein contains a G12C mutation. In some embodiments, the human K-Ras protein contains a G12V mutation. In some embodiments, the human K-Ras protein contains a G12S mutation. In some embodiments, the human K-Ras protein contains a G12D mutation. In some embodiments, the human K-Ras protein contains a G13C mutation. In some embodiments, the human K-Ras protein contains a G13D mutation. In some embodiments, the K-Ras protein is a human K-Ras4A protein. In some embodiments, the K-Ras protein is a human K-Ras4B protein. In some embodiments, the K-Ras protein is a mutant K-Ras protein. In some embodiments, the K-Ras protein is an activated K-Ras protein. In some embodiments, the K-Ras protein is within a biological cell. In some embodiments, the biological cell forms part of an organism. In some embodiments of the method of modulating the activity of a K-Ras protein includes contacting the K-Ras protein with an effective amount of a compound described herein (including in embodiments, examples, figures, and tables), the compound is less effective

at modulating the activity of an H-Ras protein (e.g., compared to the level of modulation of K-Ras). In some embodiments of the method, the compound modulates the activity of K-Ras at least two-fold more than it modulates the activity of H-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least five-fold more than it modulates the activity of H-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least ten-fold more than it modulates the activity of H-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least fifty-fold more than it modulates the activity of H-Ras. In some embodiments of the method of modulating the activity of a K-Ras protein including contacting the K-Ras protein with an effective amount of a compound described herein (including embodiments, examples, figures, and tables), the compound is less effective at modulating the activity of an N-Ras protein. In some embodiments of the method, the compound modulates the activity of K-Ras at least two-fold more than it modulates the activity of N-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least five-fold more than it modulates the activity of N-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least ten-fold more than it modulates the activity of N-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least fifty-fold more than it modulates the activity of N-Ras.

[0460] In another aspect, a method of modulating a K-Ras protein is provided. The method including contacting the K-Ras protein with an effective amount of a compound described herein (including in embodiments, examples, figures, and tables). In some embodiments, the K-Ras protein is modulated in K-Ras subcellular localization, K-Ras post-translational processing, K-Ras post-translational modifications, or a GTP bound K-Ras signaling pathway. In some embodiments, the modulating is increasing the post-translational processing or modifications of the K-Ras protein. In some embodiments, the modulating is reducing the post-translational processing or modifications of the K-Ras protein. In some embodiments, the K-Ras protein is a human K-Ras protein. In some embodiments, the human K-Ras protein contains a G12C mutation. In some embodiments, the human K-Ras protein contains a G12V mutation. In some embodiments, the human K-Ras protein contains a G12S mutation. In some embodiments, the human K-Ras protein contains a G12D mutation. In some embodiments, the human K-Ras protein contains a G13C mutation. In some embodiments, the human K-Ras protein contains a G13D mutation. In some embodiments, the K-Ras protein is a human K-Ras4A protein. In some embodiments, the K-Ras protein is a human K-Ras4B protein. In some embodiments, the K-Ras protein is a mutant K-Ras protein. In some embodiments, the K-Ras protein is an

activated K-Ras protein. In some embodiments, the K-Ras protein is within a biological cell. In some embodiments, the biological cell forms part of an organism. In embodiments, compound (e.g., compound described herein) modulates the stability of the K-Ras protein. In embodiments, compound (e.g., compound described herein) reduces the stability of the K-Ras protein relative 5 to the absence of the compound. In embodiments, compound (e.g., compound described herein) increases the rate of degradation of the K-Ras protein relative to the absence of the compound.

[0461] In embodiments, the compound (e.g., compound described herein) binds to the amino acid corresponding to His95 in K-Ras (e.g., K-Ras 4B). In embodiments, the compound (e.g., compound described herein) reacts with His95 in K-Ras (K-Ras 4B). In embodiments, the

10 compound (e.g., compound described herein) covalently binds to the amino acid corresponding to His95 in K-Ras (e.g., K-Ras 4B). In embodiments, the compound (e.g., compound described herein) covalently reacts with His95 in K-Ras (K-Ras 4B). In embodiments, the compound (e.g., compound described herein) is capable of binding to the amino acid corresponding to His95 or Cys185 in K-Ras (e.g., K-Ras 4B). In embodiments, the compound (e.g., compound described 15 herein) is capable of reacting with His95 or Cys185 in K-Ras (K-Ras 4B).

[0462] In embodiments, the compound (e.g., compound described herein) binds to the amino acid corresponding to His95 in K-Ras (e.g., K-Ras 4B) protein when the K-Ras (e.g., K-Ras 4B) protein Cys185 (or amino acid corresponding to Cys185 of K-Ras 4B) is covalently modified (e.g., prenylated, farnesylated). In embodiments, the compound (e.g., compound described

20 herein) binds to the amino acid corresponding to Cys185 in K-Ras (e.g., K-Ras 4B) protein when the K-Ras (e.g., K-Ras 4B) protein Cys185 (or amino acid corresponding to Cys185 of K-Ras 4B) is not covalently modified (e.g., prenylated, farnesylated). In embodiments, the compound (e.g., compound described herein) binds to the amino acid corresponding to Cys185 in K-Ras

25 (e.g., K-Ras 4B) protein following protein synthesis, when the K-Ras (e.g., K-Ras 4B) protein Cys185 (or amino acid corresponding to Cys185 of K-Ras 4B) has not yet been covalently modified (e.g., prenylated, farnesylated).

[0463] In embodiments, the compound prevents productive folding of K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the

30 compound. In embodiments, the compound increases misfolding of K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound increases unfolding of K-Ras protein (e.g., by

binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound increases degradation of K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound reduces GTP binding to K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound decreases GDP release by K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound decreases interactions of a second protein (e.g., pathway component, effector) with K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound decreases prenylation (e.g., farnesylation, geranylgeranylation) of K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound.

[0464] In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than about 1 hour (e.g., less than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 minutes). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than 1 hour (e.g., less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 minutes). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than about 1 day (e.g., less than about 1, 2,

3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 hours). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the 5 amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than 1 day (e.g., less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 hours). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding 10 to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than about 1 month (e.g., less than about 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, or 30 days). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., 15 by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than 1 month (e.g., less than 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, or 30 days). In embodiments, the compound binds to K-Ras (e.g., only K-Ras 4B, only K-Ras 4A, or both K-Ras 4A and K-Ras 4B).

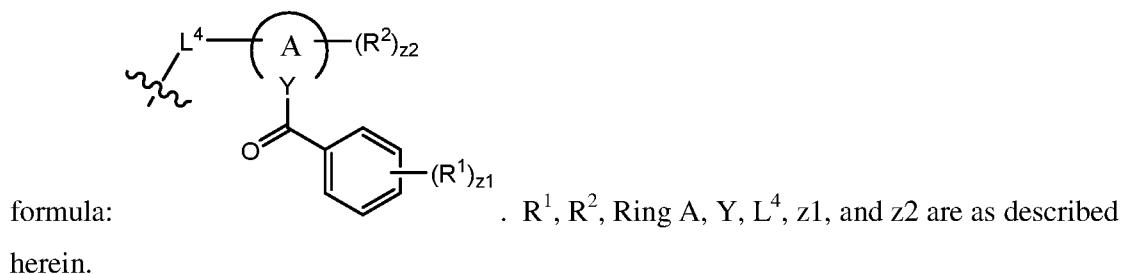
20 VI. Compositions

[0465] In another aspect is provided, a K-Ras protein covalently (e.g., reversibly or irreversibly) bonded to a compound, for example a compound as described herein (including modulators, inhibitors, embodiments, examples, in figures, and in tables). In embodiments, the compound is a compound described herein. In embodiments, the compound is covalently bonded 25 to a cysteine residue of the protein. In embodiments, the compound is irreversibly covalently bonded to a cysteine residue of the protein. In embodiments, the compound is covalently bonded to the residue corresponding to C185 of human K-Ras 4B. In embodiments, the compound is covalently bonded to a histidine residue of the protein. In embodiments, the compound is irreversibly covalently bonded to a histidine residue of the protein. In embodiments, the 30 compound is covalently bonded to the residue corresponding to H95 of human K-Ras 4B.

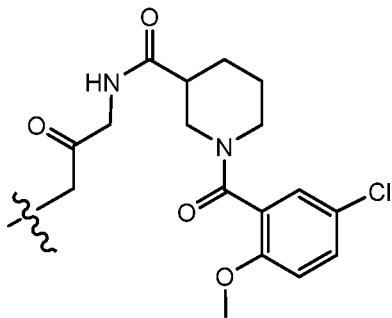
[0466] In embodiments, the covalently modified K-Ras protein has a modulated activity relative to a control, wherein the activity is selected from GTPase activity, nucleotide exchange, effector protein binding, effector protein activation, guanine exchange factor (GEF) binding,

GEF-facilitated nucleotide exchange, phosphate release, nucleotide release, nucleotide binding, K-Ras subcellular localization, K-Ras post-translational processing, and K-Ras post-translational modifications. In some embodiments, the covalently modified K-Ras protein is modulated in K-Ras subcellular localization, K-Ras post-translational processing, or K-Ras post-translational modifications. In some embodiments, the covalently modified K-Ras protein contains a G12C mutation. In some embodiments, the covalently modified K-Ras protein contains a G12V mutation. In some embodiments, the covalently modified K-Ras protein contains a G12S mutation. In some embodiments, the compound is covalently bonded to cysteine residue 185. In some embodiments, the compound is covalently bonded to histidine residue 95 (e.g., corresponding to H95 of K-Ras). In some embodiments, the covalently modified K-Ras protein contains a G13C mutation. In some embodiments, the K-Ras protein is bonded to a K-Ras inhibitor, a mutant K-Ras inhibitor, K-Ras H95 inhibitor, or a K-Ras C185 inhibitor. In some embodiments, the K-Ras protein is bonded to a K-Ras modulator, a mutant K-Ras modulator, K-Ras H95 inhibitor, or a K-Ras C185 modulator.

15 [0467] In an aspect is provided a K-Ras protein covalently bonded to a compound having the

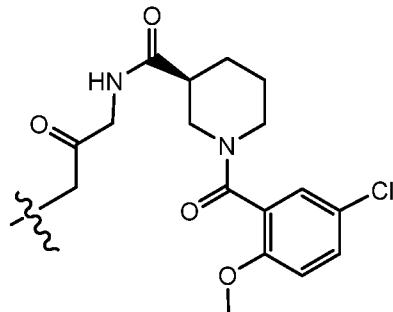


[0468] In an aspect is provided a K-Ras protein covalently bonded to a compound having the



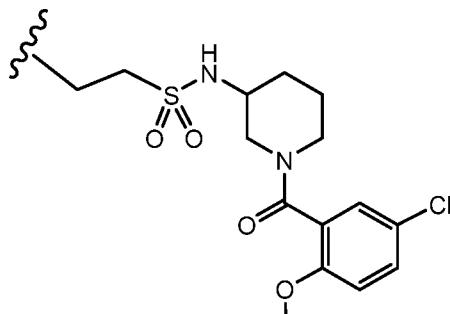
formula:

. In an embodiment, the K-Ras protein is covalently



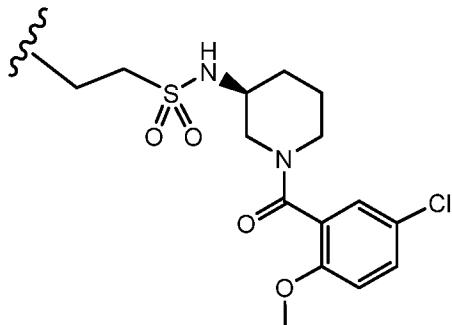
bonded to a compound having the formula:

[0469] In an aspect is provided a K-Ras protein covalently bonded to a compound having the



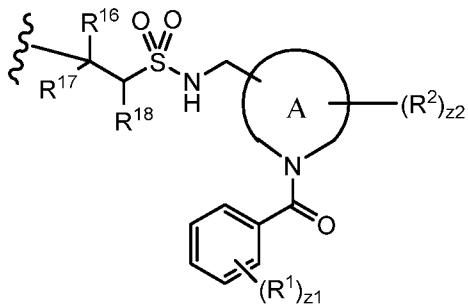
5 formula:

. In an embodiment, the K-Ras protein is

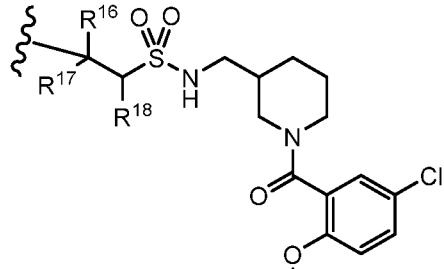


covalently bonded to a compound having the formula:

In an embodiment, the K-Ras protein is covalently bonded to a compound having the formula:

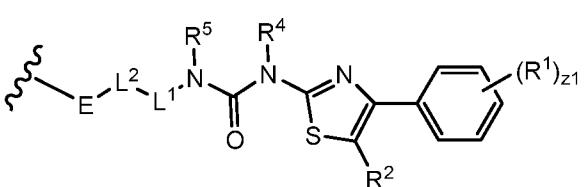
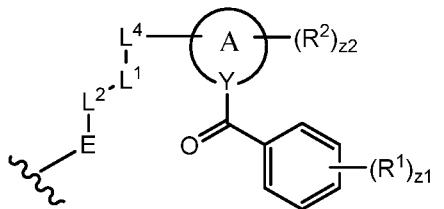


. In an embodiment, the K-Ras protein is covalently

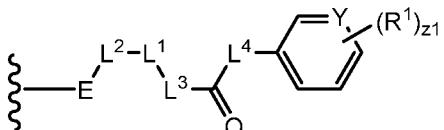


bonded to a compound having the formula:

embodiment, the K-Ras protein is covalently bonded to a compound having the formula:



5



, or . E, R¹, R², R³, R⁴, R⁵, Ring A, Y, L¹, L², L³, L⁴, z1, and z2

are as described herein.

[0470] In embodiments, the compound is covalently bonded to a cysteine residue of the protein. In embodiments, the compound is covalently bonded to a cysteine residue of the protein

10 corresponding to C185 of human K-Ras-4B. In embodiments, the compound is irreversibly covalently bonded to a cysteine (e.g., corresponding to C185 of human K-Ras-4B) of the protein.

In embodiments, the compound is covalently bonded to a histidine residue of the protein. In

embodiments, the compound is covalently bonded to a histidine residue of the protein

corresponding to H95 of human K-Ras-4B. In embodiments, the compound is irreversibly

15 covalently bonded to a histidine (e.g., corresponding to H95 of human K-Ras-4B) of the protein.

[0471] In another aspect, a Ras protein (e.g. K-Ras, N-Ras, H-Ras, or another Ras protein described herein) covalently bonded (e.g. reversibly or irreversibly) to a compound, for example

a compound as described herein (including modulators, inhibitors, embodiments, figures, examples, and tables), is provided. In some embodiments, the compound is a modulator. In some embodiments, the compound is a modulator such as an inhibitor. In some embodiments, the compound is a Ras modulator. In some embodiments, the compound is a Ras inhibitor.

- 5 [0472] In embodiments, the compound binds Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) at the CAAX box. In embodiments, the compound binds Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to the residue corresponding to C185 of human K-Ras
10 4B. In embodiments, the compound binds Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to the residue corresponding to H95 of human K-Ras 4B.

- [0473] In embodiments, the compound modulates the conformation of the protein. In embodiments, the compound modulates the conformation of the CAAX box. In embodiments, the compound modulates (e.g., reduces or inhibits) the prenylation of the protein at the CAAX box (e.g., residue corresponding to C185 of human K-Ras 4B). In embodiments, the compound inhibits (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000 fold or more) Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) activity relative to the absence of the compound. In embodiments, the compound inhibits (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%) Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) activity relative to the absence of the compound. In embodiments, the compound inhibits (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%) Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) prenylation relative to the absence of the compound. In embodiments, the compound reduces (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40,

45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%) the amount of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) protein (e.g., in a cell) relative to the absence of the compound. In embodiments, the compound reduces (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 5 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%) production of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K- 10 Ras G13C, K-Ras G12D, K-Ras G13D) protein (e.g., in a cell) relative to the absence of the compound. In embodiments, the compound increases (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%) the degradation of Ras (e.g. K- 15 Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) protein (e.g., in a cell) relative to the absence of the compound. In embodiments, the compound inhibits protein association with a membrane relative to the absence of the compound.

[0474] In embodiments, the compound inhibits proliferation of cancer cells under nutrient deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under nutrient deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under nutrient 20 deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under serum deprivation conditions relative to the absence of the compound. In embodiments, the compound inhibits proliferation of cancer cells under serum deprivation conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under conditions (e.g. local cell environment in a patient) mimicking serum deprivation relative to the absence of the compound. In embodiments, the compound inhibits proliferation of cancer cells under conditions (e.g. local cell environment in a 25 patient) mimicking serum deprivation relative to the absence of the compound.

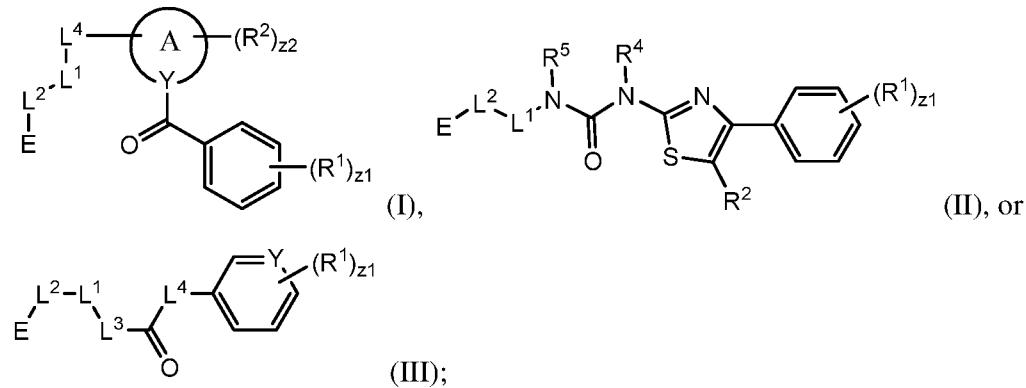
[0475] In embodiments, the compound increases the flexibility of the CAAX box (amino acid sequence at the C terminus of a protein wherein C is a cysteine that may be prenylated, A is an aliphatic amino acid, and X is an amino acid with variable sequence depending on the protein (e.g., M, S, Q, A, or C; L or E)) relative to the absence of the compound. In embodiments, the compound increases the disorder of the CAAX box relative to the absence of the compound. In embodiments, the compound inhibits the binding of Ras ((e.g. K-Ras, K-Ras 4B, human K-Ras 30

4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to another protein. In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to another protein, wherein the binding is dependent on Ras prenylation. In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to another protein, wherein the binding is dependent on Ras membrane association.

[0476] In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to Raf (e.g. Raf1). In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to SOS. In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to a GEF. In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to PI3K.

VII. Selected Embodiments

[0477] Embodiment P1. A compound having the formula:



wherein, Y is N or CH; Ring A is a C₅-C₇ cycloalkyl or 5 to 7 membered heterocycloalkyl; R¹ is independently halogen, CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR⁷R⁸, -NHNR⁷R⁸, -ONR⁷R⁸, -NHC=(O)NHNR⁷R⁸, -NHC(O)NR⁷R⁸, -N(O)_{m1}, -NR⁷R⁸, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR⁷R⁸, -OR¹⁰, -NR⁷SO₂R¹⁰, -

NR⁷C(O)R⁹, -NR⁷C(O)OR⁹, -NR⁷OR⁹, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R¹ substituents may optionally be joined to form a substituted or

5 substituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; L¹ is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene; L² is a

10 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or

15 unsubstituted arylene, substituted or unsubstituted heteroarylene; L³ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁵-, -NR⁵C(O)-, -C(O)NR⁵-, -SO₂NR⁵-, -NR⁵SO₂-, -OC(O)NR⁵-, -NR⁵C(O)O-, substituted or unsubstituted C₁-C₆ alkylene, substituted or unsubstituted 2 to 6 membered heteroalkylene; L⁴ is a

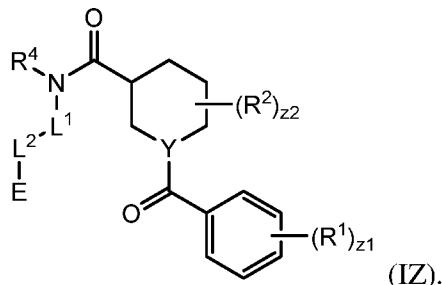
20 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁴-, -NR⁴C(O)-, -C(O)NR⁴-, -SO₂NR⁴-, -NR⁴SO₂-, -NR⁴SO₂-, -OC(O)NR⁴-, -NR⁴C(O)O-, substituted or unsubstituted C₁-C₃ alkylene, substituted or unsubstituted 2 to 3 membered heteroalkylene; E is a covalent cysteine modifier moiety; R² is independently oxo, halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -SO₂Cl, -SO_{n2}R¹⁴, -SO_{v2}NR¹¹R¹², -NHNR¹¹R¹², -ONR¹¹R¹², -NHC=(O)NHNR¹¹R¹², -NHC(O)NR¹¹R¹², -N(O)_{m2}, -NR¹¹R¹², -C(O)R¹⁴, -C(O)-OR¹⁴, -C(O)NR¹¹R¹², -OR¹⁵, -

25 NR¹¹SO₂R¹⁵, -NR¹¹C(O)R¹⁴, -NR¹¹C(O)OR¹⁴, -NR¹¹OR¹⁴, -OCX²₃, -OCHX²₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R² substituents or two R² substituents bonded to the same atom may optionally be joined to form a substituted or unsubstituted

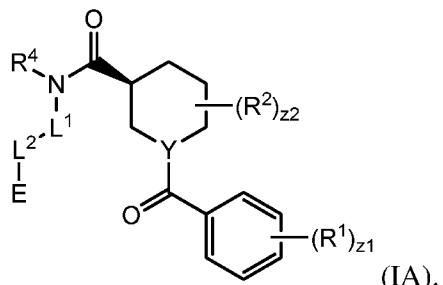
30 cycloalkyl or substituted or unsubstituted heterocycloalkyl; R⁴ is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R⁵ is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R⁷, R⁸, R⁹, R¹⁰, R^{7B}, R^{8B}, R^{9B}, R^{10B}, R¹¹, R¹², R¹⁴, and R¹⁵ are independently hydrogen, halogen, -CX₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX₃, -OCHX₂, -CHX₂, -CH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R⁷ and R⁸ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R¹¹ and R¹² substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X, X¹, and X² is independently -F, -Cl, -Br, or -I; n1, n2, v1, and v2 are independently an integer from 0 to 4; m1 and m2 are independently an integer between 1 and 2; z1 is independently an integer from 0 to 5; and z2 is independently an integer from 0 to 10.

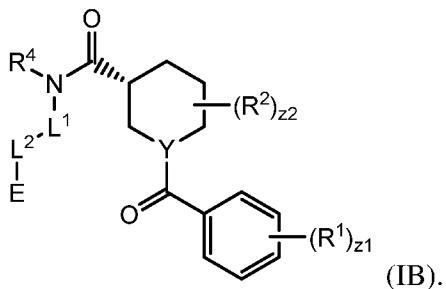
[0478] Embodiment P2. The compound of embodiment P1 having the formula:



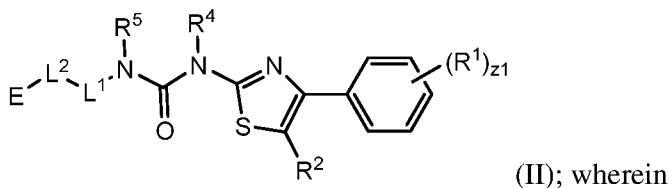
[0479] Embodiment P3. The compound of embodiment P1 having the formula:



20 **[0480]** Embodiment P4. The compound of embodiment P1 having the formula:

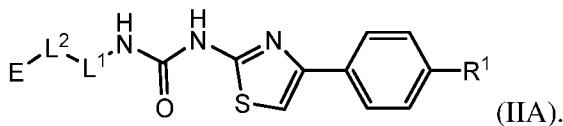


[0481] Embodiment P5. The compound of embodiment P1 having the formula:

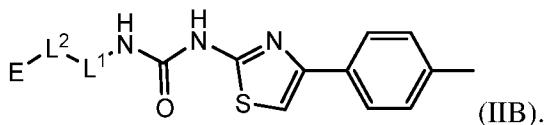


R^2 , R^4 , and R^5 are hydrogen.

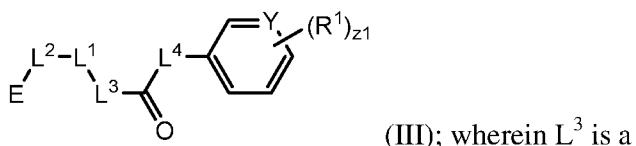
5 [0482] Embodiment P6. The compound of embodiment P5 having the formula:



[0483] Embodiment P7. The compound of embodiment P5 having the formula:



[0484] Embodiment P8. The compound of embodiment P1 having the formula:



10 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(CH₃)C(O)NH-, or unsubstituted C₁-C₃ alkylene; and L^4 is a bond, -CH₂O-, -C(O)-, -NH-, or -O-.

[0485] Embodiment P9. The compound of one of embodiments P1 to P8, wherein Y is CH.

[0486] Embodiment P10. The compound of one of embodiments P1 to P8, wherein Y is N.

15 [0487] Embodiment P11. The compound of one of embodiments P1 to P10, wherein R¹ is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH,

-SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

5 [0488] Embodiment P12. The compound of one of embodiments P1 to P10, wherein R¹ is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OH, -SH, -COOH, -OCX¹₃, -OCHX¹₂, -CH₃, -CH₂CH₃, -OC H₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃.

10 10 [0489] Embodiment P13. The compound of one of embodiments P1 to P12, wherein z1 is 2.

[0490] Embodiment P14. The compound of one of embodiments P1 to P12, wherein z1 is 3.

[0491] Embodiment P15. The compound of one of embodiments P1 to P14, wherein R² is independently oxo, halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

20 [0492] Embodiment P16. The compound of one of embodiments P1 to P14, wherein R² is independently oxo, halogen, -CX²₃, -CHX²₂, -CH₂X², -OH, -SH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -OC H₂CH₃, -SCH₃, or -SCH₂CH₃.

[0493] Embodiment P17. The compound of one of embodiments P1 to P16, wherein z2 is 0.

25 25 [0494] Embodiment P18. The compound of one of embodiments P1 to P17, wherein R⁴ is hydrogen.

[0495] Embodiment P19. The compound of one of embodiments P1 to P18, wherein R⁵ is hydrogen.

30 [0496] Embodiment P20. The compound of one of embodiments P1 to P19, wherein L¹ is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0497] Embodiment P21. The compound of one of embodiments P1 to P19, wherein L¹ is a bond, unsubstituted C₁-C₄ alkylene, or unsubstituted 2 to 4 membered heteroalkylene.

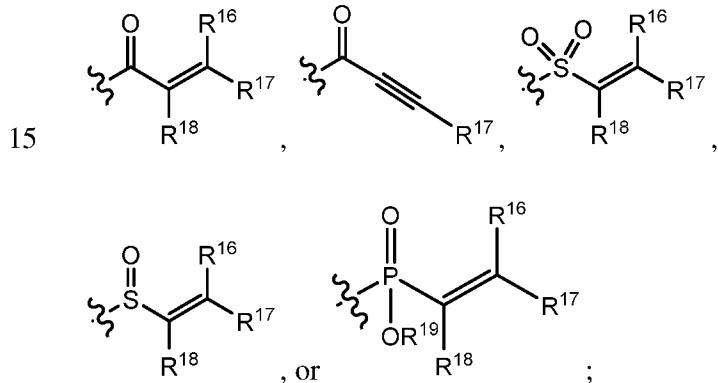
[0498] Embodiment P22. The compound of one of embodiments P1 to P19, wherein L¹ is a bond.

5 **[0499]** Embodiment P23. The compound of one of embodiments P1 to P22, wherein L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -NHC(O)NH-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

10 **[0500]** Embodiment P24. The compound of one of embodiments P1 to P22, wherein L² is a bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C₁-C₄ alkylene, or unsubstituted 2 to 4 membered heteroalkylene.

[0501] Embodiment P25. The compound of one of embodiments P1 to P22, wherein L² is a bond.

[0502] Embodiment P26. The compound of one of embodiments P1 to P25, wherein E is



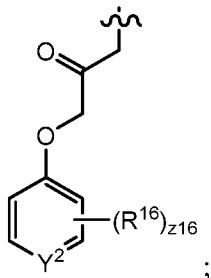
wherein R¹⁶ is independently hydrogen, halogen, CX¹⁶₃, -CHX¹⁶₂, -CH₂X¹⁶, -CN, -SO₂Cl, -SO_{n16}R^{16D}, -SO_{v16}NR^{16A}R^{16B}, -NHNR^{16A}R^{16B}, -ONR^{16A}R^{16B}, -NHC=(O)NHNR^{16A}R^{16B},
20 -NHC(O)NR^{16A}R^{16B}, -N(O)_{m16}, -NR^{16A}R^{16B}, -C(O)R^{16C}, -C(O)-OR^{16C}, -C(O)NR^{16A}R^{16B}, -OR^{16D}, -NR^{16A}SO₂R^{16D}, -NR^{16A}C(O)R^{16C}, -NR^{16A}C(O)OR^{16C}, -NR^{16A}OR^{16C}, -OCX¹⁶₃, -OCHX¹⁶₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R¹⁷ is independently hydrogen, halogen, CX¹⁷₃, -CHX¹⁷₂, -CH₂X¹⁷, -CN, -SO₂Cl, -SO_{n17}R^{17D}, -SO_{v17}NR^{17A}R^{17B}, -NHNR^{17A}R^{17B},

25

$-ONR^{17A}R^{17B}$, $-NHC=(O)NHNR^{17A}R^{17B}$,
 $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17C}$, $-C(O)-OR^{17C}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17D}$,
 $-NR^{17A}SO_2R^{17D}$, $-NR^{17A}C(O)R^{17C}$, $-NR^{17A}C(O)OR^{17C}$, $-NR^{17A}OR^{17C}$, $-OCX^{17}_3$, $-OCHX^{17}_2$,
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 5 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{18} is independently hydrogen,
 halogen, CX^{18}_3 , $-CHX^{18}_2$, $-CH_2X^{18}$, $-CN$, $-SO_2Cl$, $-SO_{n18}R^{18D}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHNR^{18A}R^{18B}$,
 $-ONR^{18A}R^{18B}$, $-NHC=(O)NHNR^{18A}R^{18B}$,
 $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-C(O)R^{18C}$, $-C(O)-OR^{18C}$, $-C(O)NR^{18A}R^{18B}$, $-OR^{18D}$,
 10 $-NR^{18A}SO_2R^{18D}$, $-NR^{18A}C(O)R^{18C}$, $-NR^{18A}C(O)OR^{18C}$, $-NR^{18A}OR^{18C}$, $-OCX^{18}_3$, $-OCHX^{18}_2$,
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{19} is independently hydrogen,
 halogen, CX^{19}_3 , $-CHX^{19}_2$, $-CH_2X^{19}$, $-CN$, $-SO_2Cl$, $-SO_{n19}R^{19D}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHNR^{19A}R^{19B}$,
 15 $-ONR^{19A}R^{19B}$, $-NHC=(O)NHNR^{19A}R^{19B}$,
 $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-C(O)R^{19C}$, $-C(O)-OR^{19C}$, $-C(O)NR^{19A}R^{19B}$, $-OR^{19D}$,
 $-NR^{19A}SO_2R^{19D}$, $-NR^{19A}C(O)R^{19C}$, $-NR^{19A}C(O)OR^{19C}$, $-NR^{19A}OR^{19C}$, $-OCX^{19}_3$, $-OCHX^{19}_2$,
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{16A} , R^{16B} , R^{16C} , R^{16D} , R^{17A} , R^{17B} ,
 20 R^{17C} , R^{17D} , R^{18A} , R^{18B} , R^{18C} , R^{18D} , R^{19A} , R^{19B} , R^{19C} , R^{19D} , are independently hydrogen,
 halogen, $-CX_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$,
 $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$,
 $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl,
 25 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 heteroaryl; R^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be
 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be
 30 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be
 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be

joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X, X¹⁶, X¹⁷, X¹⁸ and X¹⁹ is independently -F, -Cl, -Br, or -I; n16, n17, n18, n19, v16, v17, v18, and v19 are independently an integer from 0 to 4; and m16, m17, m18, and m19 are independently an integer from 1 to 2.

- 5 [0503] Embodiment P27. The compound of one of embodiments P1 to P25, wherein E is



wherein R¹⁶ is independently halogen, CX¹⁶₃, -CHX¹⁶₂, -CH₂X¹⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -

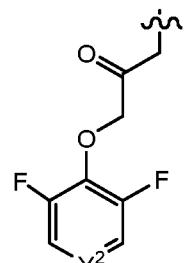
- 10 NHC(O)OH, -NHOH, -OCX¹⁶₃, -OCHX¹⁶₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; Y² is N or CH; z16 is an integer between 0 and 4; and each X¹⁶ is independently -F, -Cl, -Br, or -I.

- [0504] Embodiment P28. The compound of embodiment P27 wherein R¹⁶ is independently halogen.

[0505] Embodiment P29. The compound of embodiment P27 wherein R¹⁶ is independently -F.

- [0506] Embodiment P30. The compound of one of embodiments P27 to P29, wherein z16 is 4.

- 20 [0507] Embodiment P31. The compound of one of embodiments P27 to P29, wherein z16 is 2.

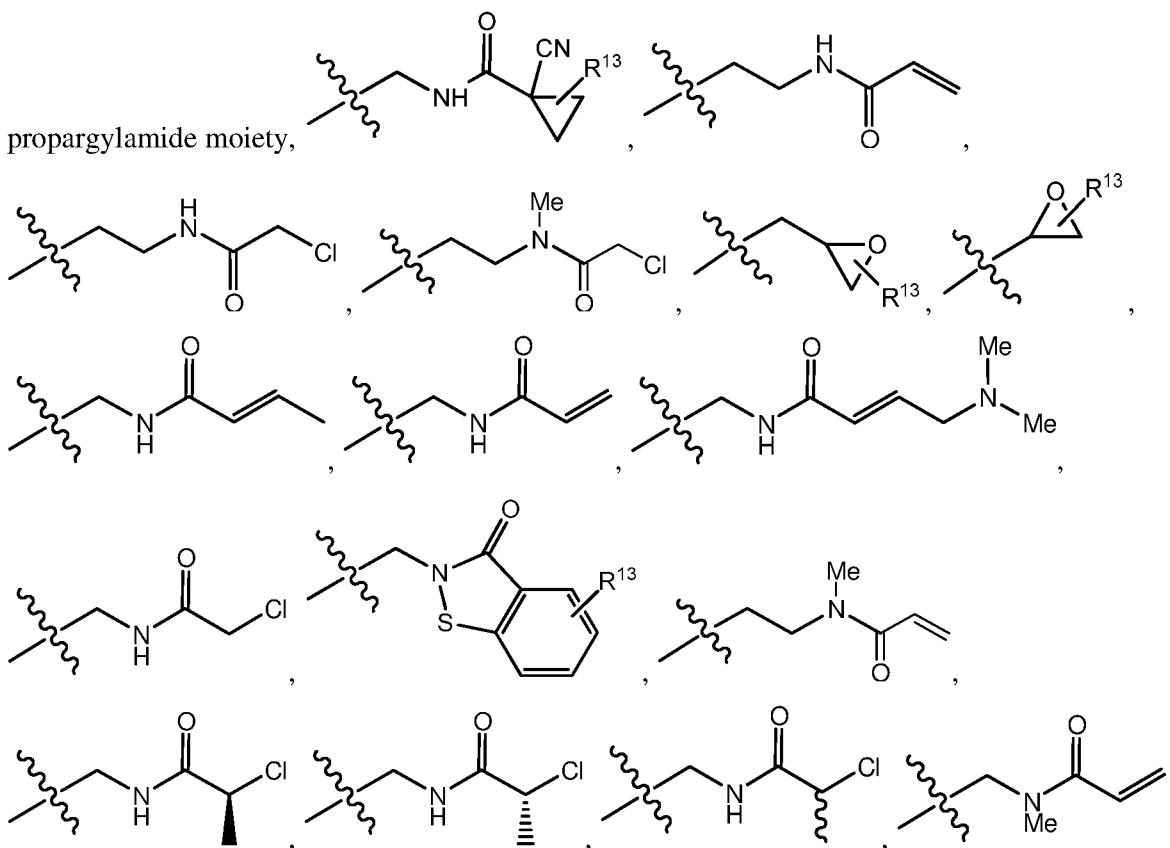


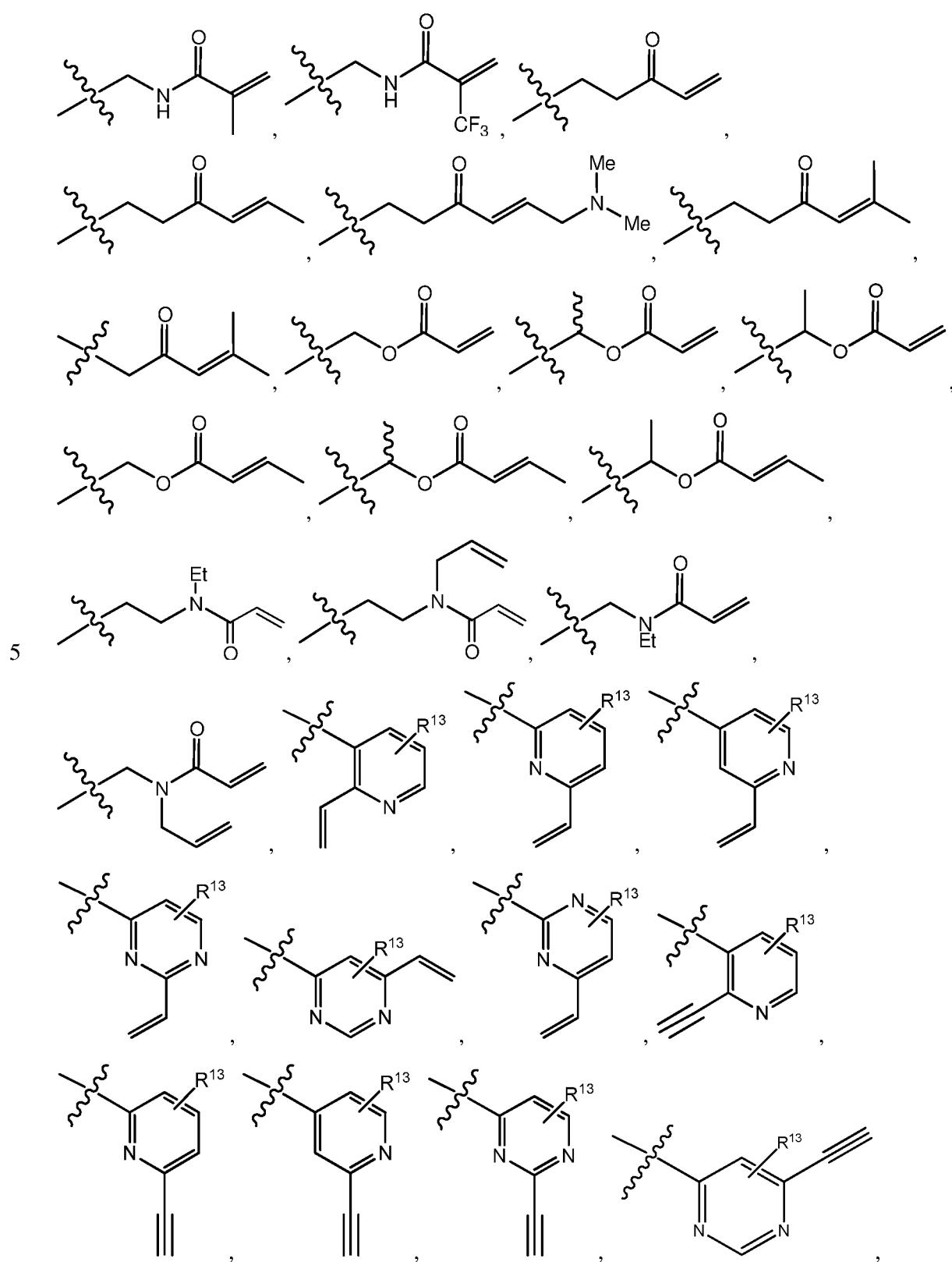
- [0508] Embodiment P32. The compound of embodiment P31 wherein E is

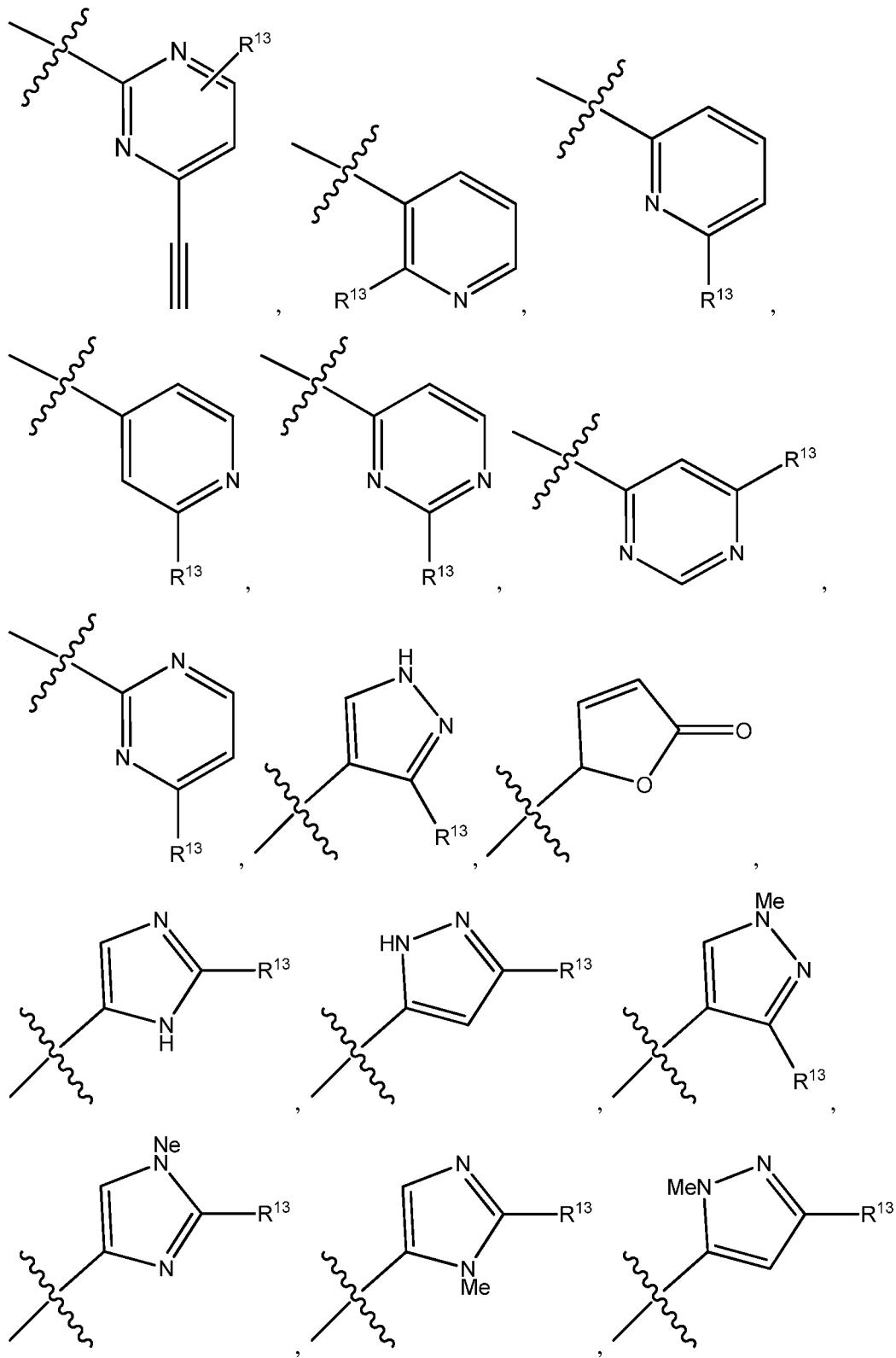
[0509] Embodiment P33. The compound of one of embodiments P27 to P32, wherein Y² is CH.

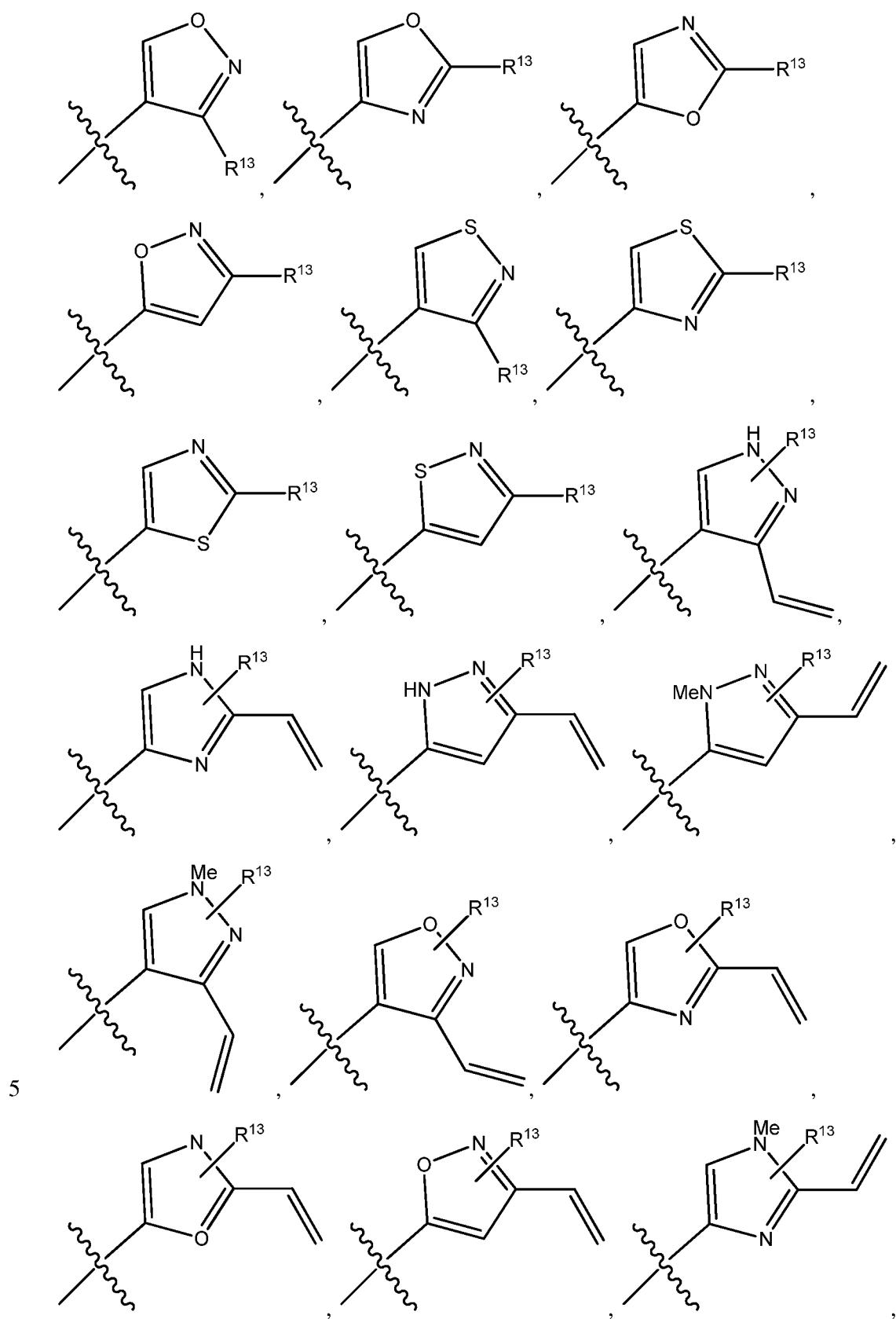
[0510] Embodiment P34. The compound of one of embodiments P27 to P32, wherein Y^2 is N.

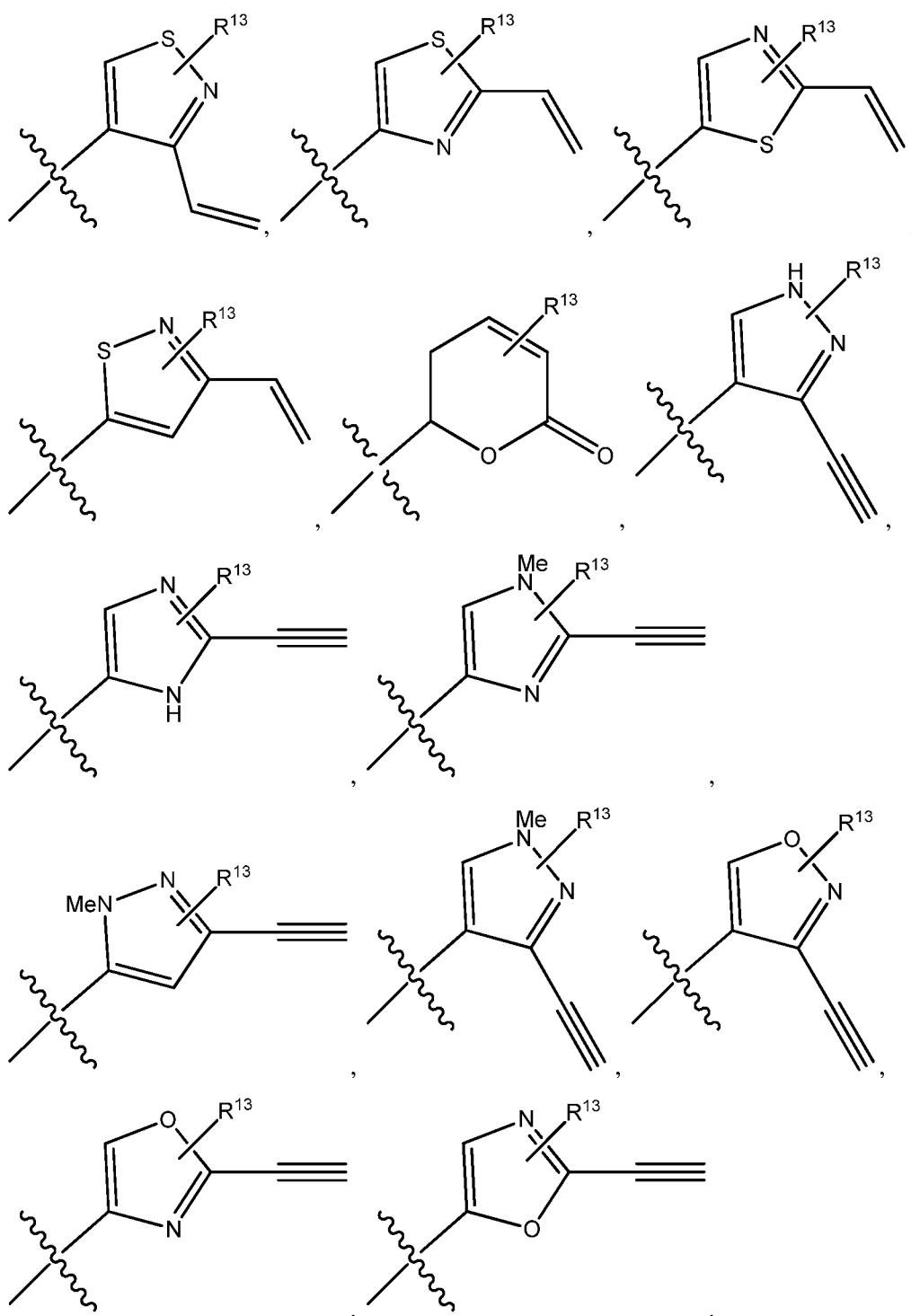
- 5 [0511] Embodiment P35. The compound of one of embodiments P1 to P25, wherein E comprises a substituted or unsubstituted vinyl sulfone moiety, substituted or unsubstituted vinyl sulfonamide moiety, substituted or unsubstituted fluoro(C₁-C₄)alkylketone moiety, substituted or unsubstituted chloro(C₁-C₄)alkylketone moiety, substituted or unsubstituted acrylamide moiety, substituted or unsubstituted disulfide moiety, substituted or unsubstituted thiol moiety,
10 substituted or unsubstituted phosphonate moiety, substituted or unsubstituted aldehyde moiety, substituted or unsubstituted enone moiety, substituted or unsubstituted diazomethylketone moiety, substituted or unsubstituted diazomethylamide moiety, substituted or unsubstituted cyanocyclopropyl carboxamide moiety, substituted or unsubstituted epoxide moiety, substituted or unsubstituted epoxyketone moiety, substituted or unsubstituted epoxyamide moiety,
15 substituted or unsubstituted aryl aldehyde moiety, substituted or unsubstituted aryl dialdehyde moiety, substituted or unsubstituted dialdehyde moiety, substituted or unsubstituted nitrogen mustard moiety, substituted or unsubstituted propargyl moiety, substituted or unsubstituted

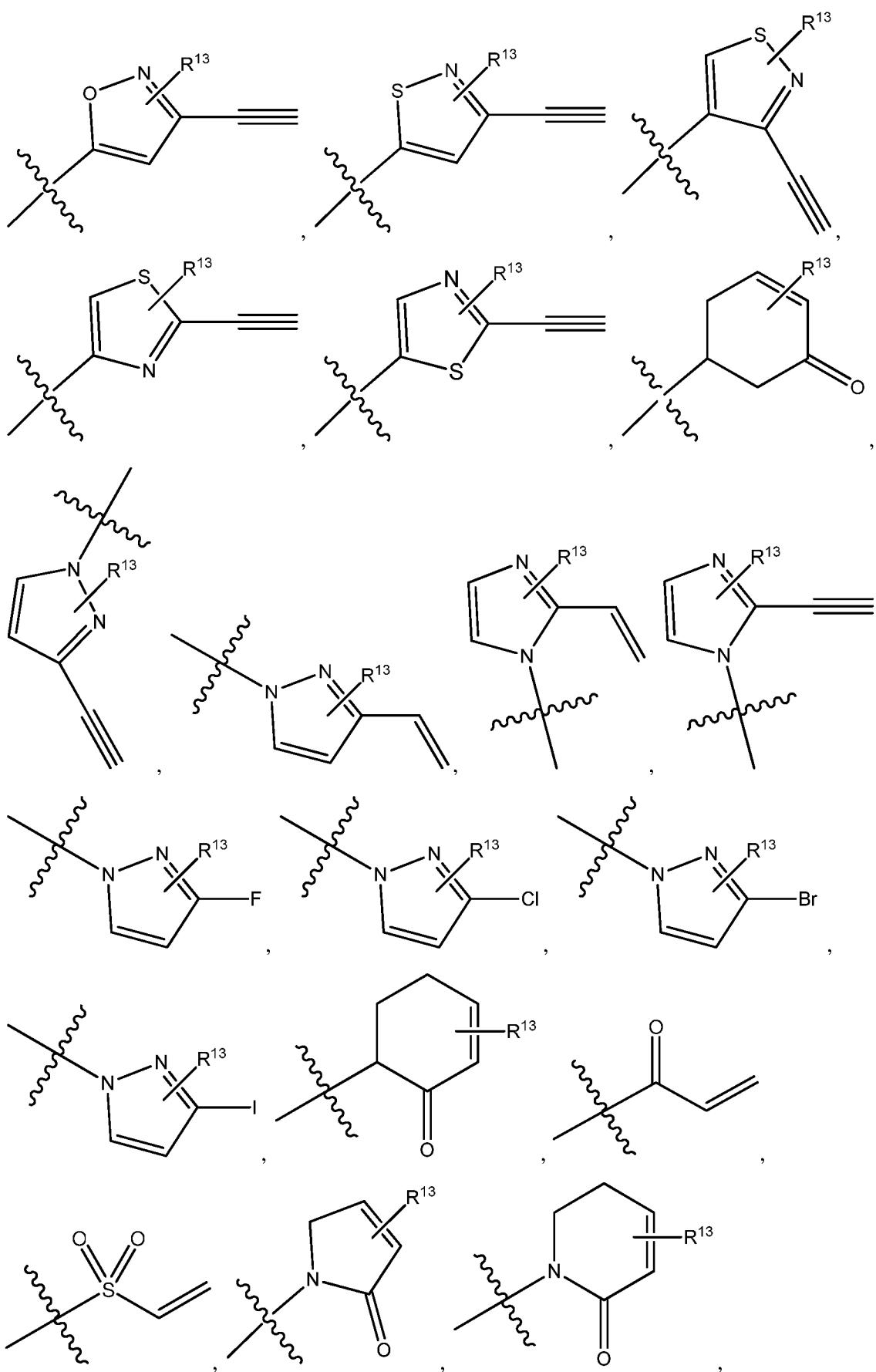


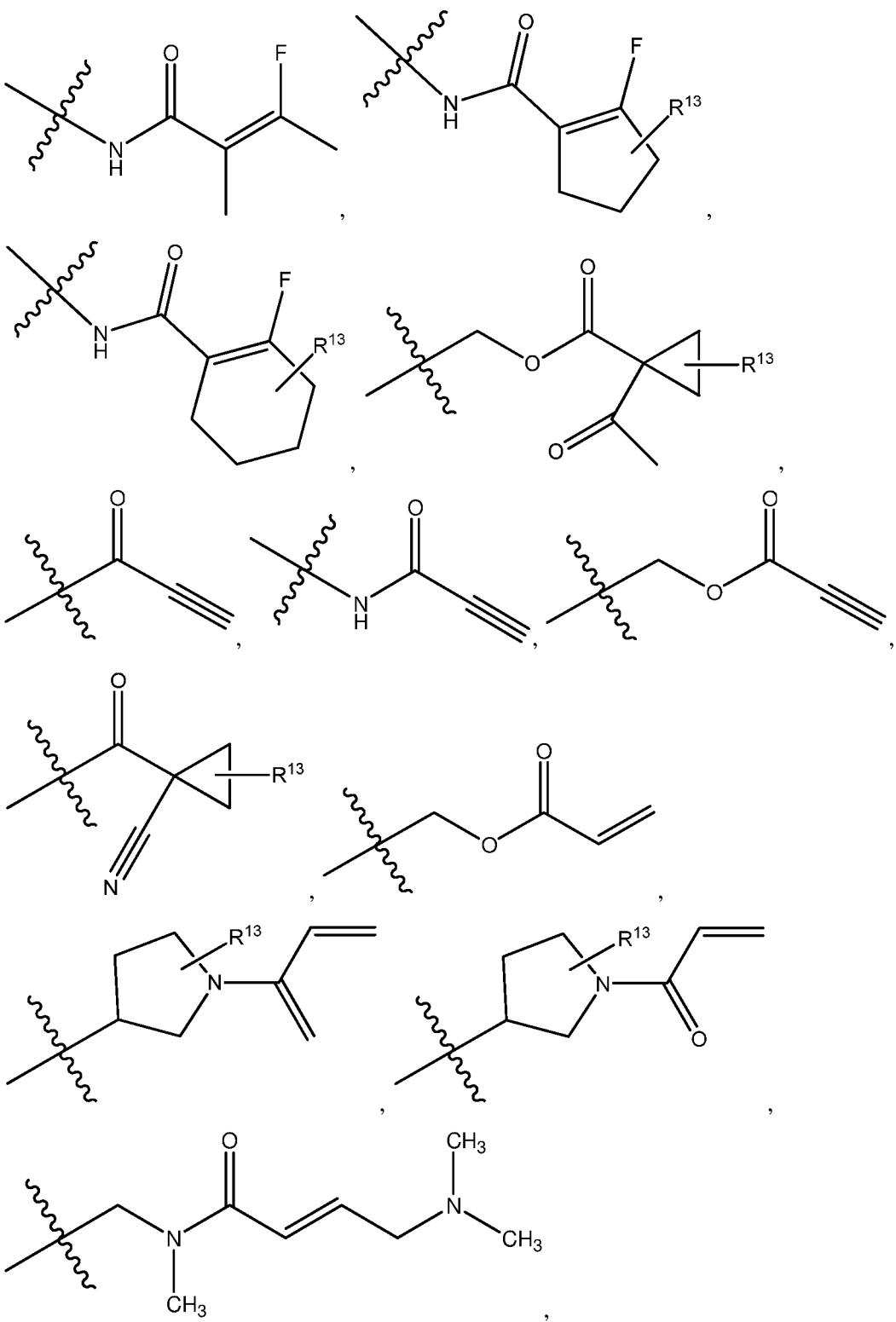


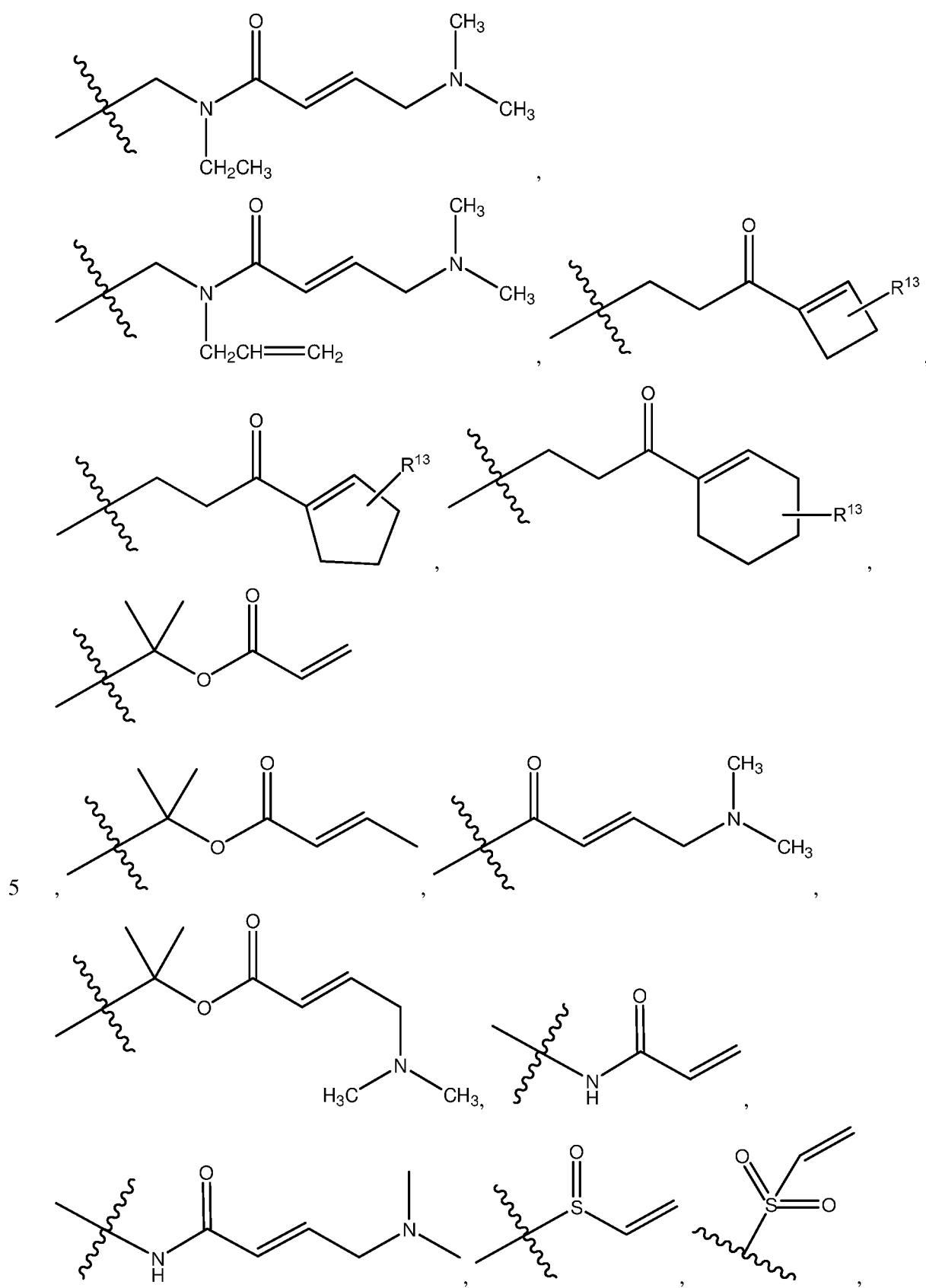


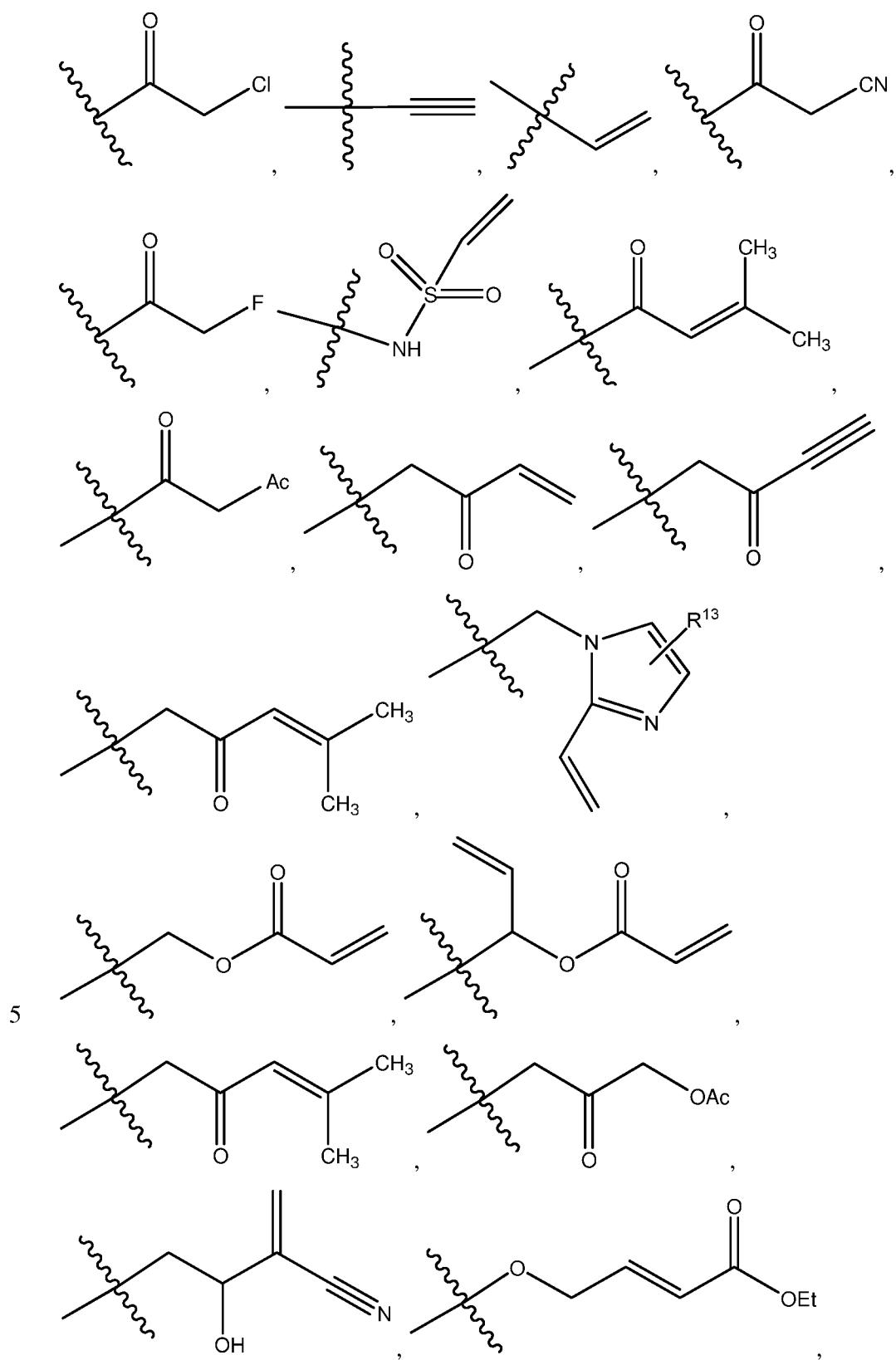


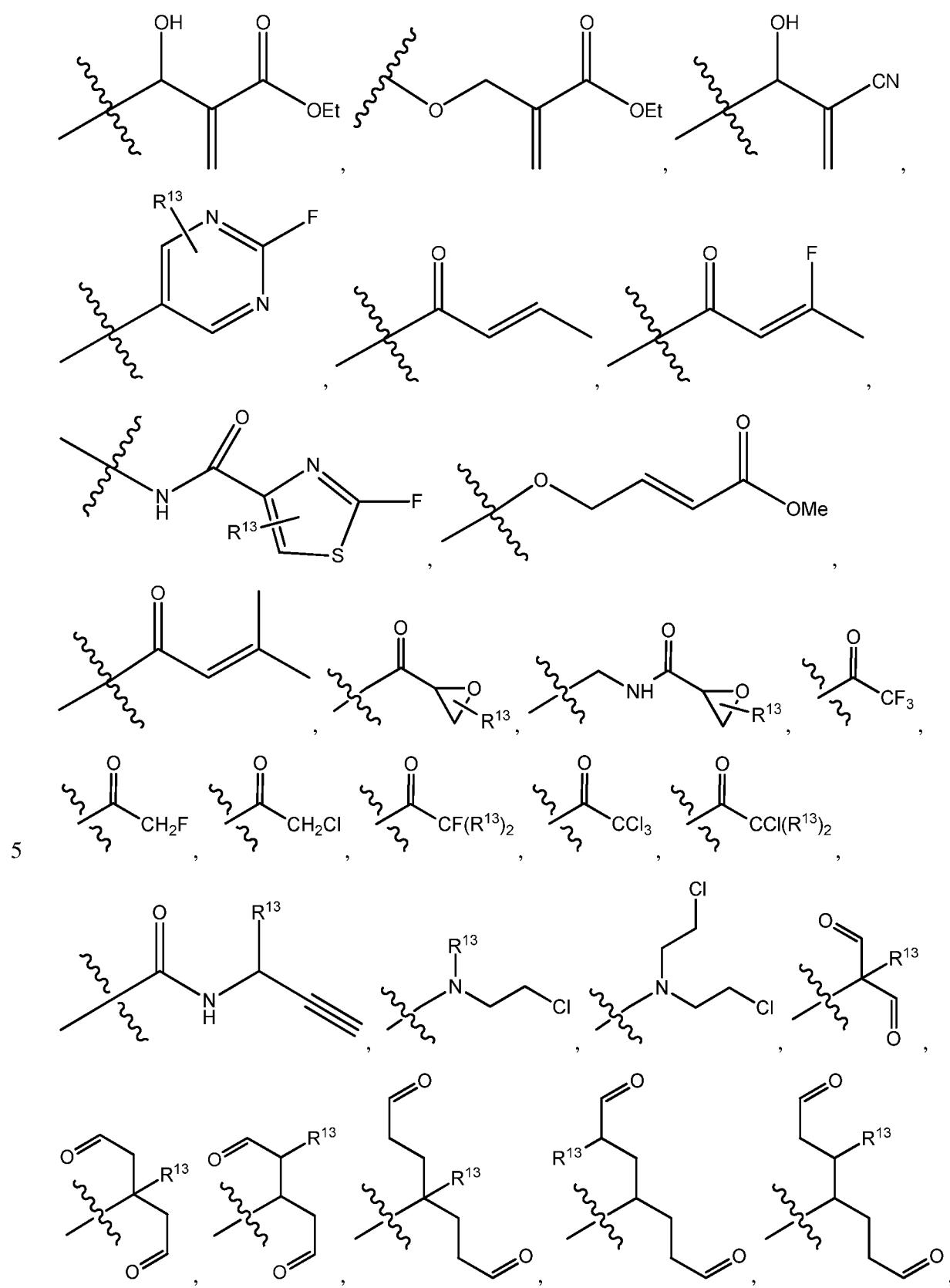


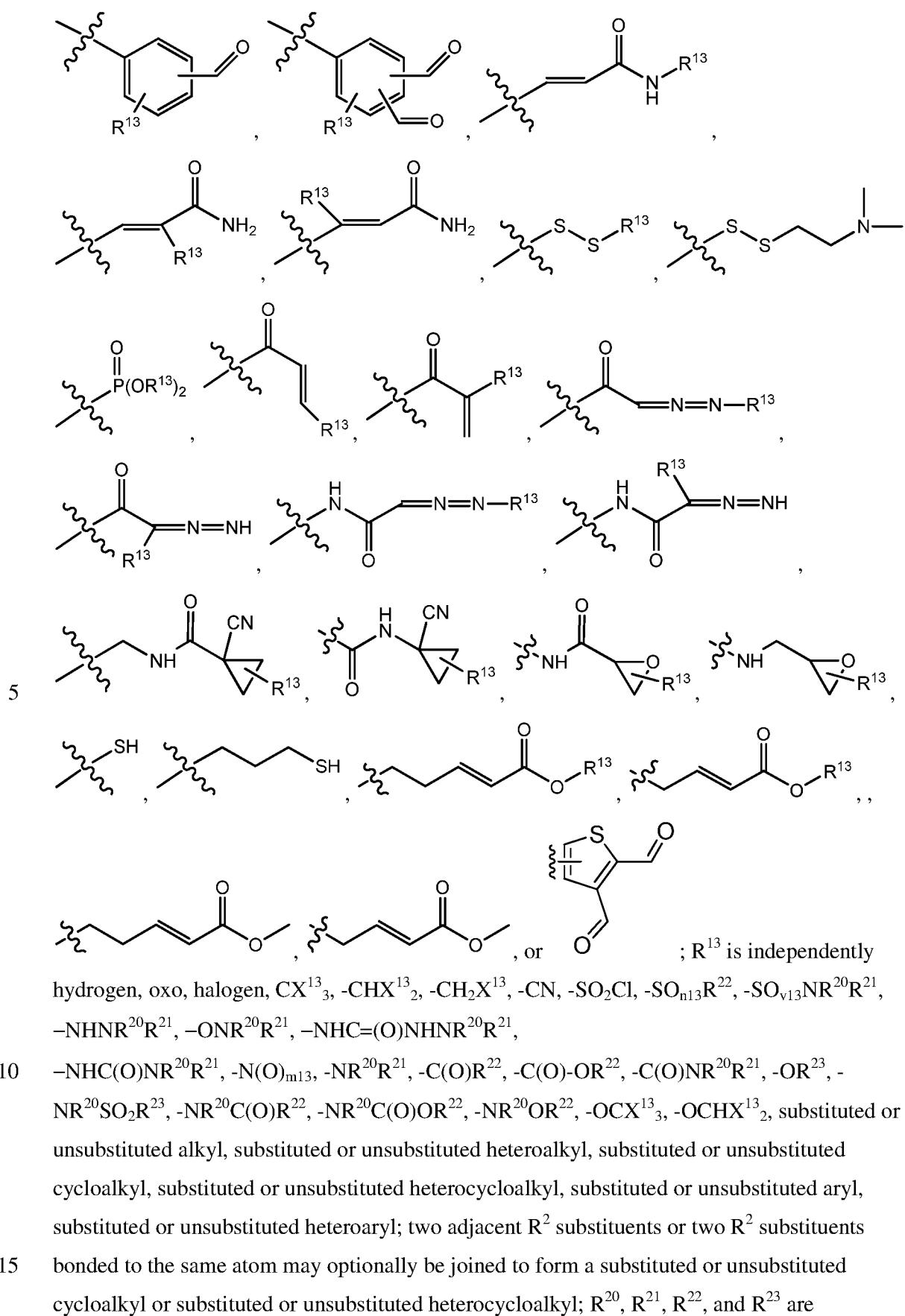










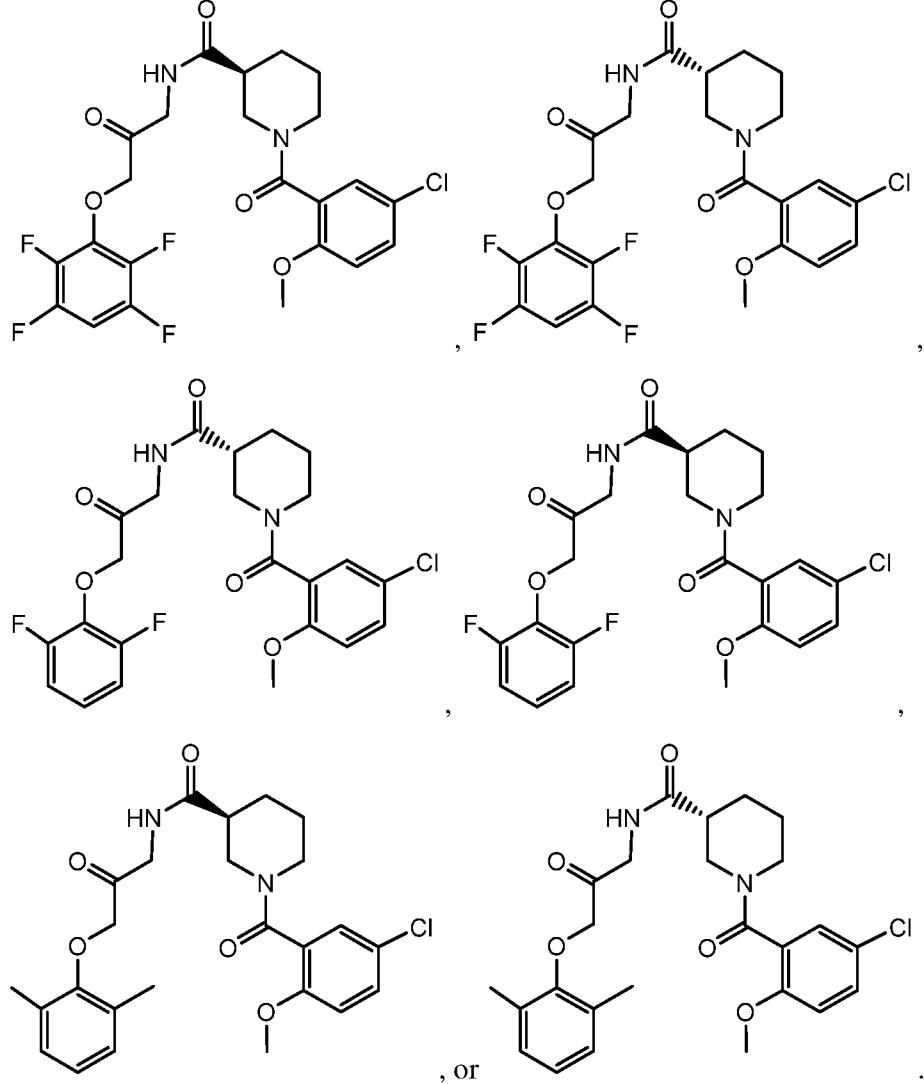


independently hydrogen, halogen, -CX^A₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX^A₃, -OCHX^A₂, -CHX^A₂, -CH₂X^A, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

5 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl; R²⁰ and R²¹ substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; each X^A and X¹³ is independently -F, -Cl, -Br, or -I; n13
and v13 are independently an integer from 0 to 4; and m13 is independently an integer from 1 to
10 2.

10 2.

[0512] Embodiment P36. A compound having the formula:



[0513] Embodiment P37. A pharmaceutical composition comprising the compound of any one of embodiments P1 to P36 and a pharmaceutically acceptable excipient.

[0514] Embodiment P38. A method of reducing the level of activity of a K-Ras protein, said method comprising contacting the K-Ras protein with a compound of one of embodiments P1 to

5 P36.

[0515] Embodiment P39. A method of reducing the level of activity of a K-Ras-4B protein, said method comprising contacting the K-Ras-4B protein with a compound of one of embodiments P1 to P36.

[0516] Embodiment P40. A method for treating cancer, said method comprising

10 administering to a subject in need thereof a therapeutically effective amount of a compound of one of embodiments P1 to P36.

[0517] Embodiment P41. The method of embodiment P40, wherein said cancer is pancreatic cancer, lung cancer, or colorectal cancer.

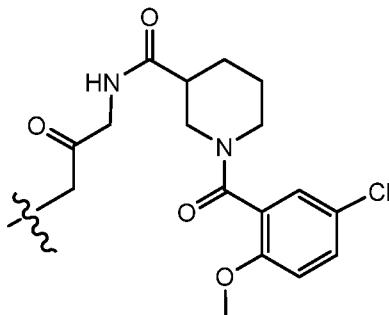
[0518] Embodiment P42. A K-Ras protein covalently bonded to a compound of one of

15 embodiments P1 to P36.

[0519] Embodiment P43. The K-Ras protein of embodiment P42, wherein the compound is covalently bonded to a cysteine residue of the protein.

[0520] Embodiment P44. The K-Ras protein of embodiment P42, wherein the compound is irreversibly covalently bonded to a cysteine residue of the protein.

20 [0521] Embodiment P45. A K-Ras protein covalently bonded to a compound having the



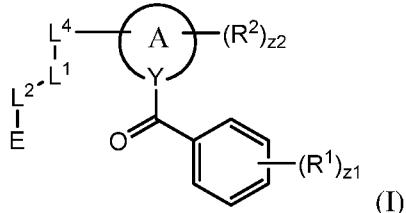
formula:

[0522] Embodiment P46. The K-Ras protein of embodiment P45, wherein the compound is covalently bonded to a cysteine residue of the protein.

[0523] Embodiment P47. The K-Ras protein of embodiment P45, wherein the compound is covalently bonded to a cysteine residue of the protein corresponding to C185 of human K-Ras-4B.

VIII. Additional Embodiments

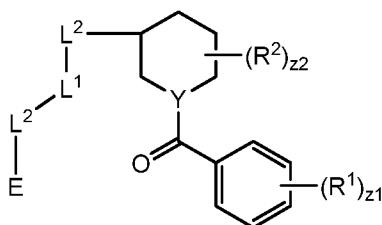
5 **[0524]** Embodiment 1. A compound having the formula:



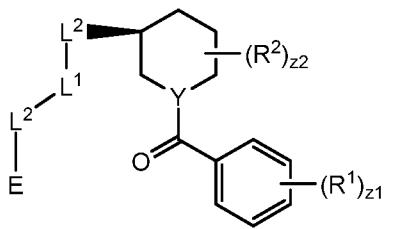
wherein, Y is N or CH; Ring A is a C₃-C₇ cycloalkyl or 3 to 7 membered heterocycloalkyl; R¹ is independently halogen, CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR⁷R⁸, -NHNR⁷R⁸, -ONR⁷R⁸, -NHC=(O)NHNR⁷R⁸,
 10 -NHC(O)NR⁷R⁸, -N(O)_{m1}, -NR⁷R⁸, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR⁷R⁸, -OR¹⁰, -NR⁷SO₂R¹⁰, -NR⁷C(O)R⁹, -NR⁷C(O)OR⁹, -NR⁷OR⁹, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R¹ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; L¹ is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene; L² is a
 15 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or
 20 unsubstituted arylene, substituted or unsubstituted heteroarylene; L⁴ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁴-, -NR⁴C(O)-, -C(O)NR⁴-, -SO₂NR⁴-, -NR⁴SO₂-, -NR⁴SO₂-, -OC(O)NR⁴-, -NR⁴C(O)O-, substituted or unsubstituted C₁-C₃ alkylene, substituted or unsubstituted 2 to 3 membered heteroalkylene; E is an electrophilic moiety; R² is independently oxo, halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -SO₂Cl, -SO_{n2}R¹⁴, -SO_{v2}NR¹¹R¹², -NHNR¹¹R¹²,

$-\text{ONR}^{11}\text{R}^{12}$, $-\text{NHC}=(\text{O})\text{NHNR}^{11}\text{R}^{12}$,
 $-\text{NHC(O)NR}^{11}\text{R}^{12}$, $-\text{N(O)}_{m2}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{C(O)R}^{14}$, $-\text{C(O)-OR}^{14}$, $-\text{C(O)NR}^{11}\text{R}^{12}$, $-\text{OR}^{15}$, -
 $\text{NR}^{11}\text{SO}_2\text{R}^{15}$, $-\text{NR}^{11}\text{C(O)R}^{14}$, $-\text{NR}^{11}\text{C(O)OR}^{14}$, $-\text{NR}^{11}\text{OR}^{14}$, $-\text{OCX}_3^2$, $-\text{OCHX}_2^2$, substituted or
 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 5 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,
 substituted or unsubstituted heteroaryl; two adjacent R^2 substituents or two R^2 substituents
 bonded to the same atom may optionally be joined to form a substituted or unsubstituted
 cycloalkyl or substituted or unsubstituted heterocycloalkyl; R^4 is independently hydrogen,
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 10 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, substituted or unsubstituted heteroaryl; R^7 , R^8 , R^9 , R^{10} , R^{7B} , R^{8B} , R^{9B} , R^{10B} ,
 R^{11} , R^{12} , R^{14} , and R^{15} are independently hydrogen,
 halogen, $-\text{CX}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, -
 SO_2NH_2 , $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC(O)H}$, -
 15 NHC(O)OH , $-\text{NHOH}$, $-\text{OCX}_3$, $-\text{OCHX}_2$, $-\text{CHX}_2$, $-\text{CH}_2\text{X}$, substituted or unsubstituted alkyl,
 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 heteroaryl; R^7 and R^8 substituents bonded to the same nitrogen atom may optionally be joined to
 form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;
 20 R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a
 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X ,
 X^1 , and X^2 is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$; $n1$, $n2$, $v1$, and $v2$ are independently an integer
 from 0 to 4; $m1$ and $m2$ are independently an integer from 1 to 2; $z1$ is independently an integer
 from 0 to 5; and $z2$ is independently an integer from 0 to 10.

25 [0525] Embodiment 2. The compound of embodiment 1, having the formula:



[0526] Embodiment 3. The compound of embodiment 1, having the formula:



[0527] Embodiment 4. The compound of one of embodiments 1 to 3, wherein Y is CH.

[0528] Embodiment 5. The compound of one of embodiments 1 to 3, wherein Y is N.

[0529] Embodiment 6. The compound of one of embodiments 1 to 5, wherein R¹ is

5 independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or 10 unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0530] Embodiment 7. The compound of one of embodiments 1 to 5, wherein R¹ is independently

halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OH, -SH, -COOH, -OCX¹₃, -OCHX¹₂, -CH₃, -CH₂CH₃, -OC H₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃.

15 **[0531]** Embodiment 8. The compound of one of embodiments 1 to 5, wherein R¹ is independently halogen or -OCH₃.

[0532] Embodiment 9. The compound of one of embodiments 1 to 8, wherein z1 is 2.

[0533] Embodiment 10. The compound of one of embodiments 1 to 8, wherein z1 is 3.

[0534] Embodiment 11. The compound of one of embodiments 1 to 10, wherein R² is

20 independently oxo, halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl,

substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0535] Embodiment 12. The compound of one of embodiments 1 to 10, wherein R² is independently oxo,

5 halogen, -CX²₃, -CHX²₂, -CH₂X², --OH, -SH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -OC H₂CH₃, -SCH₃, or -SCH₂CH₃.

[0536] Embodiment 13. The compound of one of embodiments 1 to 12, wherein z2 is 0.

[0537] Embodiment 14. The compound of one of embodiments 1 to 13, wherein L¹ is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

10 **[0538]** Embodiment 15. The compound of one of embodiments 1 to 13, wherein L¹ is a bond, unsubstituted C₁-C₄ alkylene, or unsubstituted 2 to 4 membered heteroalkylene.

[0539] Embodiment 16. The compound of one of embodiments 1 to 13, wherein L¹ is a bond.

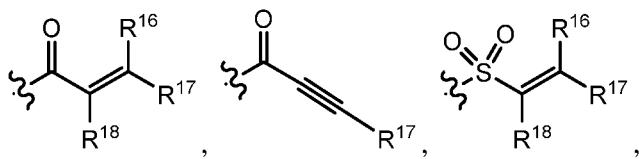
15 **[0540]** Embodiment 17. The compound of one of embodiments 1 to 16, wherein L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, - NHSO₂-, -OC(O)NH-, -NHC(O)O-, -NHC(O)NH-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

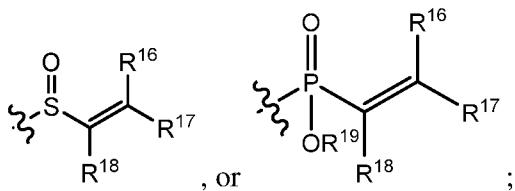
20 **[0541]** Embodiment 18. The compound of one of embodiments 1 to 16, wherein L² is a bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C₁-C₄ alkylene, or unsubstituted 2 to 4 membered heteroalkylene.

[0542] Embodiment 19. The compound of one of embodiments 1 to 16, wherein L² is a bond, -NH-.

[0543] Embodiment 20. The compound of one of embodiments 1 to 16, wherein L² is a bond.

25 **[0544]** Embodiment 21. The compound of one of embodiments 1 to 20, wherein E is





wherein R¹⁶ is independently hydrogen, halogen, CX¹⁶₃, -CHX¹⁶₂, -

CH₂X¹⁶, -CN, -SO_{n16}R^{16D}, -SO_{v16}NR^{16A}R^{16B}, -NHNR^{16A}R^{16B}, -ONR^{16A}R^{16B},
-NHC=(O)NHNR^{16A}R^{16B},

5 -NHC(O)NR^{16A}R^{16B}, -N(O)_{m16}, -NR^{16A}R^{16B}, -C(O)R^{16C}, -C(O)-OR^{16C}, -C(O)NR^{16A}R^{16B}, -OR^{16D},
-NR^{16A}SO₂R^{16D}, -NR^{16A}C(O)R^{16C}, -NR^{16A}C(O)OR^{16C}, -NR^{16A}OR^{16C}, -OCX¹⁶₃, -OCHX¹⁶₂,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, substituted or unsubstituted heteroaryl; R¹⁷ is independently hydrogen,

10 halogen, CX¹⁷₃, -CHX¹⁷₂, -CH₂X¹⁷, -CN, -SO_{n17}R^{17D}, -SO_{v17}NR^{17A}R^{17B}, -NHNR^{17A}R^{17B},
-ONR^{17A}R^{17B}, -NHC=(O)NHNR^{17A}R^{17B},
-NHC(O)NR^{17A}R^{17B}, -N(O)_{m17}, -NR^{17A}R^{17B}, -C(O)R^{17C}, -C(O)-OR^{17C}, -C(O)NR^{17A}R^{17B}, -OR^{17D},
-NR^{17A}SO₂R^{17D}, -NR^{17A}C(O)R^{17C}, -NR^{17A}C(O)OR^{17C}, -NR^{17A}OR^{17C}, -OCX¹⁷₃, -OCHX¹⁷₂,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

15 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, substituted or unsubstituted heteroaryl; R¹⁸ is independently hydrogen,
halogen, CX¹⁸₃, -CHX¹⁸₂, -CH₂X¹⁸, -CN, -SO_{n18}R^{18D}, -SO_{v18}NR^{18A}R^{18B}, -NHNR^{18A}R^{18B},
-ONR^{18A}R^{18B}, -NHC=(O)NHNR^{18A}R^{18B},
-NHC(O)NR^{18A}R^{18B}, -N(O)_{m18}, -NR^{18A}R^{18B}, -C(O)R^{18C}, -C(O)-OR^{18C}, -C(O)NR^{18A}R^{18B}, -OR^{18D},

20 -NR^{18A}SO₂R^{18D}, -NR^{18A}C(O)R^{18C}, -NR^{18A}C(O)OR^{18C}, -NR^{18A}OR^{18C}, -OCX¹⁸₃, -OCHX¹⁸₂,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, substituted or unsubstituted heteroaryl; R¹⁹ is independently hydrogen,
halogen, CX¹⁹₃, -CHX¹⁹₂, -CH₂X¹⁹, -CN, -SO_{n19}R^{19D}, -SO_{v19}NR^{19A}R^{19B}, -NHNR^{19A}R^{19B},

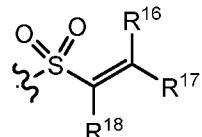
25 -ONR^{19A}R^{19B}, -NHC=(O)NHNR^{19A}R^{19B},
-NHC(O)NR^{19A}R^{19B}, -N(O)_{m19}, -NR^{19A}R^{19B}, -C(O)R^{19C}, -C(O)-OR^{19C}, -C(O)NR^{19A}R^{19B}, -OR^{19D},
-NR^{19A}SO₂R^{19D}, -NR^{19A}C(O)R^{19C}, -NR^{19A}C(O)OR^{19C}, -NR^{19A}OR^{19C}, -OCX¹⁹₃, -OCHX¹⁹₂,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

30 unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B},

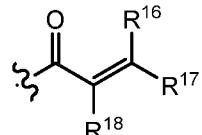
R^{17C} , R^{17D} , R^{18A} , R^{18B} , R^{18C} , R^{18D} , R^{19A} , R^{19B} , R^{19C} , R^{19D} , are independently hydrogen, halogen, -CX₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -

NHC(O)OH, -NHOH, -OCX₃, -OCHX₂, -CHX₂, -CH₂X, substituted or unsubstituted alkyl,

- 5 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be
10 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X, X¹⁶, X¹⁷, X¹⁸ and X¹⁹ is independently -F, -Cl, -Br, or -I; n16, n17, n18, n19,
15 v16, v17, v18, and v19 are independently an integer from 0 to 4; and m16, m17, m18, and m19 are independently an integer from 1 to 2.



[0545] Embodiment 22. The compound of embodiment 21, wherein E is .

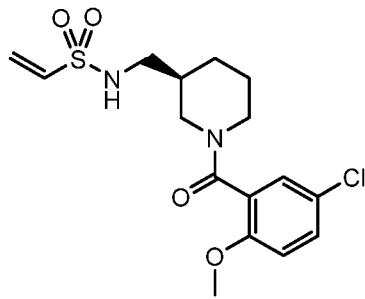


[0546] Embodiment 23. The compound of embodiment 21, wherein E is .

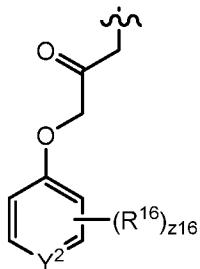
- 20 [0547] Embodiment 24. The compound of one of embodiments 21 to 23, wherein R¹⁶, R¹⁷, and R¹⁸ are independently hydrogen, -CH₂NH₂, -CH₂CH₂NH₂, -CH₂N(CH₃)₂, or -CH₂CH₂N(CH₃)₂.

[0548] Embodiment 25. The compound of one of embodiments 21 to 24, wherein L⁴ is a bond or -CH₂-.

- 25 [0549] Embodiment 26. The compound of one of embodiments 21, 22, 24, or 25, having the formula:



[0550] Embodiment 27. The compound of one of embodiments 1 to 20, wherein E is



; wherein R^{16} is independently halogen, CX^{16}_3 , $-\text{CHX}^{16}_2$, -

CH_2X^{16} , -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂,

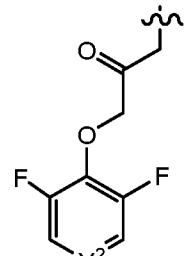
- 5 -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NSO₂H, -NHC(O)H, -
 NHC(O)OH, -NHOH, -OCX¹⁶₃, -OCHX¹⁶₂, substituted or unsubstituted alkyl, substituted or
 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; Y² is
 N or CH; z16 is an integer from 0 to 4; and each X¹⁶ is independently -F, -Cl, -Br, or -I.

10 **[0551]** Embodiment 28. The compound of embodiment 27 wherein R¹⁶ is independently
 halogen.

[0552] Embodiment 29. The compound of embodiment 27 wherein R¹⁶ is independently -F.

[0553] Embodiment 30. The compound of one of embodiments 27 to 29, wherein z16 is 4.

[0554] Embodiment 31. The compound of one of embodiments 27 to 29, wherein z16 is 2.



- 15 **[0555]** Embodiment 32. The compound of embodiment 31 wherein E is

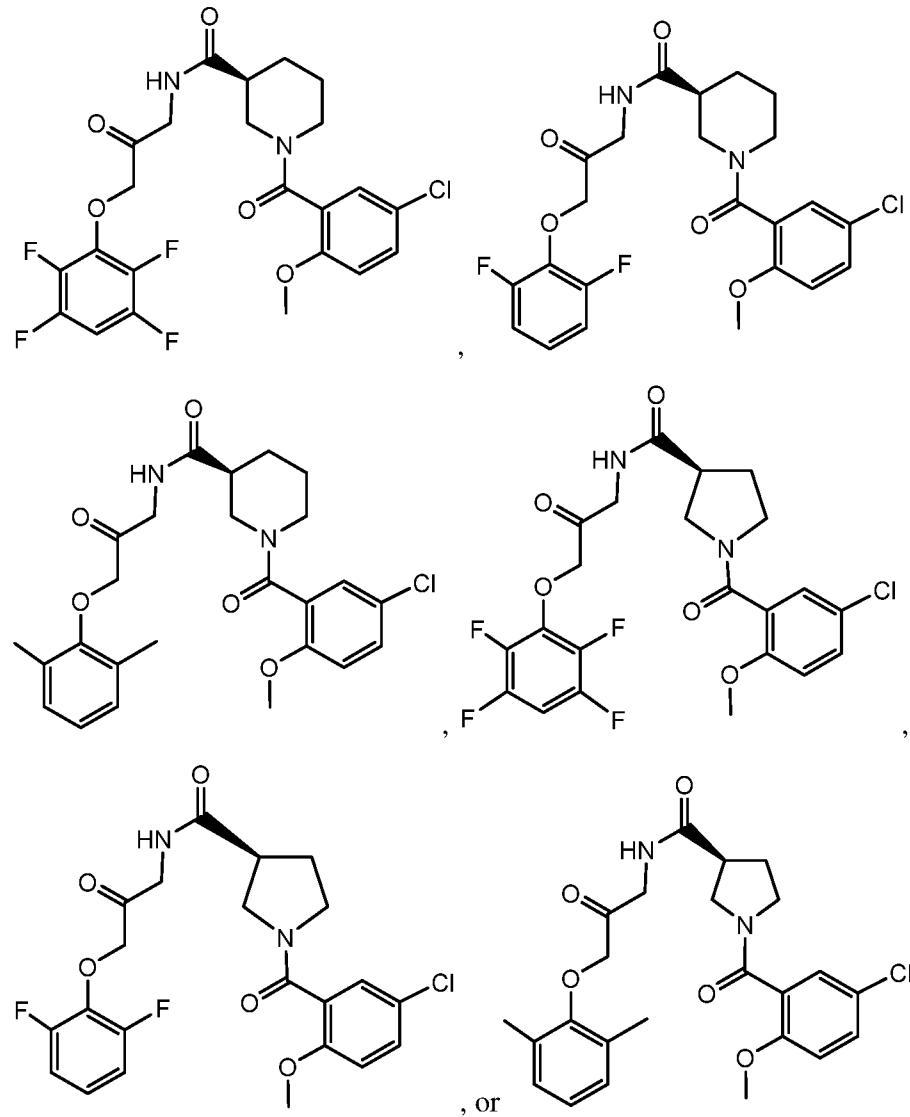
[0556] Embodiment 33. The compound of one of embodiments 27 to 32, wherein Y² is CH.

[0557] Embodiment 34. The compound of one of embodiments 27 to 32, wherein Y² is N.

[0558] Embodiment 35. The compound of one of embodiments 27 to 34, wherein L⁴ is –N(R⁴)C(O)-.

5 [0559] Embodiment 36. The compound of one of embodiments 27 to 35, wherein R⁴ is hydrogen.

[0560] Embodiment 37. The compound of one of embodiments 27 to 36, having the formula:



[0561] Embodiment 38. A pharmaceutical composition comprising the compound of any one of embodiments 1 to 37 and a pharmaceutically acceptable excipient.

[0562] Embodiment 39. A method of reducing the level of activity of a K-Ras protein, said method comprising contacting the K-Ras protein with a compound of one of embodiments 1 to 5 37.

[0563] Embodiment 40. A method of reducing the level of activity of a K-Ras-4B protein, said method comprising contacting the K-Ras-4B protein with a compound of one of embodiments 1 to 37.

[0564] Embodiment 41. A method for treating cancer, said method comprising 10 administering to a subject in need thereof a therapeutically effective amount of a compound of one of embodiments 1 to 37.

[0565] Embodiment 42. The method of embodiment 41, wherein said cancer is pancreatic cancer, lung cancer, or colorectal cancer.

[0566] Embodiment 43. A K-Ras protein covalently bonded to a compound of one of 15 embodiments 1 to 37.

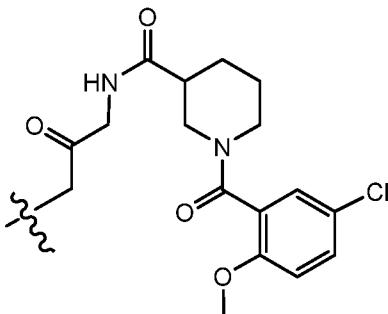
[0567] Embodiment 44. The K-Ras protein of embodiment 43, wherein the compound is covalently bonded to a cysteine residue of the protein.

[0568] Embodiment 45. The K-Ras protein of embodiment 43, wherein the compound is irreversibly covalently bonded to a cysteine residue of the protein.

20 **[0569]** Embodiment 46. The K-Ras protein of embodiment 43, wherein the compound is covalently bonded to a histidine residue of the protein.

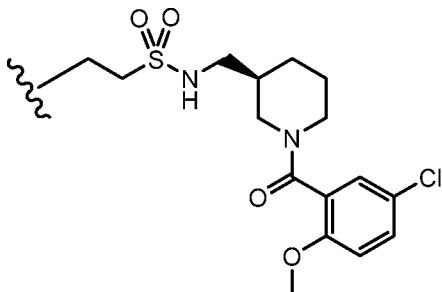
[0570] Embodiment 47. The K-Ras protein of embodiment 43, wherein the compound is irreversibly covalently bonded to a histidine residue of the protein.

[0571] Embodiment 48. A K-Ras protein covalently bonded to a compound having the



formula:

[0572] Embodiment 49. A K-Ras protein covalently bonded to a compound having the



formula:

5 **[0573]** Embodiment 50. The K-Ras protein of one of embodiments 48 to 49, wherein the compound is covalently bonded to a cysteine residue of the protein.

[0574] Embodiment 51. The K-Ras protein of embodiment 48, wherein the compound is covalently bonded to a cysteine residue of the protein corresponding to C185 of human K-Ras-4B.

10 **[0575]** Embodiment 52. The K-Ras protein of one of embodiments 48 to 49, wherein the compound is covalently bonded to a histidine residue of the protein.

[0576] Embodiment 53. The K-Ras protein of embodiment 48, wherein the compound is covalently bonded to a histidine residue of the protein corresponding to H95 of human K-Ras-4B.

15 IX. Examples

Example 1. Covalent modification of H95 residue in Kras using tethering small molecule compounds.

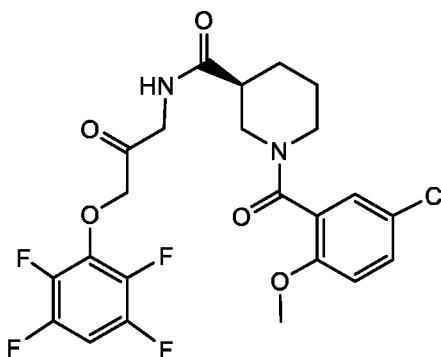
[0577] K-Ras is the most frequently mutated oncogene, with activating mutations in this small GTPase found in 30% of human cancers. Mutations in K-Ras are associated with resistance to chemotherapy or radiation. Patients whose tumors harbor these mutations are often excluded

from targeted therapies, and tend to have poor overall survival. Despite decades of research effort, there are no effective treatments for cancers with mutant K-Ras.

[0578] The development of small-molecule inhibitors that directly target Ras is highly desirable but has proven to be a major challenge. The isoforms of the Ras protein (H-Ras, N-Ras and K-Ras) play essential roles in normal cells. Therefore, the ideal Ras-targeting drug would specifically target the oncogenic form of the protein. However, targeting K-Ras (i.e. without distinguishing between wildtype and mutant protein) could be an effective approach, since all isoforms are redundant in normal tissues, and eliminating one is expected to be tolerable.

[0579] Considerable effort has been directed towards inhibiting Ras posttranslational processing. Inhibitors of farnesyl transferases (FTIs) have been investigated for their potential to attenuate C-terminal lipid modification of Ras required for correct plasma membrane localization and subsequent signaling. This approach is challenging since K-Ras was found to undergo alternative prenylation and remain oncogenically active.

[0580] The covalent modification of the CAAX-box cysteine of K-Ras may block prenylation at that site and inhibit the subsequent translocation/attachment of the K-Ras protein to the membrane that is necessary for its activity. This could be achieved with small molecule inhibitors designed for binding to the CAAX-box cysteine of K-Ras. The complication of alternative prenylation, inherent in alternative methods of inhibiting Ras prenylation, would be bypassed. Tethering compounds are composed of a fragment group that confers a non-covalent interaction with a potential pocket on the protein. Additionally, there is a disulfide moiety that interacts covalently with the CAAX-box cysteine under reducing conditions in a reversible fashion by disulfide exchange. The screen of recombinant His-tagged K-Ras G12D protein against the library of 1600 tethering compounds, followed by SAR, led to development of the FB9, depicted below:



(FB9).

25

[0581] In embodiments, compounds described herein (e.g., FB9) covalently labeled C185 in the full-length recombinant K-Ras4B. However, if FB9 is reacted with recombinant FME-Kras4B protein (farnesylated-carboxymethylated), where C185 is modified/blocked by farnesyl (as it is in the native, fully post-translationally processed K-Ras 4B *in vivo*), FB9 is not able to 5 displace the farnesyl from C185; instead, it covalently modifies other residues in the K-Ras4B protein.

[0582] Herein we show that in embodiments the recombinant FME-Kras4B, FB9 covalently 10 modifies histidine 95 residue (H95), that is unique for Kras (Q in H-Ras or L in N-Ras). This residue is nucleophilic, making it vulnerable to electrophilic attack. This modification not only was observed with recombinant FME-Kras4B protein; it was also detected in Kras4B G12V that was purified from cells treated with the compound.

[0583] **Chemical modification of unprocessed KRAS-4b at His-95** (protein G-Hs.KRAS4b(1-188), mass (average) 21481.59 Da).

[0584] KRAS4b (FIG. 43) was modified by FB9 *in vitro* (using 8.8-fold molar excess of FB9 15 for 1h at 37 °C, followed by 16 h at room temperature, 22 °C). MALDI-TOF MS analysis revealed that chemical modification of the protein was close to complete. Molecular species with 1 and 2 and 3 modification groups were present (FIG. 44).

[0585] To identify the modified amino acid residues, the protein preparation was digested by 20 protease Glu-C. Analysis of the digest by MALDI-TOF MS revealed the presence of peptides with m/z 2324 and 2674 with 2324 corresponding to unmodified peptide KMSKDGKKKKKSCKVCIM (SEQ ID NO:4) (170-189) and 2674 to the same peptide modified by FB9 at Cys-186 (FIG. 45) (confirmed by fragmentation). Peptide with m/z 1735 corresponds to sequence GKKKKKSCKVCIM (SEQ ID NO: 3) (174-189) and m/z 2085 corresponds to the same peptide modified by FB9 at Cys-186 (confirmed by fragmentation).

[0586] To identify other potential residues modified by FB9, peptides obtained after digestion 25 by Glu-C were further digested by trypsin (FIG. 46A). Fragmentation spectrum of a peptide with m/z 1320.614 revealed major fragment of 969, which is close to m/z of peptide DIHHYRE (SEQ ID NO:2) (expected m/z 969.4537, 93-99), suggesting that m/z 1320 corresponds to peptide DIHHYRE (SEQ ID NO:2) modified by FB9 (FIG. 45). Indeed, comparison of fragmentation spectra of peptides 969.485 and 1320.614 demonstrated their relationship. Common fragments 30 are indicated in FIG. 46B.

[0587] Modification of processed (farnesylated and carboxymethylated KRAS4b).

Protein prep GG-HsKRAS-4b, RP1151105092454 FmeKRAS4b (FIG. 47A) was modified by FB9 with 7.6-fold molar excess of FB9 for 1 h at 37 °C, followed by 16 h at room temperature (22 °C). MALDI-TOF MS analysis of chemical modification to the protein revealed that major form represented species with 1 added modification group, less protein had 2 modification groups, and a little with 3 modification groups, some protein was left un-modified (FIG. 47B). To identify the modified amino acid residues protein preparation was digested by trypsin.

[0588] MALDI-TOF MS demonstrated that K-RAS tryptic peptides with m/z 1203

(SFEDIHHYR, SEQ ID NO:6), 1702 (SFEDIHHYREQIK, SEQ ID NO:8), 1858

10 (SFEDIHHYREQIKR, SEQ ID NO:7) are present also in modified form +(350-351) Da. During fragmentation, these modified peptides yielded intensive fragment corresponding to unmodified peptide and fragments of peptide (mostly without modification).

[0589] These peptides were modified on His residues. To identify which His was modified

(i.e. 95 or 96 in the sequence of used recombinant KRAS) fragmentation spectra were analyzed

15 in BioTools when FB9 modification (C17H20Cl1N2O4, 350/351) was set on one of these His residues in Sequence Editor.

[0590] Analysis of fragmentation of m/z 1203.660 and 1554.856 observed in reflector mode

(low intensity in reflector mode but well detected in linear mode as 1554.7) allowed to conclude that in peptide SFEDIHHYR (SEQ ID NO:6) His7 (i.e. H95 in the native protein) is modified. In

20 fragmentation spectrum of 1554 a fragment 825.409 was present but not in a spectrum of 1203. When FB9 modification was on His-7 this fragment was assigned by BioTools as modified y-3. Manual examination of the spectrum confirmed this conclusion.

[0591] Modification of H95 in Kras4B G12V in cells.**[0592] Mouse lung type II epithelial cell line E10 was transduced with HA-tagged KRas4B**

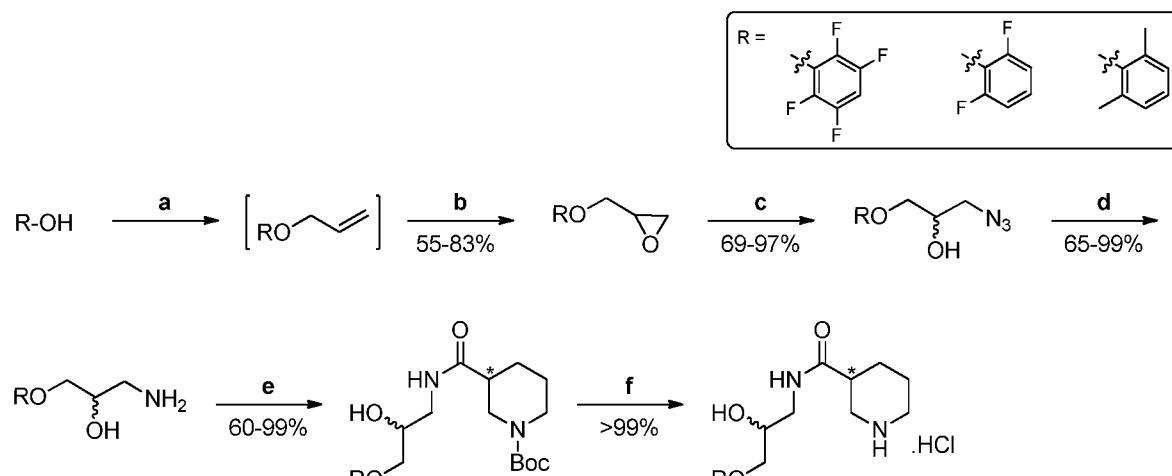
25 G12V, in a tetracycline-inducible retroviral expression vector. Individual clones were developed. Expression of the KRas4B transgene was induced with 500 ng/ml doxycycline for 48 h, then cells were treated with 20 µM of a close analogue of FB9, compound SMDC 993784, for 30 min. Cells homogenates were cleared by centrifugation, and Kras4B G12V was purified from lysates using HA-agarose immunoaffinity chromatography, resolved by SDS-PAGE, and subjected to MALDI-TOF analysis of modification to Kras4B G12V. FIG. 42 shows the fragment of Kras4b peptide containing H95 modified with the compound. This fragment is not

present in the control sample (FIG. 41), obtained from cells that were not subjected to the drug treatment.

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Example 2. Synthetic schemes

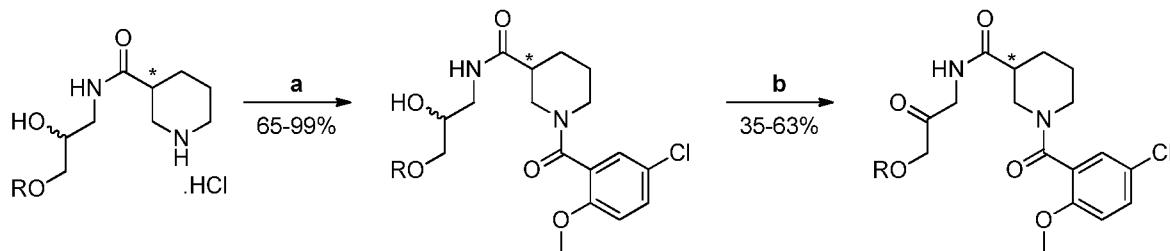
[0593] Scheme 1. Synthesis of covalent analogues of 6B9.



[0594] Conditions: (a) allyl bromide, K₂CO₃, DMF, RT, 24 h; (b) mCPBA, DCM, RT, 24 h; (c) NaN₃, NH₄Cl, MeOH/H₂O (8:1), RT, 72 h; (d) 10% Pd/C, H₂, MeOH, RT, 18 h; (e) (R)-Boc-nipecotic acid or (S)-Boc-nipecotic acid, HATU, DIPEA, DMF, RT, 18 h; (f) 4N dioxane HCl, RT, 3 h.

[0595] A six-step enantioselective synthesis of the electrophilic precursor group was devised starting from the appropriate phenol (scheme 1). Each step occurred in an acceptable yield and was well suited for performance on a gram scale.

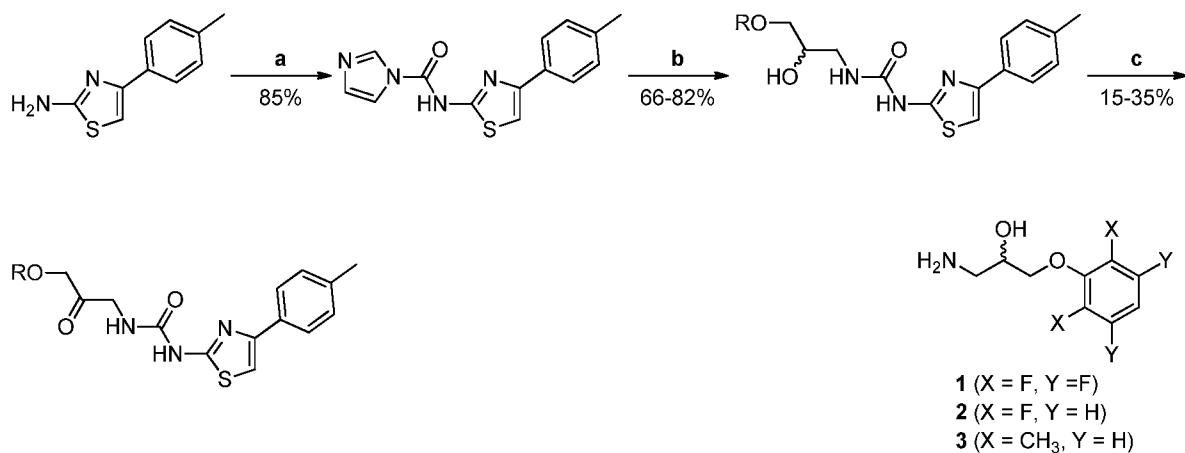
[0596] Scheme 2. Synthesis of covalent analogues of 6B9 (continued)



Conditions: (a) HATU, DIPEA, DMF, RT, 18 h; (b) Dess-Martin periodinane, DCM, 0°C – RT, 72 h.

[0598] The electrophilic precursor group was attached to the acid fragment in good yield using peptide coupling conditions (scheme 2a). In the final step of the reaction scheme the alcohol functionality was oxidized to the ketone using Dess-Martin periodinane, which formed the reactive covalent species. By varying the acid fragment in this synthetic route (scheme 2a) it was possible to prepare a small library of 6B9 analogues for use in future SAR studies.

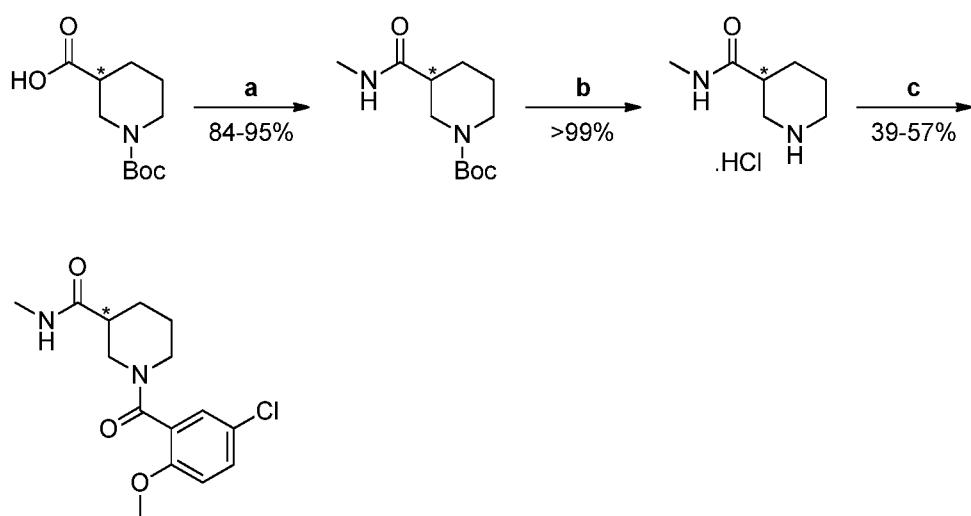
[0599] **Scheme 3.** Synthesis of covalent analogues of 3G4



[0600] Conditions: (a) CDI, THF, RT, 18 h; (b) **1,2**, or **3**, THF, RT, 18 h; (c) Dess-Martin periodinane, DCM, 0 °C - RT, 72 h.

[0601] Electrophilic derivatives of 3G4 were synthesized over three-steps following scheme 3. In contrast to the first two steps, which were high yielding, a modest yield (15-35%) was obtained for the final reaction (scheme 3c), which was attributed to formation of multiple unidentified side products.

[0602] **Scheme 4.** Synthesis of non-covalent analogues of 6B9 for SPR studies

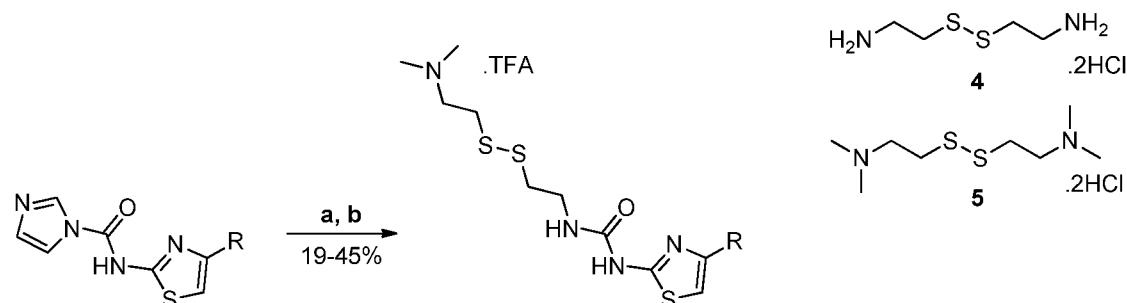


[0603] Conditions: (a) MeNH₂.HCl, EDC.HCl, HOEt, Et₃N, THF/DCM (1:3), RT, 18 h; (b) 4N dioxane HCl, RT, 3 h; (c) HATU, DIPEA, DMF, RT, 18 h.

[0604] Non-tethering analogues of 6B9 were prepared in satisfactory yield over three-steps

5 following scheme 4. Boc-protected (*R*) or (*S*)-nipecotic acid was chosen as the starting material and allowed for enantioselective synthesis of the target molecule. This synthetic approach would likely be appropriate for future non-tethering derivatives, including the *N*-ethylamide and *N*-propylamide analogues of 6B9.

[0605] **Scheme 5.** Synthesis of 34G urea analogues

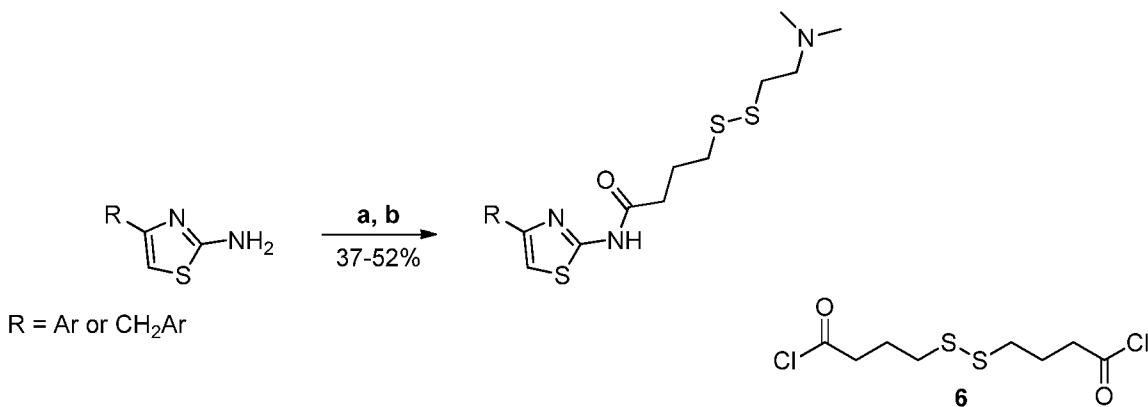


10 R = Ar or CH₂Ar

[0606] Conditions: (a) **4**, Et₃N, water/DMF (1:2); (b) **5**, TCEP (0.1 equiv.), Et₃N, water/DMF.

[0607] A simple two-step one-pot approach allowed the preparation of a small library of urea based analogues of 6B9 from their respective CDI adducts. Solubility issues of the urea product made purification problematic, which likely accounts of the modest yield.

15 [0608] **Scheme 6.** Synthesis of 6B9 propylamide analogues

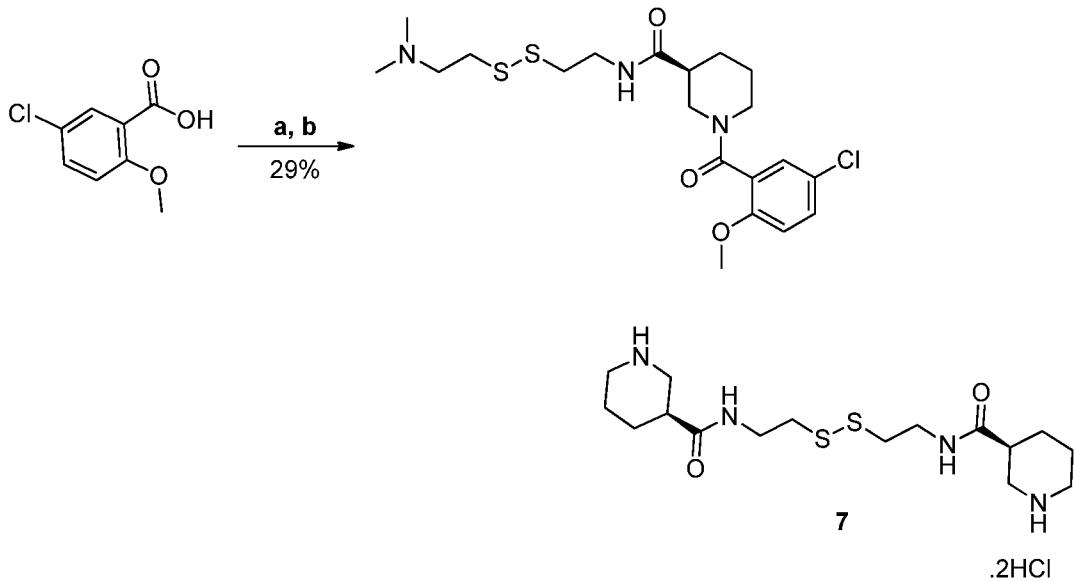


[0609] Conditions: (a) **6** (0.5 equiv.), DIPEA, DCM, RT, 3 h; (b) **5**, TCEP (0.1 equiv.), Et_3N , water/DMF, RT, 18 h.

[0610] A small library of propylamides were prepared *via* the reaction of 2-aminothiazoles

5 with acid chloride **6** followed by disulfide exchange with dimethyl cystamine **5** in the presence of TCEP.

[0611] **Scheme 7.** Synthesis of disulfide tethering agent 6B9



[0612] Conditions: (a) **7** (0.5 equiv.), EDC.HCl, HOBT, Et_3N , DMF, RT, 18 h; (b) **5**, TCEP

10 (0.1 equiv.), Et_3N , water/DMF, RT, 18 h

[0613] 5-Chloro-2-methoxybenzoic acid was coupled with amine **7** followed by disulfide

exchange with cystamine **5** in the presence of TCEP using a method developed in-house for the preparation of disulfide fragment libraries.

[0614] QC Validation

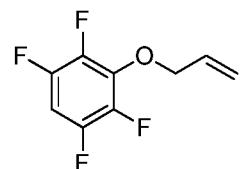
[0615] ^1H -NMR and LC-MS analysis was performed upon all intermediates and target molecules to allow structural determination. Compounds submitted for biological evaluation were deemed to be in excess of 95% purity and were stored at -80 °C to prevent decomposition.

5 **[0616]** Equipment

[0617] ^1H -NMR spectra were obtained from samples dissolved in deuterated chloroform (CDCl_3) using a Bruker Avance III 300 MHz Spectrometer. Chemical shift values (δ) are reported in parts per million (ppm) with splitting patterns abbreviated to: s (singlet), br. s (broad singlet), d (doublet), t (triplet) and m (multiplet). The coupling constant (J) is given in Hz and 10 was calculated using the software package ACD LabsTM 12.0. Chemical shift values (δ) are reported in parts per million (ppm) with splitting patterns abbreviated to: s (singlet), br. s (broad singlet), d (doublet), t (triplet) and m (multiplet). The coupling constant (J) is given in Hz and was calculated using the software package ACD LabsTM 12.0.

[0618] LC-MS analysis was performed using a Waters Micromass ZQ mass spectrometer with 15 a Waters 2795 chromatography separations module, Waters 2996 photodiode array detector and Waters 2424 evaporative light scattering detector (ELSD) system controlled by MassLynx 4.1 software. The HPLC column used was a Waters XTerra MS C18 5 μm 4.6x50 mm column with a mobile phase of water (0.01% formic acid) / MeOH (0.01% formic acid).

1,2,4,5-Tetrafluoro-3-(prop-2-en-1-yloxy)benzene

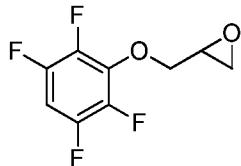


20

[0619] To a solution of 2,3,5,6-tetrafluorophenol (1.0g, 6.02 mmol) in DMF (15 mL) was added K₂CO₃ (1.66 g, 0.12 mol) followed by the dropwise addition of allyl bromide (547 uL, 6.32 mmol). The reaction mixture was stirred (RT, 3h), after which no starting material remained (observed by silica TLC, 1:9 EtOAc/Hexane). The reaction mixture was diluted with water (100 mL) then extracted with DCM (150 mL). The aqueous layer was removed and the remaining organic layer was washed with water (4 x 100 mL) and then dried (Na₂SO₄). The volume of solvent was reduced by half in-vacuo and the resulting DCM solution was used directly in the next reaction without further purification.

[0620] Rf = 0.75 (1:9 EtOAc/Hexane).

2-(2,3,5,6-Tetrafluorophenoxy)methyl)oxirane

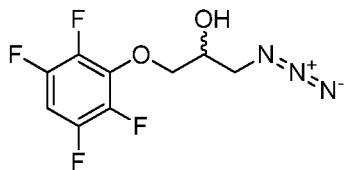


[0621] To a solution of 1,2,4,5-tetrafluoro-3-(prop-2-en-1-yloxy)benzene (1.24g, 6.02 mmol)

5 at 0 oC in DCM (50 mL) (prepared previously) was added 3-Chloroperbenzoic acid (2.7g, 12.0 mmol). The reaction was stirred at 0 oC then warmed to room temperature for an additional 3 days. The resulting solution was poured into a saturated aqueous solution of sodium thiosulfate (50 mL) and was allowed to stir for 30 minutes. The organic layer was removed then washed sequentially with saturated NaHCO3 (50 mL), water (50 mL), and brine (50 mL), dried (Na2SO4), and purified by MPLC on silica (0-50% EtOAc/Hexane) to give 2-(2,3,5,6-tetrafluorophenoxy)methyl)oxirane (735 mg, 3.31 mmol, 55%) as a colorless oil.

[0622] Rf = 0.28 (1:9 EtOAc/Hexane); 1H NMR (300 MHz, CDCl3) δ 6.70-6.93 (m, 1H), 4.49 (dd, J=2.92, 11.59 Hz, 1H), 4.12-4.25 (m, 1H), 3.30-3.50 (m, 1H), 2.89 (dd, J=3.70, 4.90 Hz, 1H), 2.73 (dd, J=2.64, 4.90 Hz, 1H).

15 1-Azido-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol



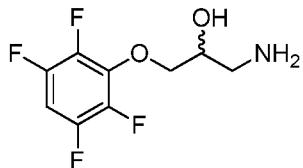
[0623] A solution of 2-(2,3,5,6-tetrafluorophenoxy)methyl)oxirane (1.89 g, 8.5 mmol) in

MeOH (30 mL) was added to a suspension of sodium azide (5.11 g, 78.6 mmol) in water (3.8 mL). Ammonium chloride (915 mg, 210 mmol) was added and reaction was stirred at room

20 temperature for 24 hours. The reaction mixture was diluted with brine (100 mL) then extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried (Na2SO4) and the solvent was removed in-vacuo. The crude product was purified by MPLC on silica (1:9 EtOAc:Hexane) to give the title compound (1.92 g, 7.3 mmol, 85%) as a colorless oil.

25 **[0624]** Rf = 0.14 (1:9 EtOAc/Hexane); 1H NMR (300 MHz, CDCl3) δ 6.72-6.93 (m, 1H), 4.22-4.36 (m, 2H), 4.07-4.22 (m, 1H), 3.45-3.65 (m, 2H), 2.56 (br. s., 1H).

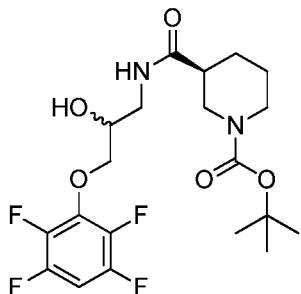
1-Amino-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol



[0625] To a solution of 1-azido-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol (1.9 g, 7.3 mmol) in MeOH (15 ml) was added 10% palladium on carbon (386 mg, 3.6 mmol). The reaction vessel
5 was placed under an atmosphere of hydrogen and stirred overnight (RT, 18 h). The resulting mixture was filtered through Celite and the solvent was removed to give 1-amino-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol (1.2 g, 5.0 mmol, 69%) as a white solid.

[0626] ^1H NMR (300 MHz, MeOD) δ 7.01-7.21 (m, 1H), 4.22 (d, $J=5.09$ Hz, 2H), 3.85-3.99 (m, 1H), 2.90 (dd, $J=3.96, 12.81$ Hz, 1H), 2.77 (dd, $J=7.70, 13.00$ Hz, 1H); LRMS (ES+) m/z = 10 239.9 [M+H] $^+$.

tert-Butyl (3S)-3-{[2-hydroxy-3-(2,3,5,6-tetrafluorophenoxy)propyl]carbamoyl}piperidine-1-carboxylate

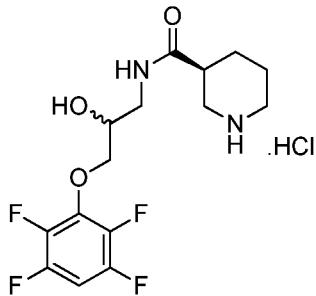


[0627] To a solution of 1-amino-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol (1.1 g, 4.6 mmol)
15 in DMF (26 ml) was added hydroxybenzotriazole (HOBT) (59 mg, 0.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) (1.84 g, 11.9 mmol) and water (4.1 ml). Triethylamine (608 μ l, 4.4 mmol) was added and the resulting mixture was stirred (RT, 3h) resulting in consumption of the starting material (observed by TLC). The reaction was added to a saturated brine solution (100 mL) then extracted with EtOAc (150 mL). The organic layer
20 was removed then washed sequentially with saturated aqueous NaHCO₃ (100 mL) and brine (100 mL) then dried (MgSO₄) and the solvent was removed in-vacuo. The crude product was purified by MPLC on silica (0-10% MeOH/DCM) to give the title compound (1.94 g, 4.3 mmol, 99%) as a colorless oil.

[0628] $R_f = 0.45$ (1:9 MeOH/DCM); 1H NMR (300 MHz, CDCl₃) δ 6.73-6.93 (m, 1H), 4.01-4.30 (m, 3H), 3.55-4.00 (m, 3H), 3.24-3.54 (m, 2H), 3.12 (m, 1H), 2.84-3.01 (m, 1H), 2.29-2.50 (m, 1H), 1.77-2.05 (m, 2H), 1.57-1.77 (m, 1H), 1.47 (s, 9H); LRMS (ES+) m/z = 451.1 [M+H]⁺.

(3S)-N-[2-Hydroxy-3-(2,3,5,6-tetrafluorophenoxy)propyl]piperidine-3-carboxamide

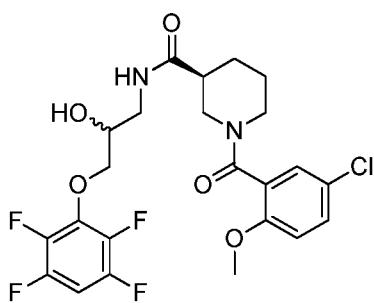
5 hydrochloride



[0629] To a flask containing tert-butyl (3S)-3-{[2-hydroxy-3-(2,3,5,6-tetrafluorophenoxy)propyl]carbamoyl} piperidine-1-carboxylate (50 mg, 0.1 mmol) was added 4N Hydrochloric acid in dioxane (500 μ l, 2.0 mmol). The resulting solution was stirred at room 10 temperature for 30 minutes then the solvent was removed in-vacuo to give the title compound (41 mg, 0.1 mmol, 96%) as a colorless oil.

[0630] 1H NMR (300 MHz, CDCl₃) δ 8.95 (br. s., 2H), 7.75-8.43 (m, 1H), 6.77 (br. s., 1H), 4.02-4.68 (m, 3H), 2.65-3.97 (m, 9H), 1.55-2.32 (m, 3H); LRMS (ES+) m/z = 351.1 [M+H]⁺.

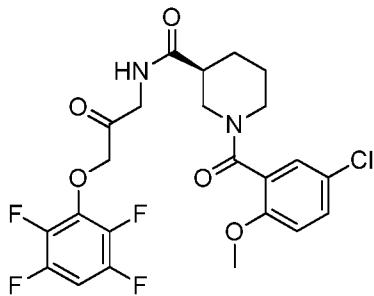
[0631] To a solution of (3S)-N-[2-hydroxy-3-(2,3,5,6-tetrafluorophenoxy)propyl]piperidine-3-carboxamide hydrochloride (155 mg, 0.40 mmol), (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU) (168 mg, 0.44 mmol) and N,N-diisopropylethylamine (243 μ l, 1.4 mmol) in DMF (2.3 ml) was added 5-chloro-2-methoxybenzoic acid (75 mg, 0.40 mmol). The reaction mixture was stirred overnight (RT, 18 h)



[0631] To a solution of (3S)-N-[2-hydroxy-3-(2,3,5,6-tetrafluorophenoxy)propyl]piperidine-3-carboxamide hydrochloride (155 mg, 0.40 mmol), (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU) (168 mg, 0.44 mmol) and N,N-diisopropylethylamine (243 μ l, 1.4 mmol) in DMF (2.3 ml) was added 5-chloro-2-methoxybenzoic acid (75 mg, 0.40 mmol). The reaction mixture was stirred overnight (RT, 18 h)

then added to saturated brine solution (25 mL). The aqueous mixture was extracted with EtOAc (2 x 25 mL) and the organic layers were combined, washed with brine (25 mL), dried (Na₂SO₄), and the solvent was removed in-vacuo. The crude product was purified by MPLC on silica (0-80% Hexane/EtOAc) to give the title product (206 mg, 0.40 mmol) as a colorless oil.

- 5 [0632] R_f = 0.40 (10% MeOH/DCM); 1H NMR (300 MHz, CDCl₃) δ 7.32 (dd, J=2.45, 8.85 Hz, 1H), 7.13-7.21 (m, 1H), 6.86 (d, J=8.85 Hz, 1H), 6.68-6.79 (m, 1H), 4.16-4.30 (m, 1H), 3.99-4.16 (m, 2H), 3.80-3.87 (s, 3H), 3.66-3.76 (m, 1H), 3.43-3.65 (m, 1H), 3.07-3.43 (m, 3H), 2.67-2.78 (m, 1H), 2.55 (m, 1H), 1.96-2.31 (m, 1H), 1.71-1.95 (m, 1H), 1.41-1.69 (m, 2H); LRMS (ES+) m/z = 519.1 [M+H]⁺.
- 10 (3S)-1-[(5-Chloro-2-methoxyphenyl)carbonyl]-N-[2-oxo-3-(2,3,5,6-tetrafluorophenoxy)propyl]piperidine-3-carboxamide ('FB9')



- [0633] To a solution of (3S)-1-[(5-chloro-2-methoxyphenyl)carbonyl]-N-[2-hydroxy-3-(2,3,5,6-tetrafluoro phenoxy)propyl]piperidine-3-carboxamide (17 mg, 3.4 x 10⁻² mmol) in DCM (500 μL, 7.8 mmol) at 0 oC was added Dess-Martin periodinane (28 mg, 6.8 x 10⁻² mmol). The reaction mixture was stirred at 0 oC for 1 hour and was then allowed to warm to room temperature for an additional 72 hours. The crude product was diluted with DCM (2 mL) then added to a saturated solution of sodium thiosulfate in aqueous NaHCO₃ (3 mL). The resulting mixture was stirred rapidly for 1 hour at which point the aqueous layer was removed. The remaining organic layer was washed sequentially with NaHCO₃ (3 mL) and brine (3 mL) then dried (Na₂SO₄) and the solved was removed in-vacuo. The crude product was purified by MPLC on silica (0-10% MeOH/DCM) to give the title compound (12 mg, 2.3 x 10⁻² mmol, 69%) as a colorless oil.

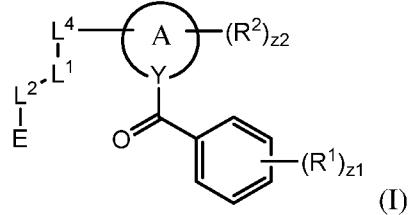
- [0634] R_f = 0.43 (1:9 MeOH/DCM); 1H NMR (300 MHz, CDCl₃) δ 7.31 (dd, J=2.64, 8.85 Hz, 1H), 7.16-7.25 (m, 1H), 6.75-6.92 (m, 2H), 4.80-4.97 (m, 2H), 4.17-4.59 (m, 2H), 3.75-3.95 (m, 3H), 3.51-3.74 (m, 1H), 3.11-3.38 (m, 2H), 2.52-2.72 (m, 2H), 2.00-2.22 (m, 1H), 1.89 (d,

J=11.87 Hz, 1H), 1.35-1.80 (m, 2H); ^{19}F NMR (282 MHz, CDCl_3) δ -138.0, -156.7; LRMS (ES+) m/z = 517.1 [M+H]+.

[0635] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

- 1 1. A compound having the formula:



2

3 wherein,

4 Y is N or CH

5 Ring A is a C₃-C₇ cycloalkyl or 3 to 7 membered heterocycloalkyl;

6 R¹ is independently halogen, CX¹₃, -CHX¹₂, -

7 CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR⁷R⁸, -NHNR⁷R⁸, -ONR⁷R⁸, -NHC=(O)NHNR⁷R⁸,

8 -NHC(O)NR⁷R⁸, -N(O)_{m1}, -NR⁷R⁸, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR⁷R⁸, -OR¹⁰, -NR⁷SO₂R¹⁰,

9 -NR⁷C(O)R⁹, -NR⁷C(O)OR⁹, -NR⁷OR⁹, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted

10 alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,

11 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or

12 unsubstituted heteroaryl; two adjacent R¹ substituents may optionally be joined to form a

13 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

14 substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

15 L¹ is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted

16 heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted

17 heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted

18 heteroarylene;

19 L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -

20 NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -

21 NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-,

22 -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or

23 unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or

24 unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or

25 unsubstituted arylene, substituted or unsubstituted heteroarylene;

26 L⁴ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁴-, -

27 NR⁴C(O)-, -C(O)NR⁴-, -SO₂NR⁴-, -NR⁴SO₂-, -NR⁴SO₂-, -OC(O)NR⁴-, -NR⁴C(O)O-,

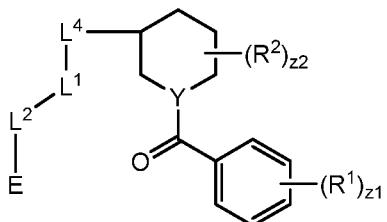
28 substituted or unsubstituted C₁-C₃ alkylene, substituted or unsubstituted 2 to 3 membered

29 heteroalkylene;

30 E is an electrophilic moiety;
31 R² is independently oxo, halogen, CX²₃, -CHX²₂, -
32 CH₂X², -CN, -SO₂Cl, -SO_{n2}R¹⁴, -SO_{v2}NR¹¹R¹², -NHNR¹¹R¹², -ONR¹¹R¹², -
33 -NHC=(O)NHNR¹¹R¹²,
34 -NHC(O)NR¹¹R¹², -N(O)_{m2}, -NR¹¹R¹², -C(O)R¹⁴, -C(O)-OR¹⁴, -C(O)NR¹¹R¹², -OR¹⁵, -
35 NR¹¹SO₂R¹⁵, -NR¹¹C(O)R¹⁴, -NR¹¹C(O)OR¹⁴, -NR¹¹OR¹⁴, -OCX²₃, -OCHX²₂, substituted or
36 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
37 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,
38 substituted or unsubstituted heteroaryl; two adjacent R² substituents or two R² substituents
39 bonded to the same atom may optionally be joined to form a substituted or unsubstituted
40 cycloalkyl or substituted or unsubstituted heterocycloalkyl;
41 R⁴ is independently hydrogen, substituted or unsubstituted alkyl, substituted or
42 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
43 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;
44 R⁷, R⁸, R⁹, R¹⁰, R^{7B}, R^{8B}, R^{9B}, R^{10B}, R¹¹, R¹², R¹⁴, and R¹⁵ are independently
45 hydrogen, halogen, -CX₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -
46 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -
47 NHC(O)H, -NHC(O)OH, -NHOH, -OCX₃, -OCHX₂, -CHX₂, -CH₂X, substituted or
48 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
49 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
50 substituted or unsubstituted heteroaryl; R⁷ and R⁸ substituents bonded to the same nitrogen
51 atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
52 substituted or unsubstituted heteroaryl; R¹¹ and R¹² substituents bonded to the same nitrogen
53 atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
54 substituted or unsubstituted heteroaryl;
55 each X, X¹, and X² is independently -F, -Cl, -Br, or -I;
56 n1, n2, v1, and v2 are independently an integer from 0 to 4;
57 m1 and m2 are independently an integer from 1 to 2;
58 z1 is independently an integer from 0 to 5; and
59 z2 is independently an integer from 0 to 10.

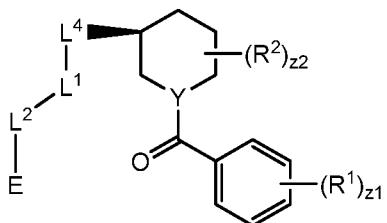
1 2. The compound of claim 1, having the formula:

2



2

1 3. The compound of claim 1, having the formula:



2

1 4. The compound of claim 1, wherein Y is CH.

1

1 5. The compound of claim 1, wherein Y is N.

1

2 6. The compound of claim 1, wherein R¹ is independently
3 halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
4 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -HSO₂H, -
5 NHC(O)H, -NHC(O)OH, -NHOH, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted C₁-C₆
6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted
7 C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted
or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

1

2 7. The compound of claim 1, wherein R¹ is independently
3 halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OH, -SH, -COOH, -OCX¹₃, -OCHX¹₂, -CH₃, -CH₂CH₃, -
OCH₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃.

1

2 8. The compound of claim 1, wherein R¹ is independently halogen
or -OCH₃.

1

1 9. The compound of claim 1, wherein z1 is 2.

1

1 10. The compound of claim 1, wherein z1 is 3.

1

2 11. The compound of claim 1, wherein R² is independently oxo, halogen,
CX²₃, -CHX²₂, -CH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -

3 SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NSO₂H, -NHC(O)H, -
 4 NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl,
 5 substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈
 6 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or
 7 unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

1 12. The compound of claim 1, wherein R² is independently oxo,
 2 halogen, -CX²₃, -CHX²₂, -CH₂X², --OH, -SH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -O
 3 CH₂CH₃, -SCH₃, or -SCH₂CH₃.

1 13. The compound of claim 1, wherein z2 is 0.

1 14. The compound of claim 1, wherein L¹ is a bond, substituted or
 2 unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

1 15. The compound of claim 1, wherein L¹ is a bond, unsubstituted C₁-C₄
 2 alkylene, or unsubstituted 2 to 4 membered heteroalkylene.

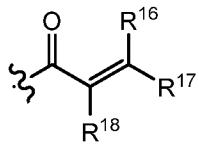
1 16. The compound of claim 1, wherein L¹ is a bond.

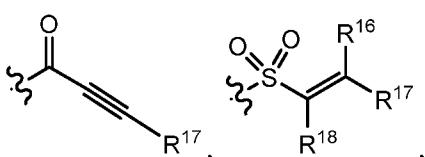
1 17. The compound of claim 1, wherein L² is a
 2 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -
 3 NSO₂-, -OC(O)NH-, -NHC(O)O-, -NHC(O)NH-, substituted or unsubstituted alkylene, or
 4 substituted or unsubstituted heteroalkylene.

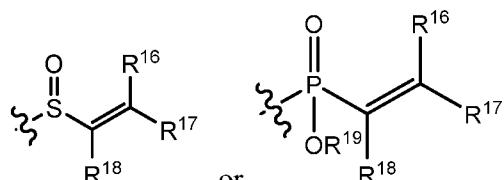
1 18. The compound of claim 1, wherein L² is a
 2 bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C₁-C₄ alkylene, or
 3 unsubstituted 2 to 4 membered heteroalkylene.

1 19. The compound of claim 1, wherein L² is -NH-.

1 20. The compound of claim 1, wherein L² is a bond.

1 21. The compound of claim 1, wherein E is 

2 



4 wherein R¹⁶ is independently hydrogen, halogen, CX¹⁶₃, -CHX¹⁶₂, -

5 CH_2X^{16} , -CN, $-\text{SO}_{n16}\text{R}^{16D}$, $-\text{SO}_{v16}\text{NR}^{16A}\text{R}^{16B}$, $-\text{NHNR}^{16A}\text{R}^{16B}$, $-\text{ONR}^{16A}\text{R}^{16B}$,

$$6 \quad -\text{NHC}=(\text{O})\text{NHNR}^{16A}\text{R}^{16B},$$

NR^{16A}C(O)OR^{16C}, -NR^{16A}OR^{16C}, -OCX¹⁶₃, -OCHX¹⁶₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted

12 heteroaryl;

R' is independently hydrogen, halogen, -CH₃, -CH₂-, -

14 CH₂X, -CN, -SO_nR, ,

15 -NHC(=O)NHNR¹,
 16 -NHC(O)NR^{17A}R^{17B}, -N(O)_mR^{17A}, -NR^{17A}R^{17B}, -C(O)R^{17C}, -C(O)-OR^{17C}, -C(O)NR^{17A}R^{17B}, -OR^{17D}, NR^{17A}CO₂R^{17D}, NR^{17A}C(O)R^{17C}

17 -NR-SO₂R-, -NR-C(O)R-, -

18 NR-C(O)OR¹, -NR-OR¹, -OC(X)₃, -OCH(X)₂, substituted or unsubstituted alkyl,
19 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
20 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
21 heteroaryl;

22 R¹⁸ is independently hydrogen, halogen, CX¹⁸₃, -CHX¹⁸₂, -

23 CH_2X^{18} , -CN, $-\text{SO}_{n18}\text{R}^{18D}$, $-\text{SO}_{v18}\text{NR}^{18A}\text{R}^{18B}$, $-\text{NHNR}^{18A}\text{R}^{18B}$, $-\text{ONR}^{18A}\text{R}^{18B}$,

$$24 \quad -\text{NHC}=(\text{O})\text{NHNR}^{18\text{A}}\text{R}^{18\text{B}},$$

25 -NHC(O)NR^{18A}R^{18B}, -N(O)_mR^{18A}R^{18B}, -NR^{18A}R^{18B}, -C(O)R^{18C}, -C(O)-OR^{18C}, -C(O)NR^{18A}R^{18B}, -OR
 26^{18D}, -NR^{18A}SO₂R^{18D}, -NR^{18A}C(O)R^{18C}, -

27 NR^{18A}C(O)OR^{18C}, -NR^{18A}OR^{18C}, -OCX¹⁸₃, -OCHX¹⁸₂, substituted or unsubstituted alkyl,

28 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
29 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
30 heteroaryl;

31 R¹⁹ is independently hydrogen, halogen, CX¹⁹₃, -CHX¹⁹₂, -

32 CH_2X^{19} , -CN, $-\text{SO}_{n19}\text{R}^{19D}$, $-\text{SO}_{v19}\text{NR}^{19A}\text{R}^{19B}$, $-\text{NHNR}^{19A}\text{R}^{19B}$, $-\text{ONR}^{19A}\text{R}^{19B}$,

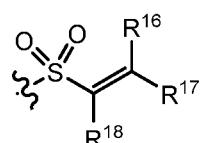
33 $-\text{NHC}=(\text{O})\text{NHNR}^{19\text{A}}\text{R}^{19\text{B}},$

34 -NHC(O)NR^{19A}R^{19B}, -N(O)_{m19}, -NR^{19A}R^{19B}, -C(O)R^{19C}, -C(O)-OR^{19C}, -C(O)NR^{19A}R^{19B}, -OR
 35 ^{19D}, -NR^{19A}SO₂R^{19D}, -NR^{19A}C(O)R^{19C}, -
 36 NR^{19A}C(O)OR^{19C}, -NR^{19A}OR^{19C}, -OCX¹⁹₃, -OCHX¹⁹₂, substituted or unsubstituted alkyl,
 37 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 38 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
 39 heteroaryl;

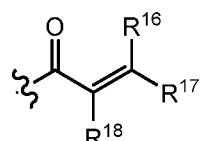
40 R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B}, R^{17C}, R^{17D}, R^{18A}, R^{18B}, R^{18C}, R^{18D}, R^{19A},
 41 R^{19B}, R^{19C}, R^{19D}, are independently hydrogen,
 42 halogen, -CX₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂,
 43 -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NSO₂H, -NHC(O)H, -
 44 NHC(O)OH, -NHOH, -OCX₃, -OCHX₂, -CHX₂, -CH₂X, substituted or unsubstituted alkyl,
 45 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 46 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 47 unsubstituted heteroaryl; R^{16A} and R^{16B} substituents bonded to the same nitrogen atom may
 48 optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
 49 unsubstituted heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may
 50 optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
 51 unsubstituted heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may
 52 optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
 53 unsubstituted heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may
 54 optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
 55 unsubstituted heteroaryl;

56 each X, X¹⁶, X¹⁷, X¹⁸ and X¹⁹ is independently -F, -Cl, -Br, or -I;
 57 n16, n17, n18, n19, v16, v17, v18, and v19 are independently an integer from
 58 0 to 4; and

59 m16, m17, m18, and m19 are independently an integer from 1 to 2.



1 22. The compound of claim 21, wherein E is .

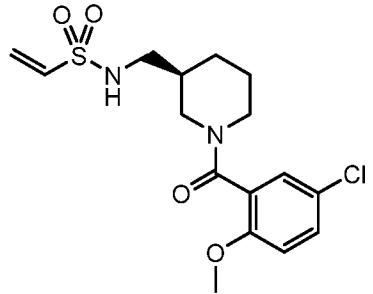


1 23. The compound of claim 21, wherein E is .

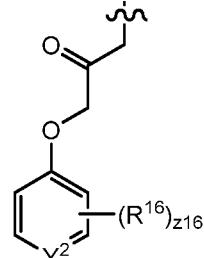
1 24. The compound of claim 21, wherein
 2 R¹⁶, R¹⁷, and R¹⁸ are independently hydrogen, -CH₂NH₂, -CH₂CH₂NH₂, -
 3 CH₂N(CH₃)₂, or -CH₂CH₂N(CH₃)₂.

1 25. The compound of claim 21, wherein L⁴ is a bond or -CH₂-.

1 26. The compound of claim 21, having the formula:



2



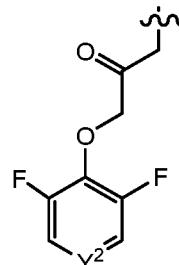
1 27. The compound of claim 1, wherein E is ;
 2 wherein R¹⁶ is independently halogen, CX¹⁶₃, -CHX¹⁶₂, -
 3 CH₂X¹⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂,
 4 -NHNH₂, -ONH₂, -NHC(O)NNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -
 5 NHC(O)OH, -NHOH, -OCX¹⁶₃, -OCHX¹⁶₂, substituted or unsubstituted alkyl, substituted or
 6 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 7 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;
 8 Y² is N or CH;
 9 z16 is an integer from 0 to 4; and
 10 each X¹⁶ is independently -F, -Cl, -Br, or -I.

1 28. The compound of claim 27 wherein R¹⁶ is independently halogen.

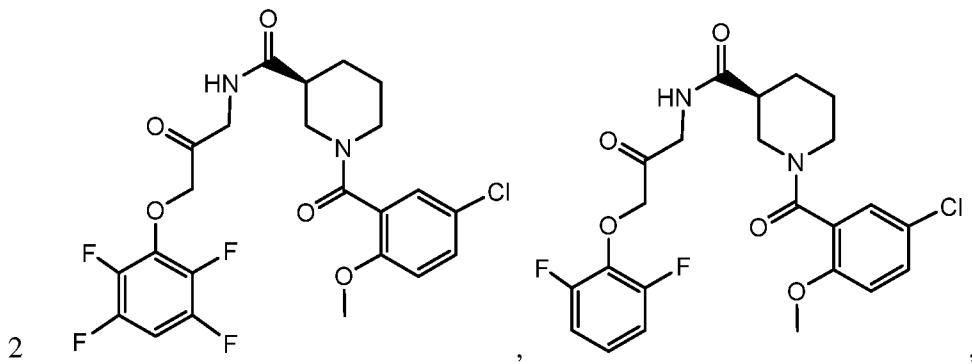
1 29. The compound of claim 27 wherein R¹⁶ is independently -F.

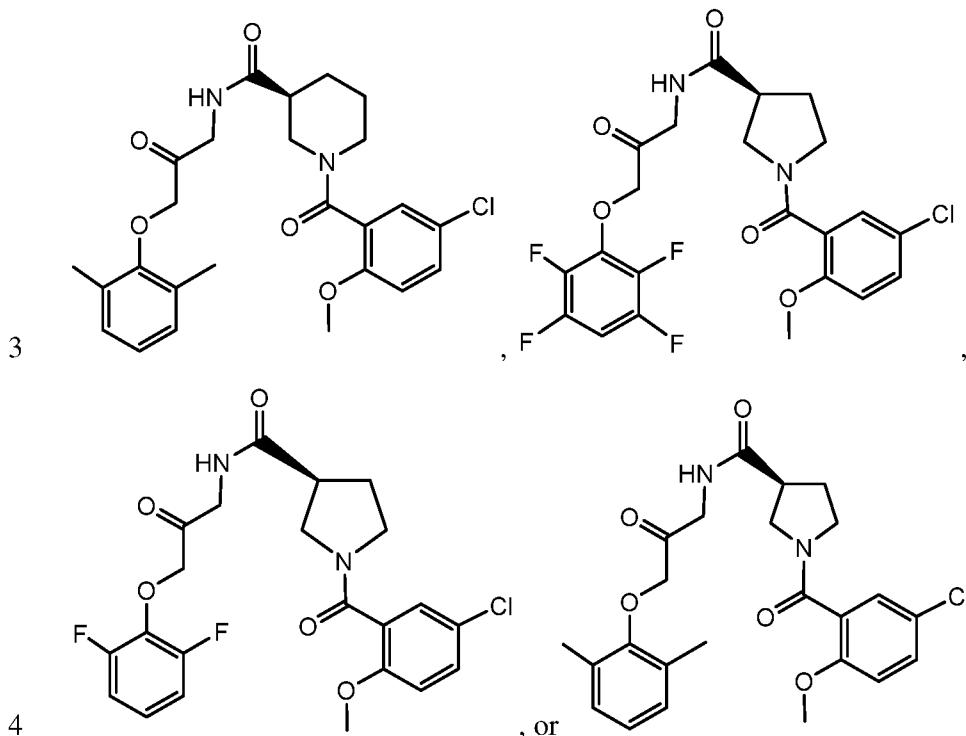
1 30. The compound of claim 27, wherein z16 is 4.

1 31. The compound of claim 27, wherein z16 is 2.



- 1 32. The compound of claim 31 wherein E is .
- 1 33. The compound of claim 27, wherein Y² is CH.
- 1 34. The compound of claim 27, wherein Y² is N.
- 1 35. The compound of claim 27, wherein L⁴ is -N(R⁴)C(O)-.
- 1 36. The compound of claim 27, wherein R⁴ is hydrogen.
- 1 37. The compound of claim 27, having the formula:





38. A pharmaceutical composition comprising the compound of any one of
claims 1 to 37 and a pharmaceutically acceptable excipient.

1 39. A method of reducing the level of activity of a K-Ras protein, said
2 method comprising contacting the K-Ras protein with a compound of one of claims 1 to 37.

1 40. A method of reducing the level of activity of a K-Ras-4B protein, said
2 method comprising contacting the K-Ras-4B protein with a compound of one of claims 1 to
3 37.

1 41. A method for treating cancer, said method comprising administering to
2 a subject in need thereof a therapeutically effective amount of a compound of one of claims 1
3 to 37.

1 42. The method of claim 41, wherein said cancer is pancreatic cancer, lung
2 cancer, or colorectal cancer.

1 43. A K-Ras protein covalently bonded to a compound of one of claims 1
2 to 37.

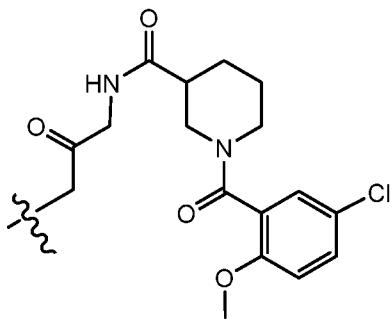
1 44. The K-Ras protein of claim 43, wherein the compound is covalently
2 bonded to a cysteine residue of the protein.

1 45. The K-Ras protein of claim 43, wherein the compound is irreversibly
2 covalently bonded to a cysteine residue of the protein.

1 46. The K-Ras protein of claim 43, wherein the compound is covalently
2 bonded to a histidine residue of the protein.

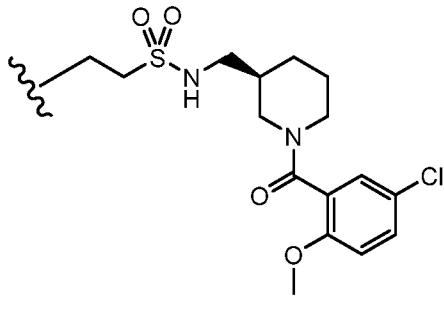
1 47. The K-Ras protein of claim 43, wherein the compound is irreversibly
2 covalently bonded to a histidine residue of the protein.

1 48. A K-Ras protein covalently bonded to a compound having the formula:



2 .

1 49. A K-Ras protein covalently bonded to a compound having the formula:



2 .

1 50. The K-Ras protein of one of claims 48 to 49, wherein the compound is
2 covalently bonded to a cysteine residue of the protein.

1 51. The K-Ras protein of claim 48, wherein the compound is covalently
2 bonded to a cysteine residue of the protein corresponding to C185 of human K-Ras-4B.

1 52. The K-Ras protein of one of claims 48 to 49, wherein the compound is
2 covalently bonded to a histidine residue of the protein.

1 53. The K-Ras protein of claim 48, wherein the compound is covalently
2 bonded to a histidine residue of the protein corresponding to H95 of human K-Ras-4B.

FIG. 1A

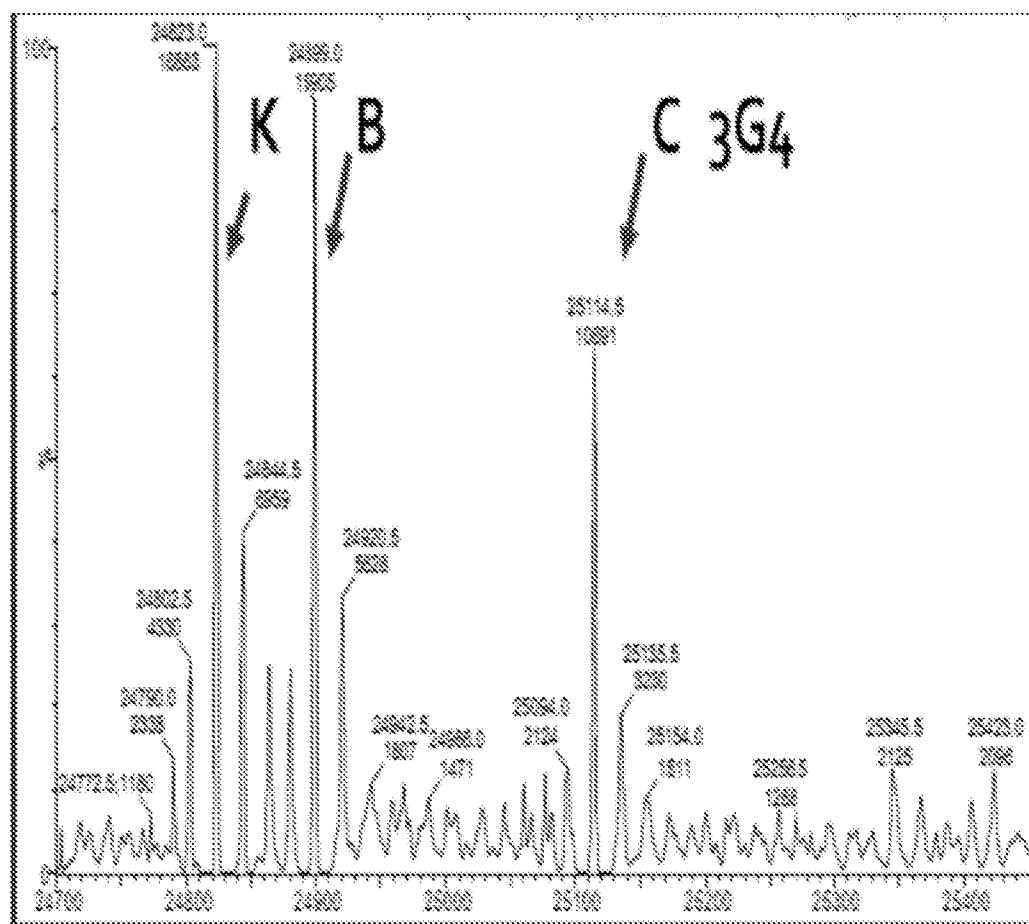


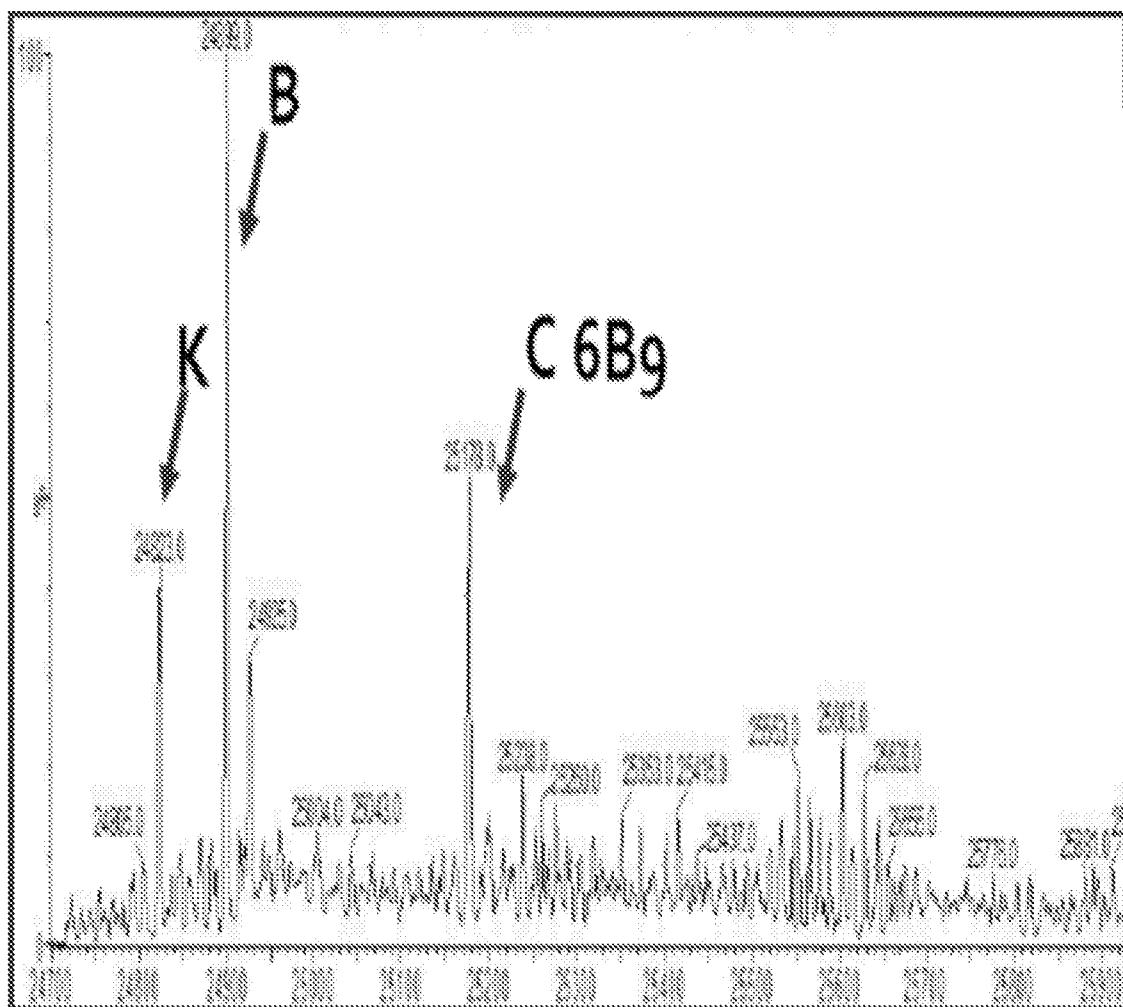
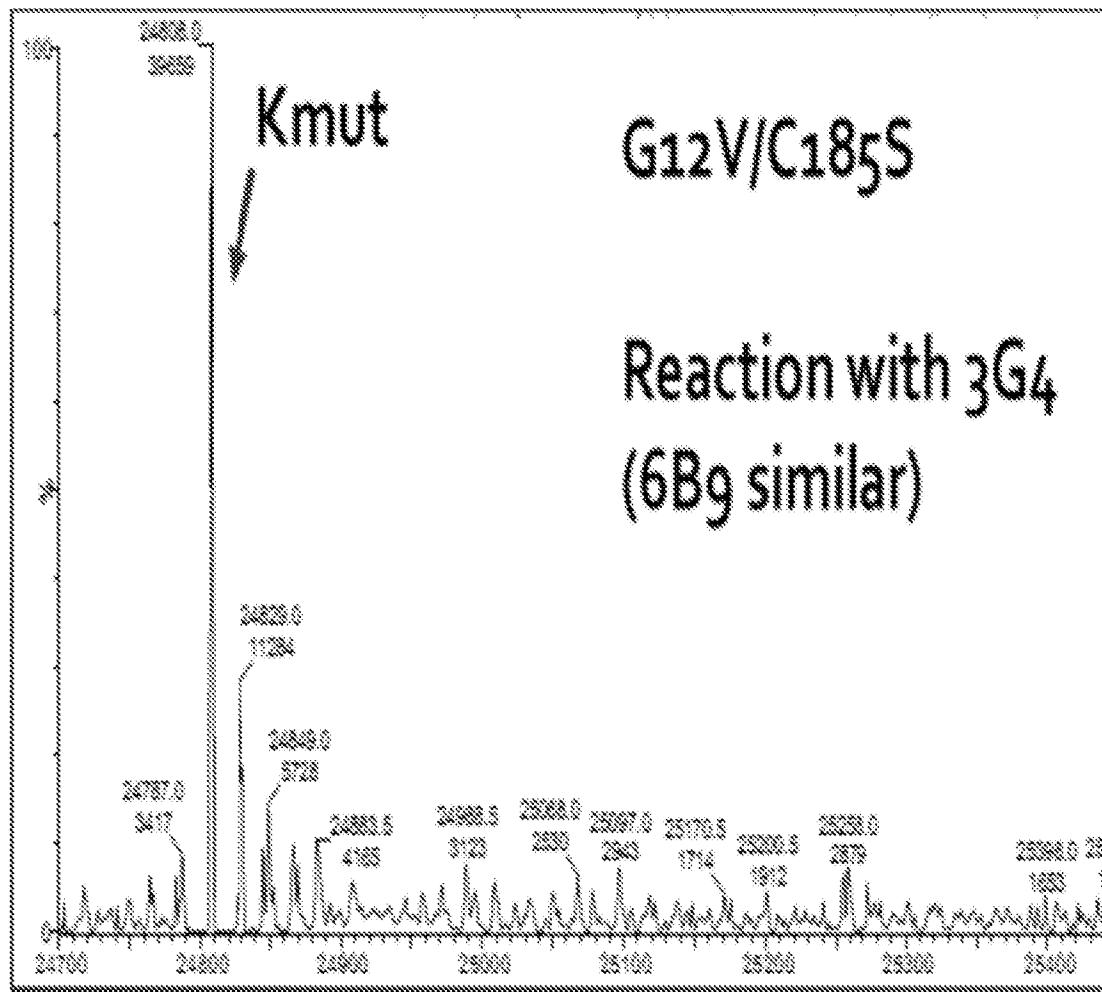
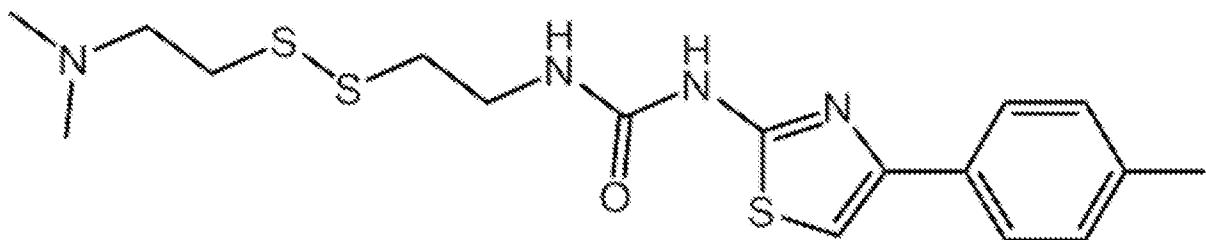
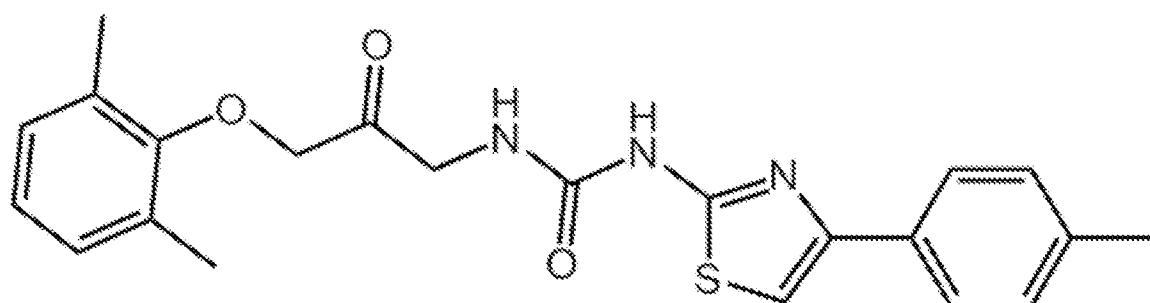
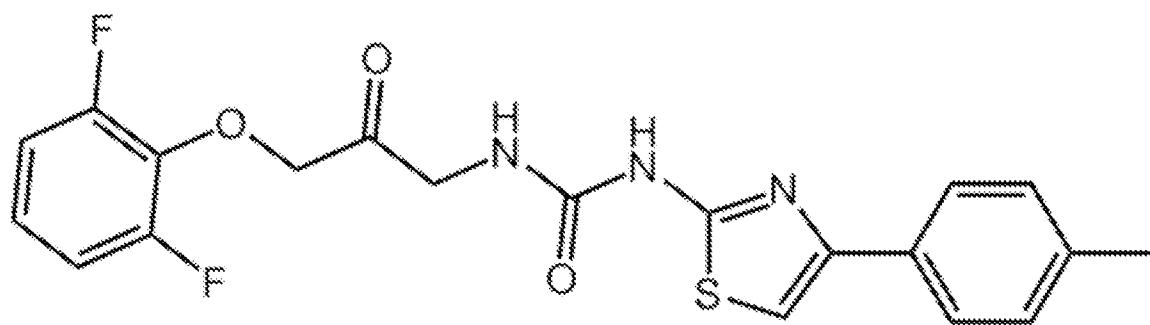
FIG. 1B

FIG. 1C**FIG. 2A**

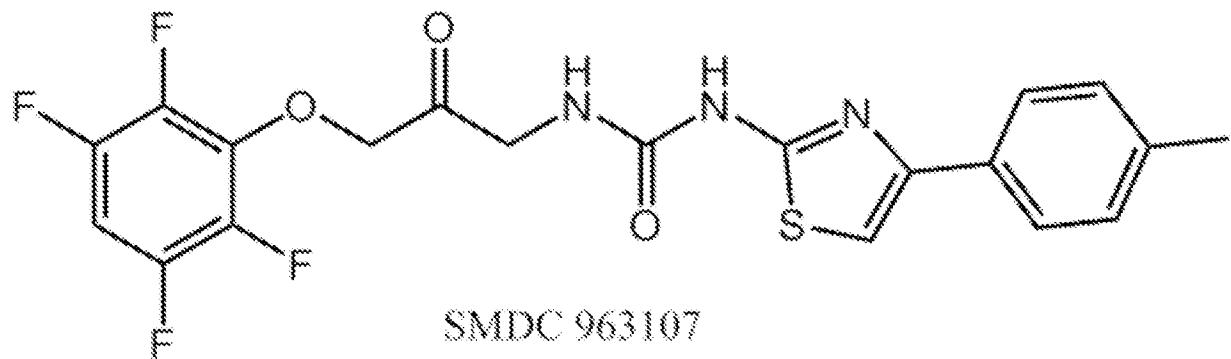
SMDC 917069 (also known as 3G4)

FIG. 2B

SMDC 963109

FIG. 2C

SMDC 963108

FIG. 2D

SMDC 963107

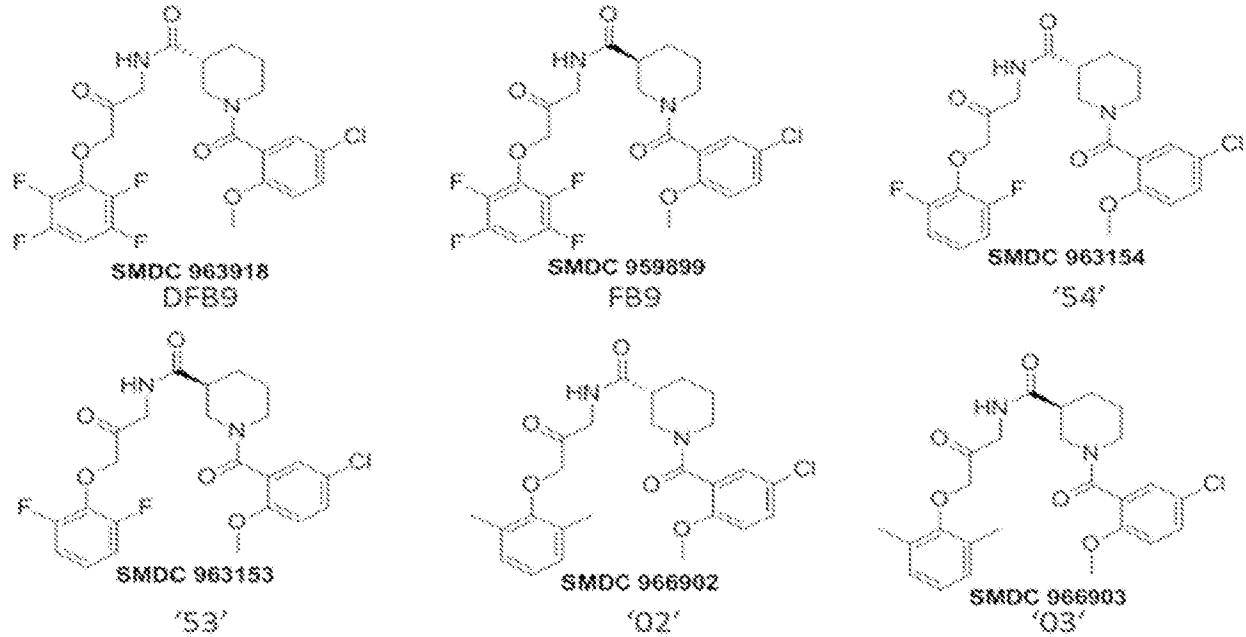
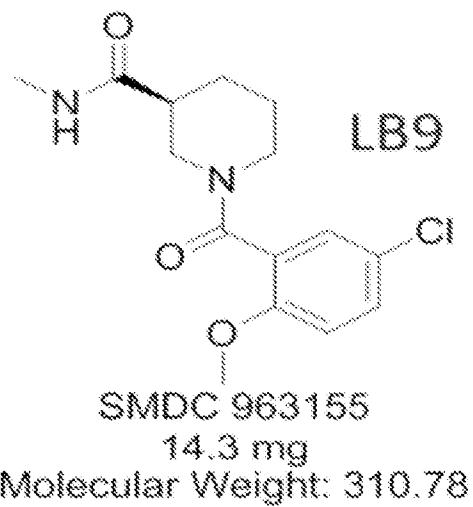
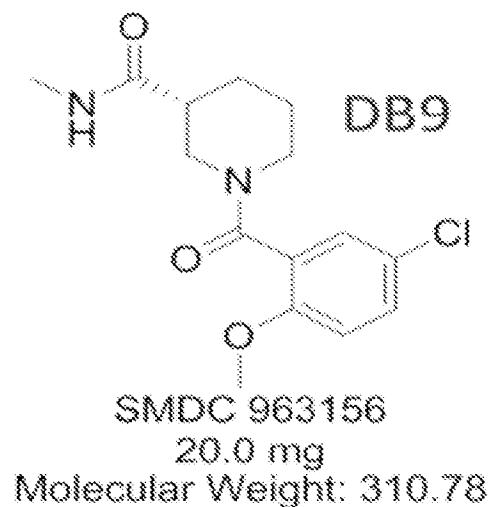
FIG. 3A**FIG. 3B****FIG. 3C**

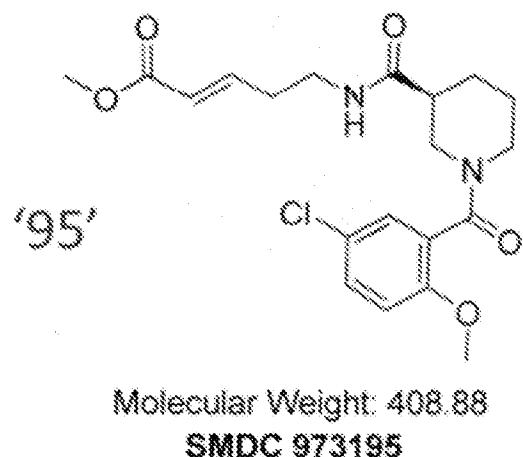
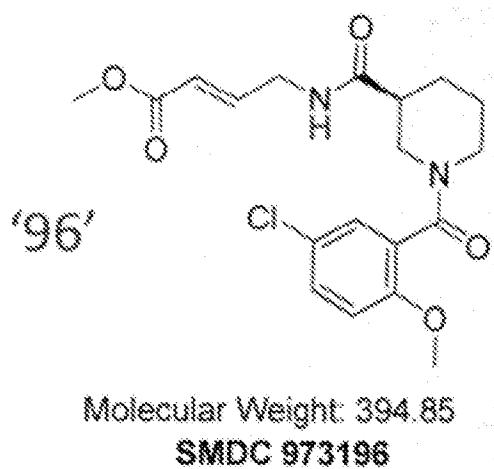
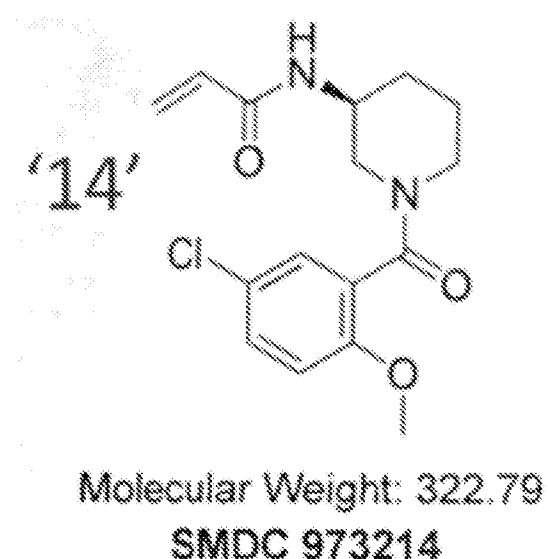
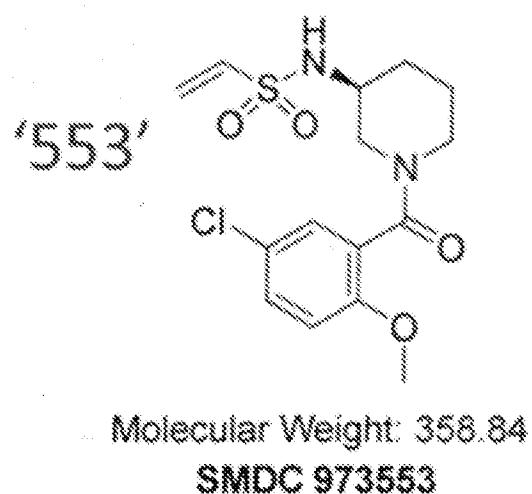
FIG. 4A**FIG. 4B****FIG. 4C****FIG. 4D**

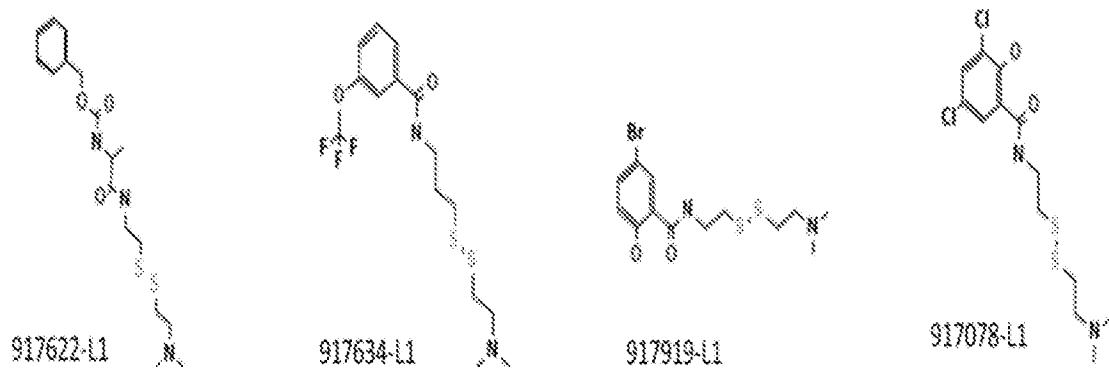
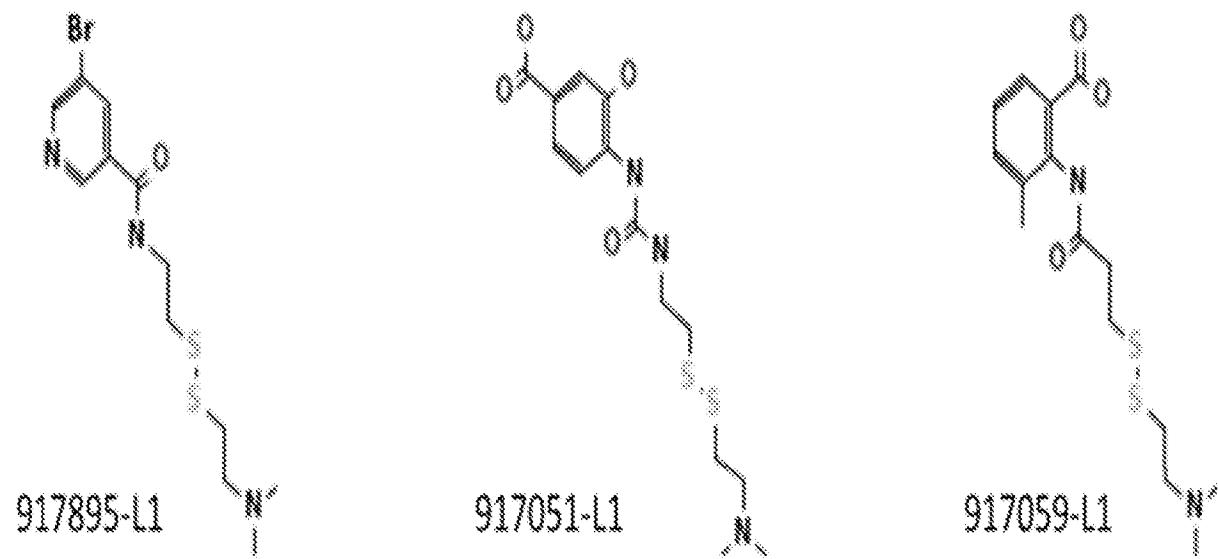
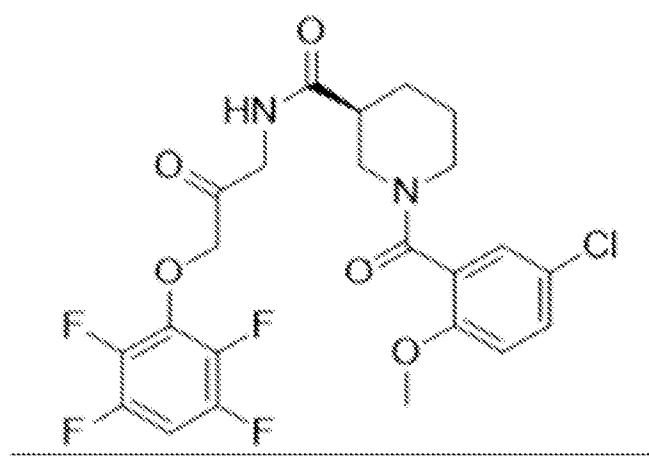
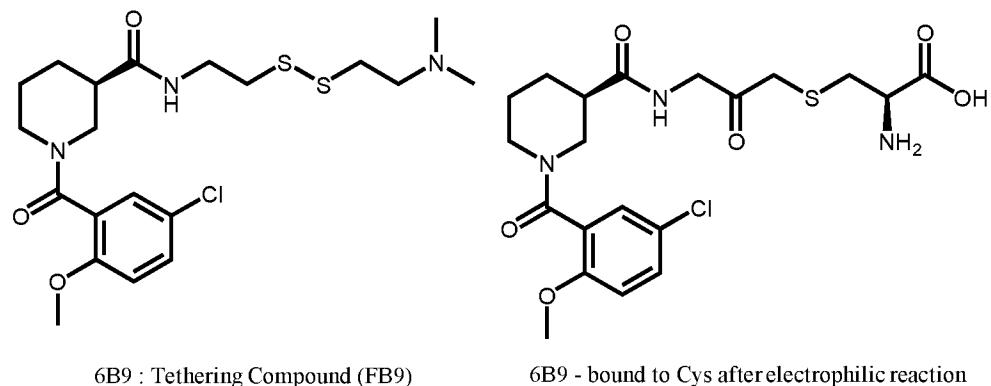
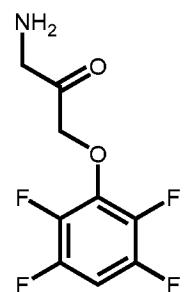
FIG. 5A**FIG. 5B****FIG. 6A**

FIG. 6B

6B9 : Tethering Compound (FB9)

6B9 - bound to Cys after electrophilic reaction



Electrophilic modification

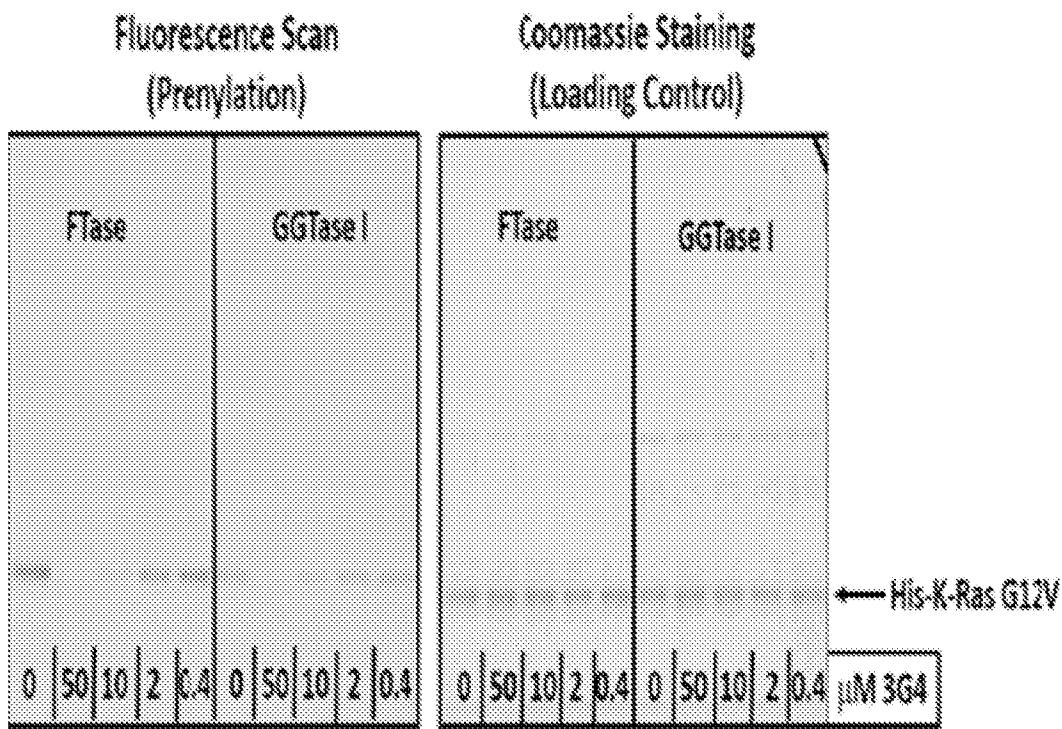
FIG. 7A

FIG. 7B

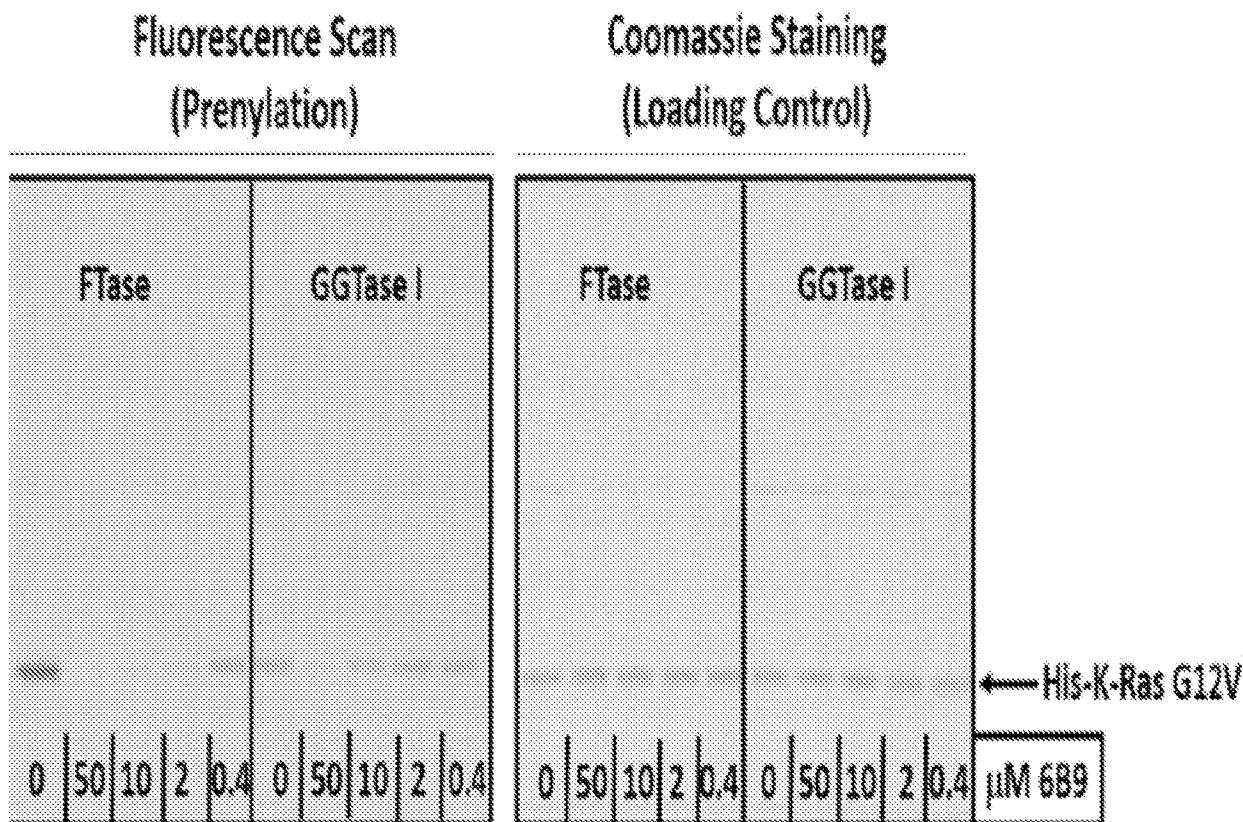


FIG. 8A

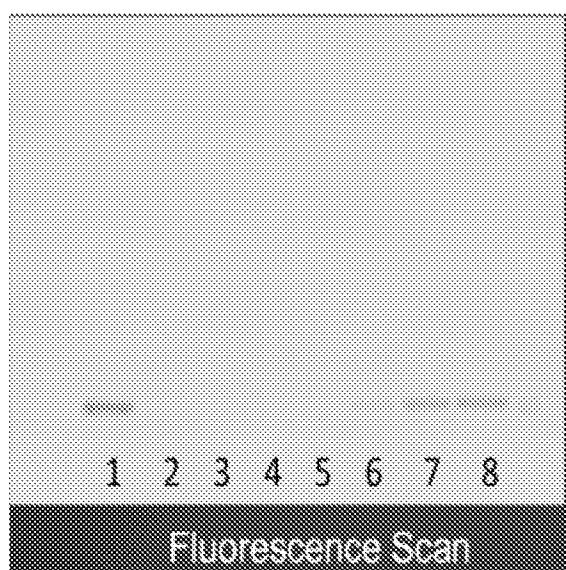


FIG. 8B

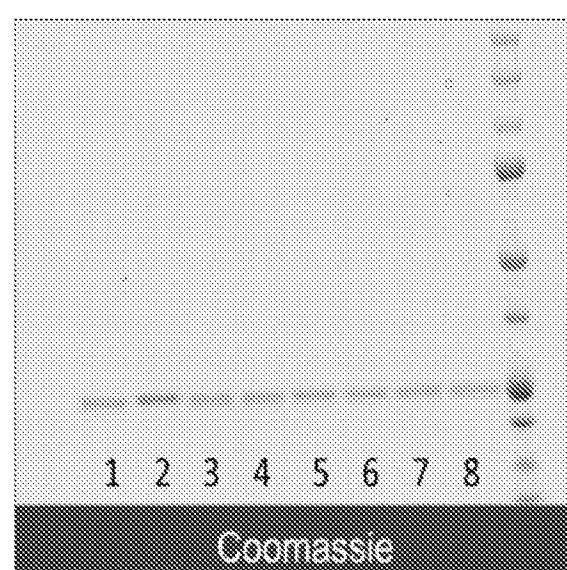


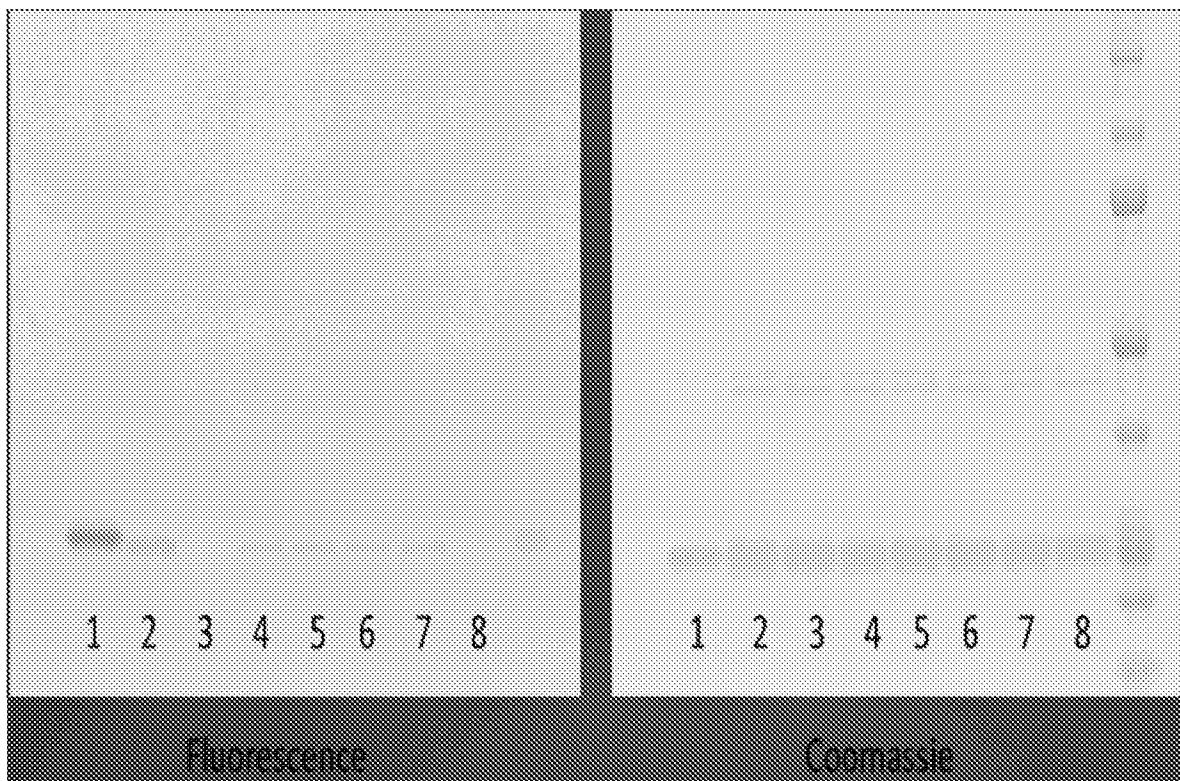
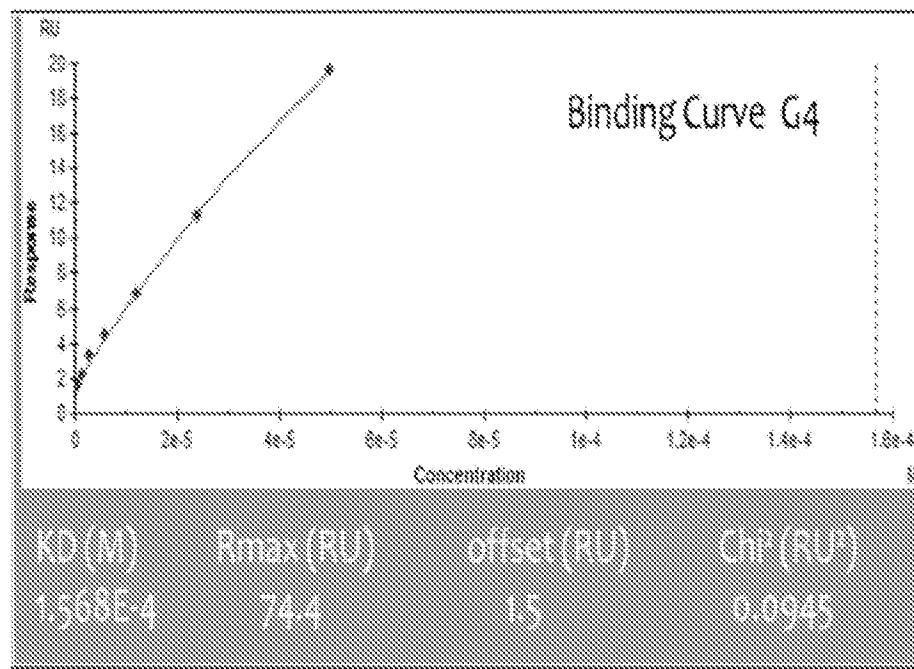
FIG. 9**FIG. 10**

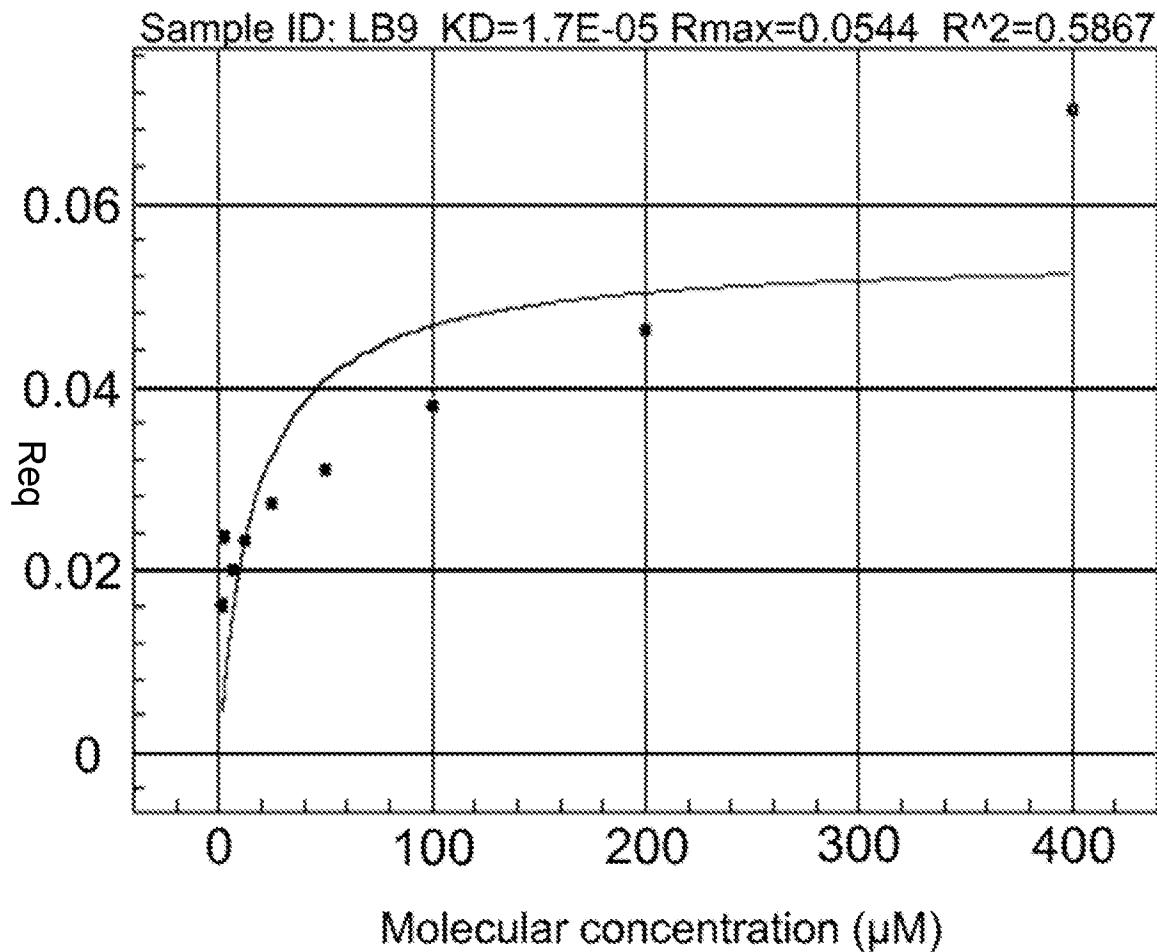
FIG. 11A**K-Ras4B G12D – GTP γ S - LB9**

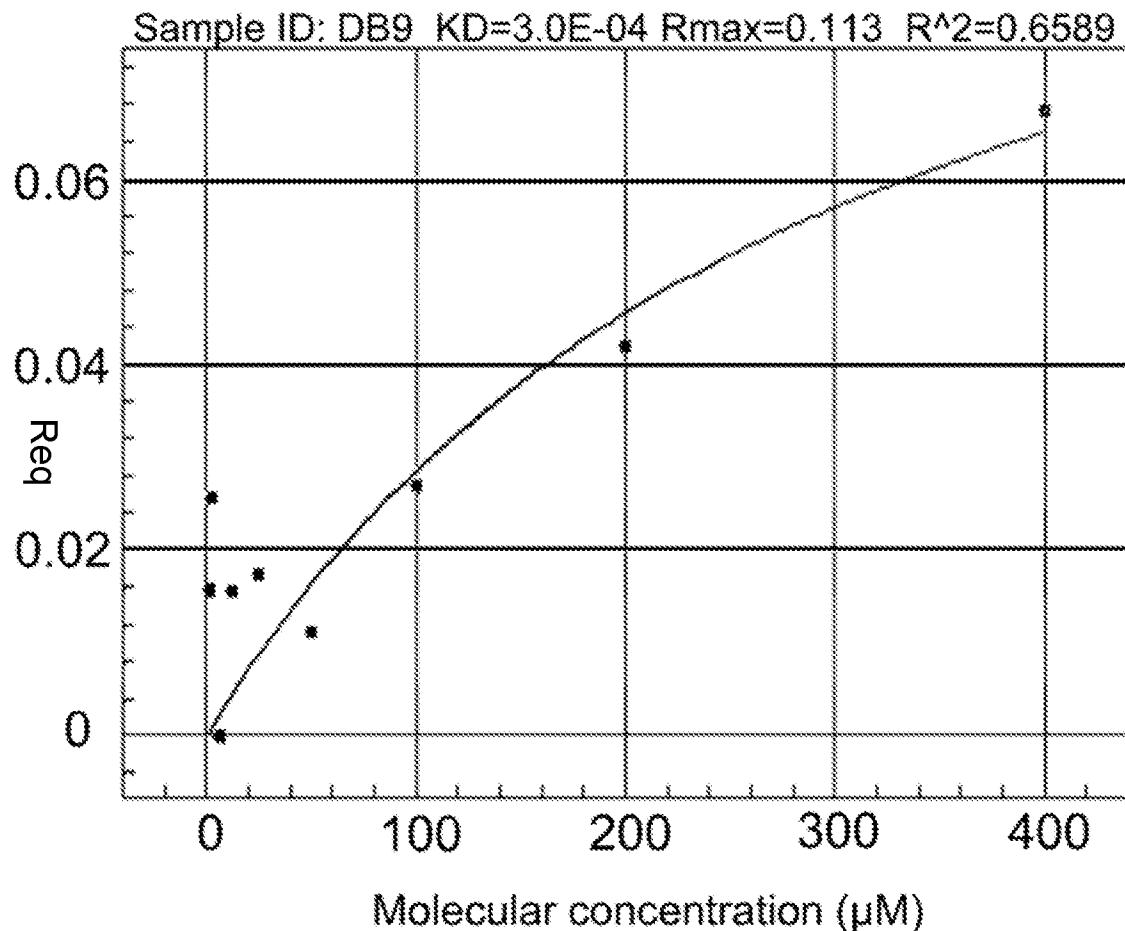
FIG. 11B**K-Ras4B G12D – GTP γ S - DB9**

FIG. 12A

EDA-GTP-ATTO 390
(K-Ras 4B G12V C185S)

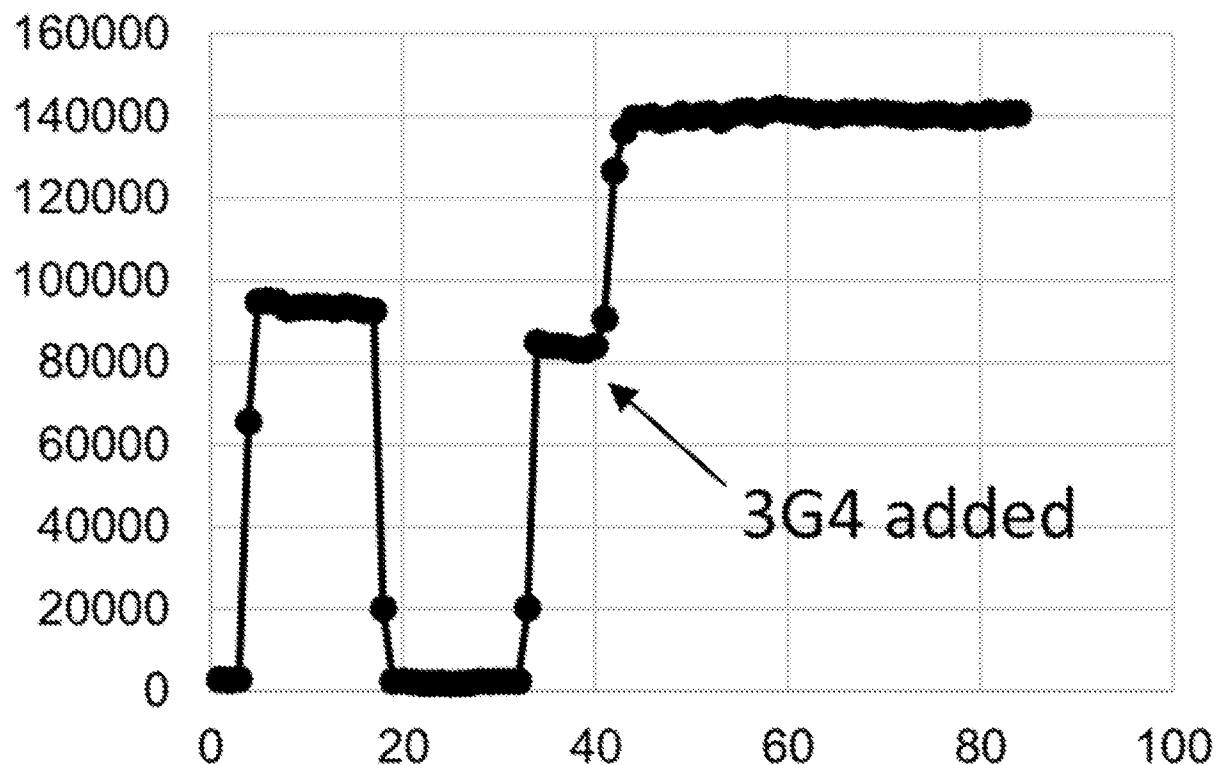


FIG. 12B

**PyMPO-Maleimide
(K-Ras 4B G12V C185S)**

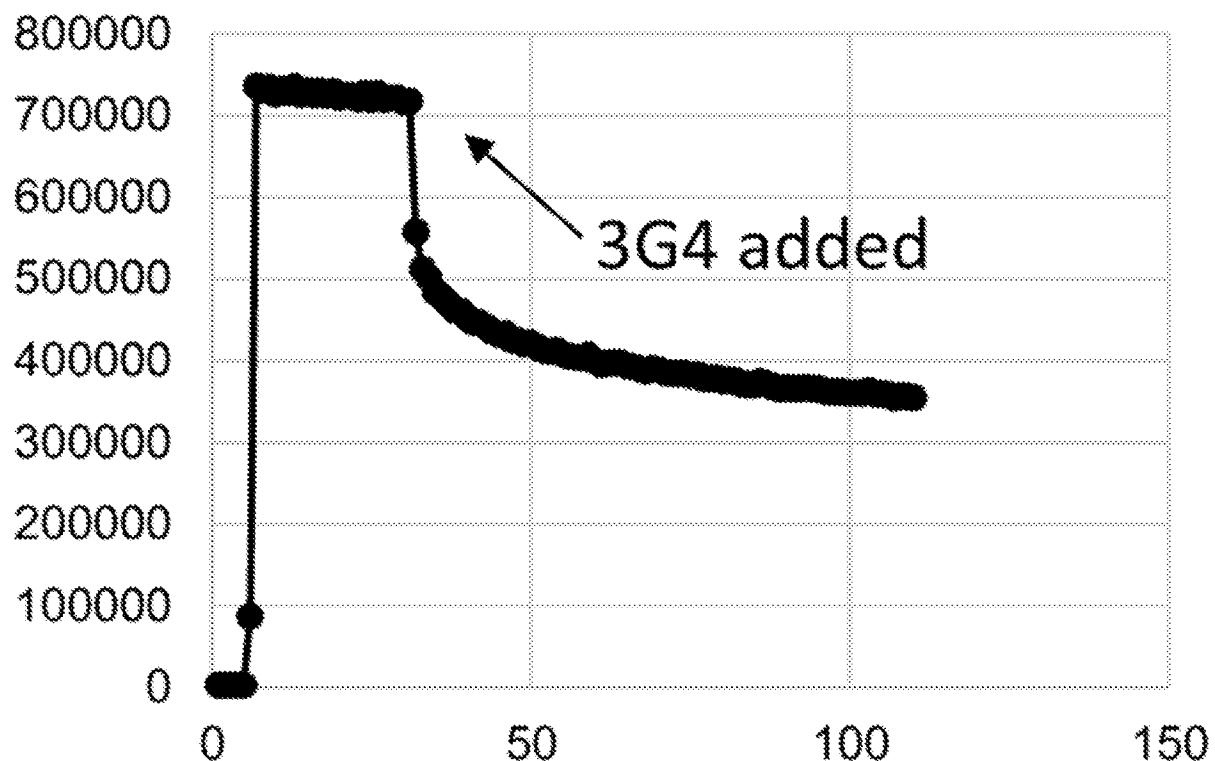


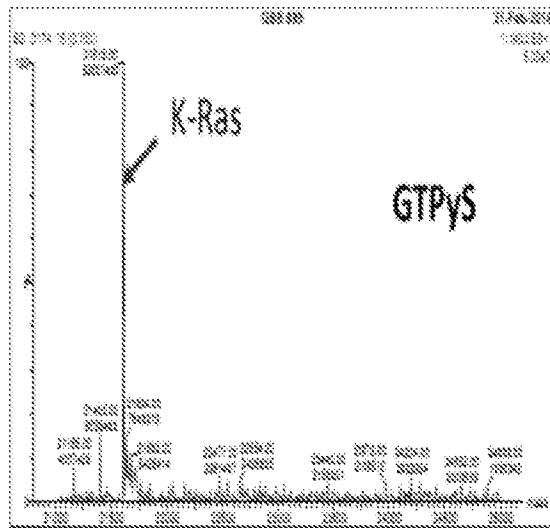
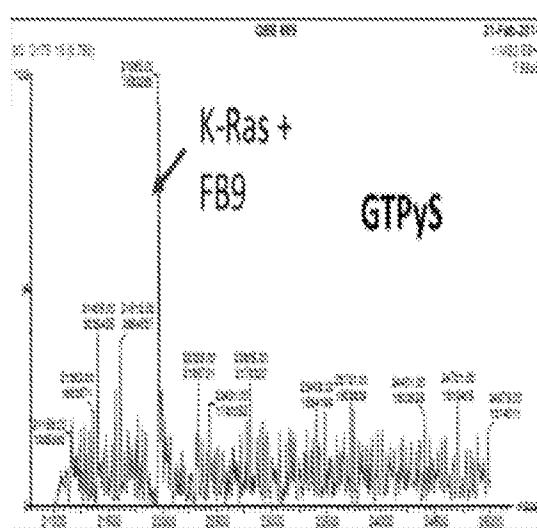
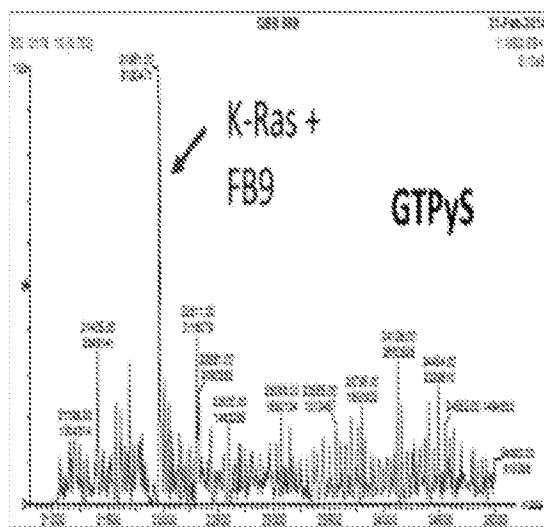
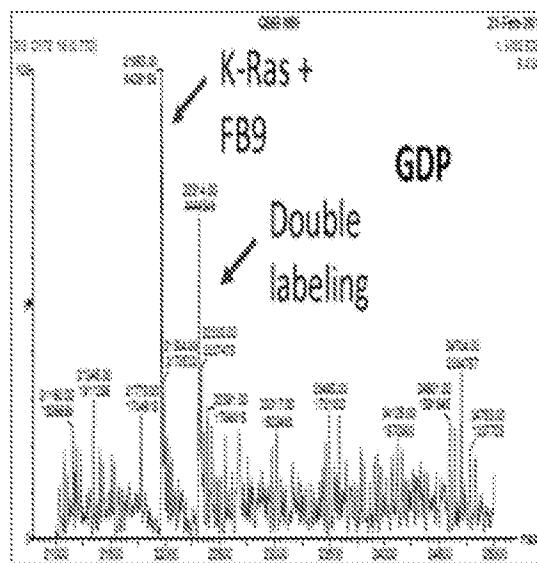
FIG. 13A**FIG. 13B****FIG. 13C****FIG. 13D**

FIG. 13E

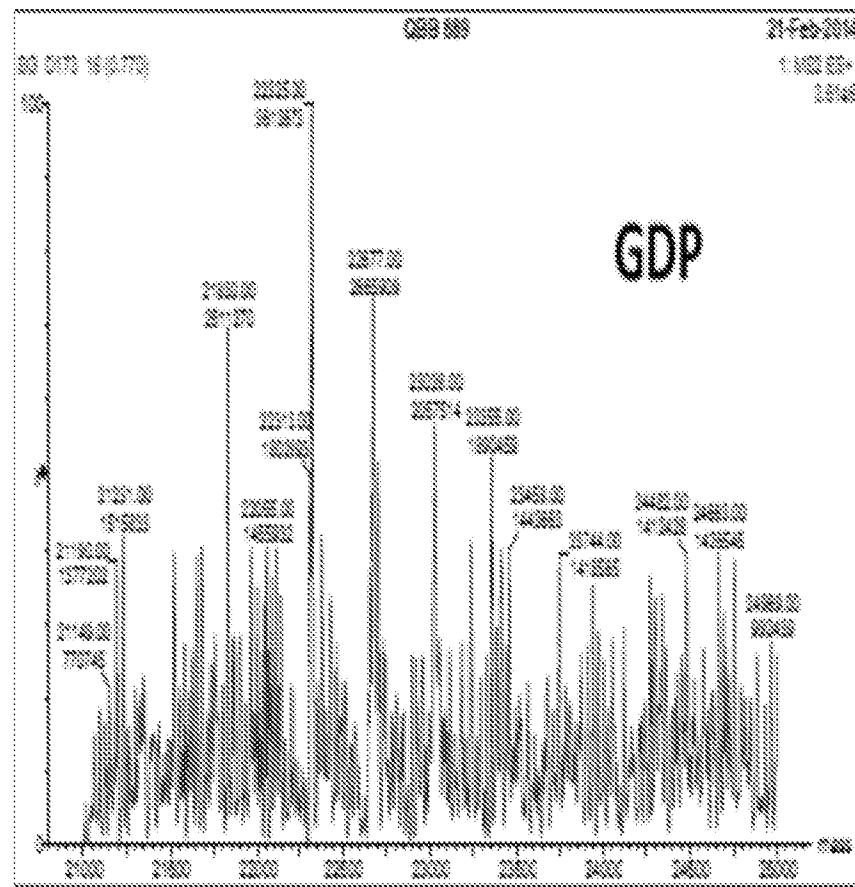


FIG. 14A

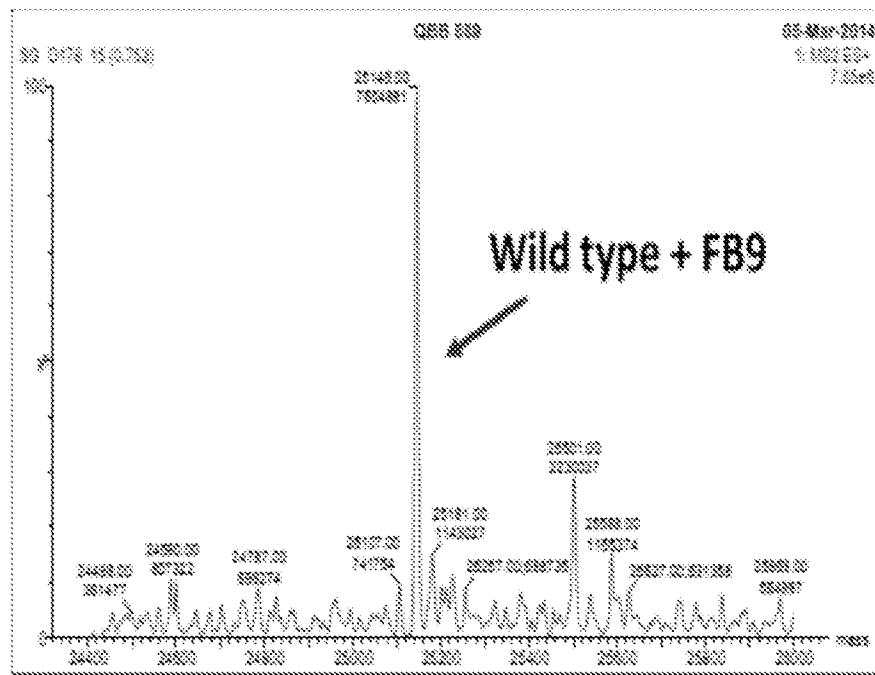


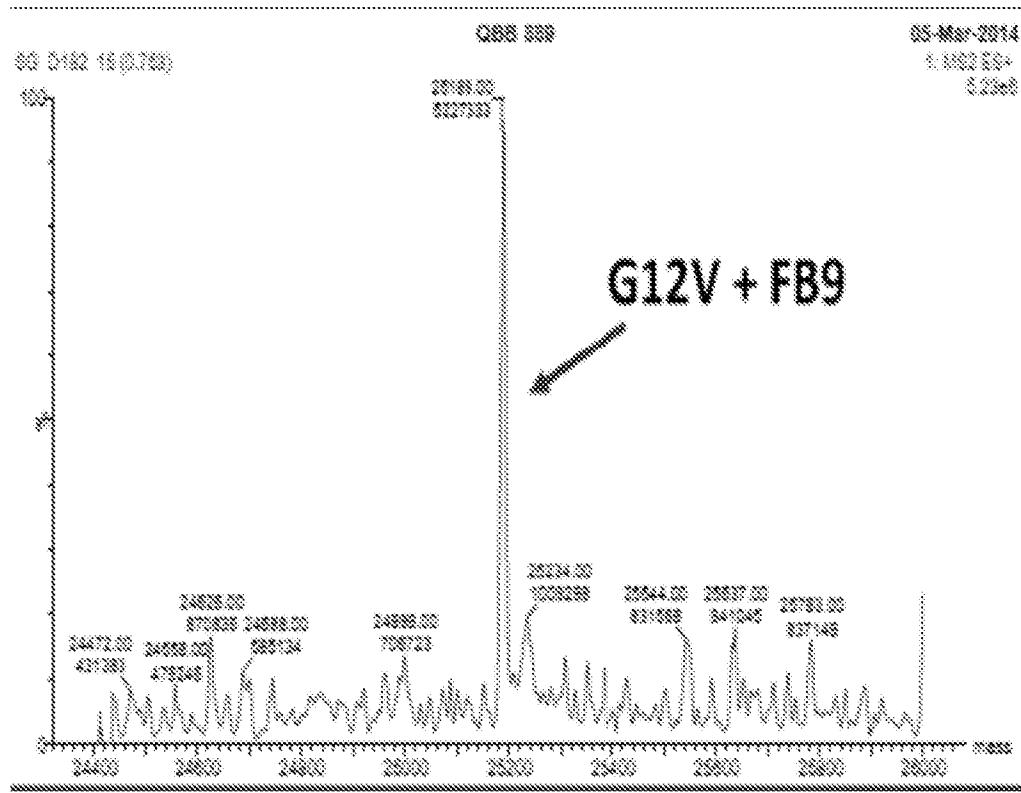
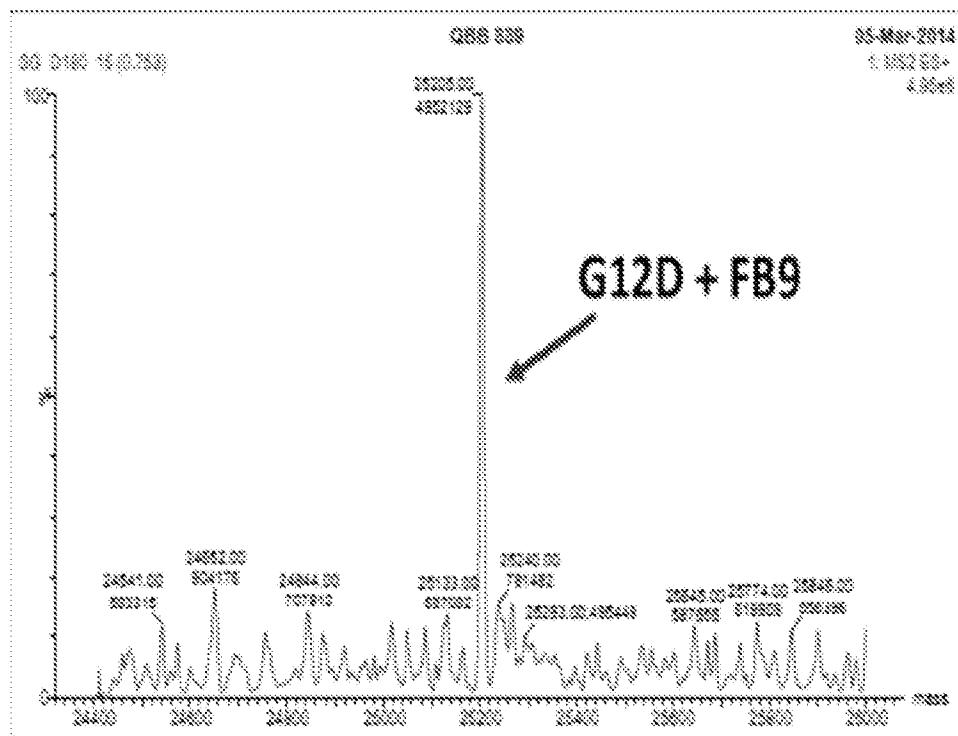
FIG. 14B**FIG. 14C**

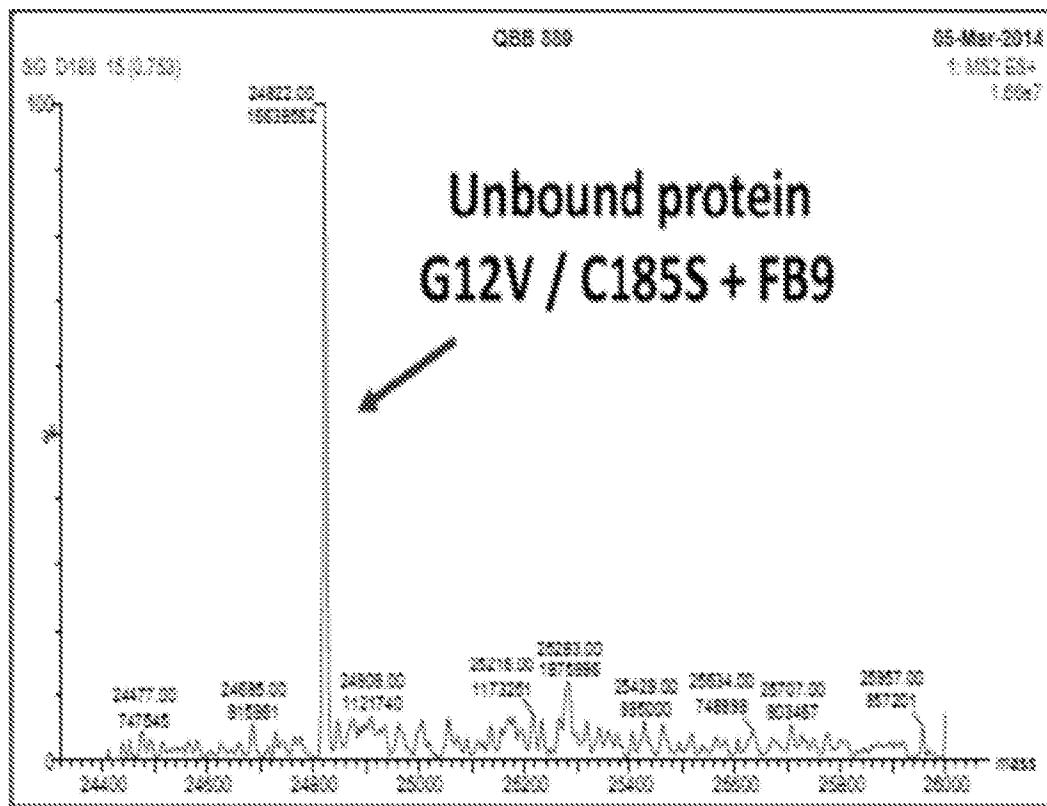
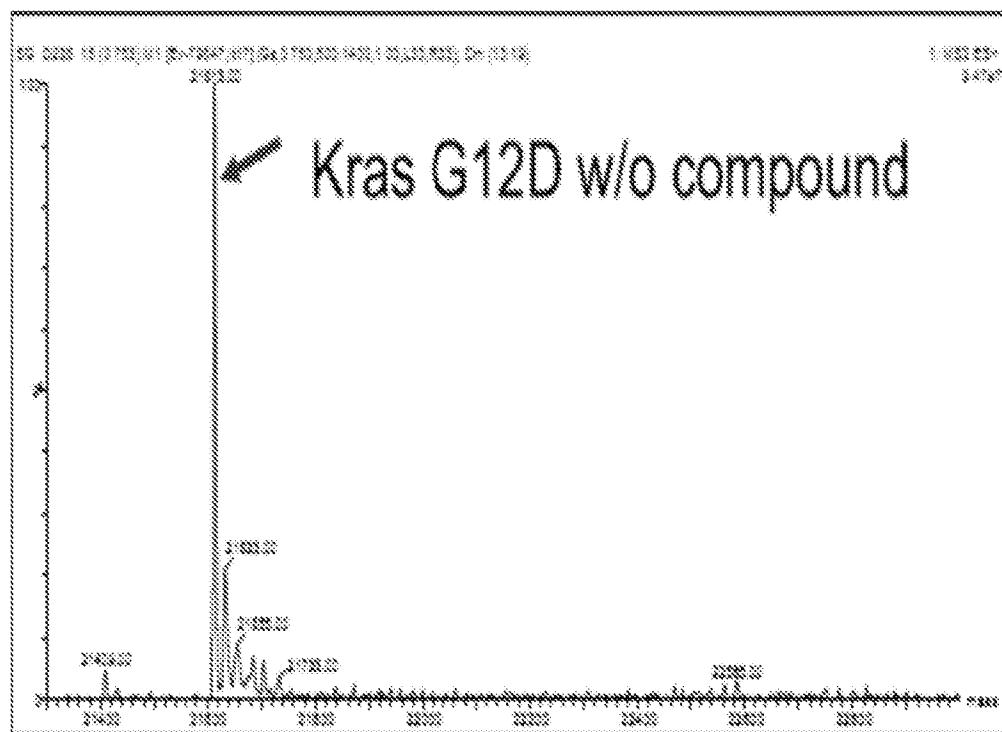
FIG. 14D**FIG. 15A**

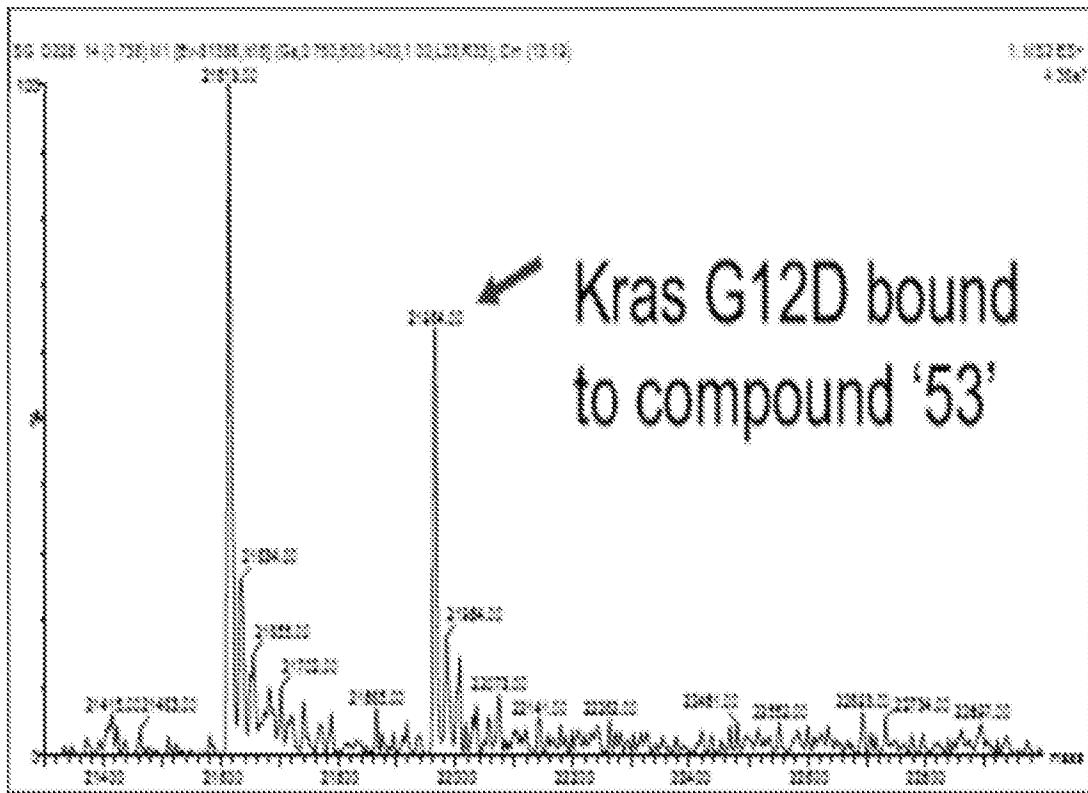
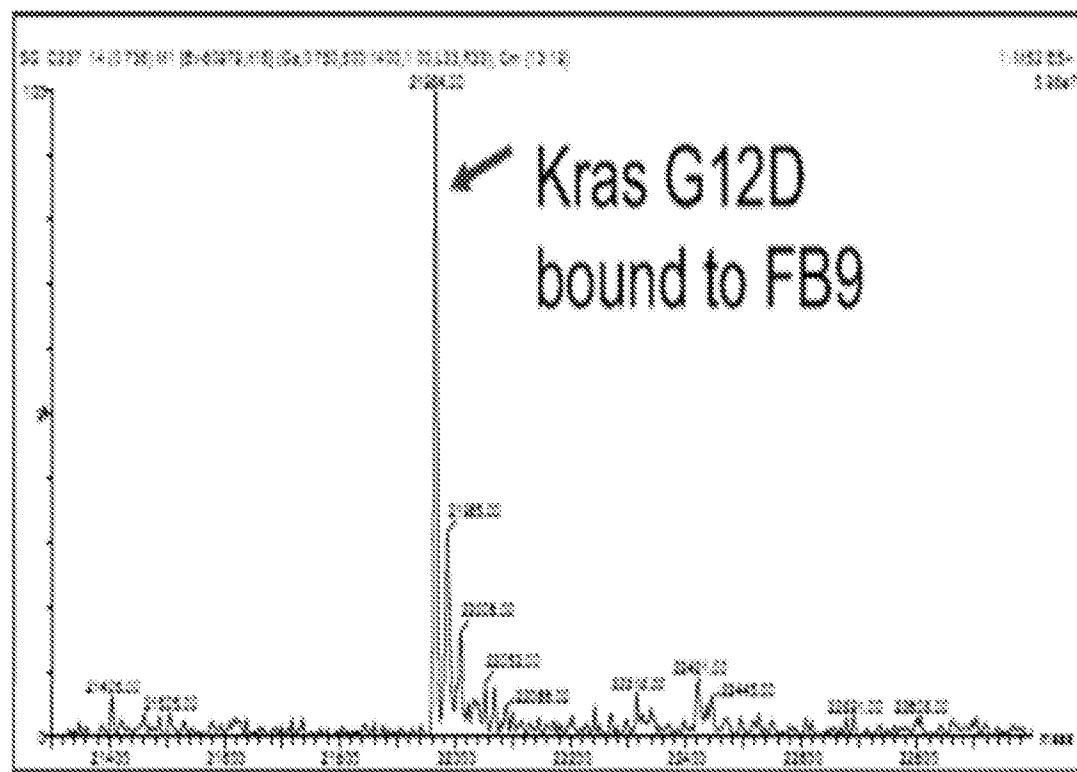
FIG. 15B**FIG. 15C**

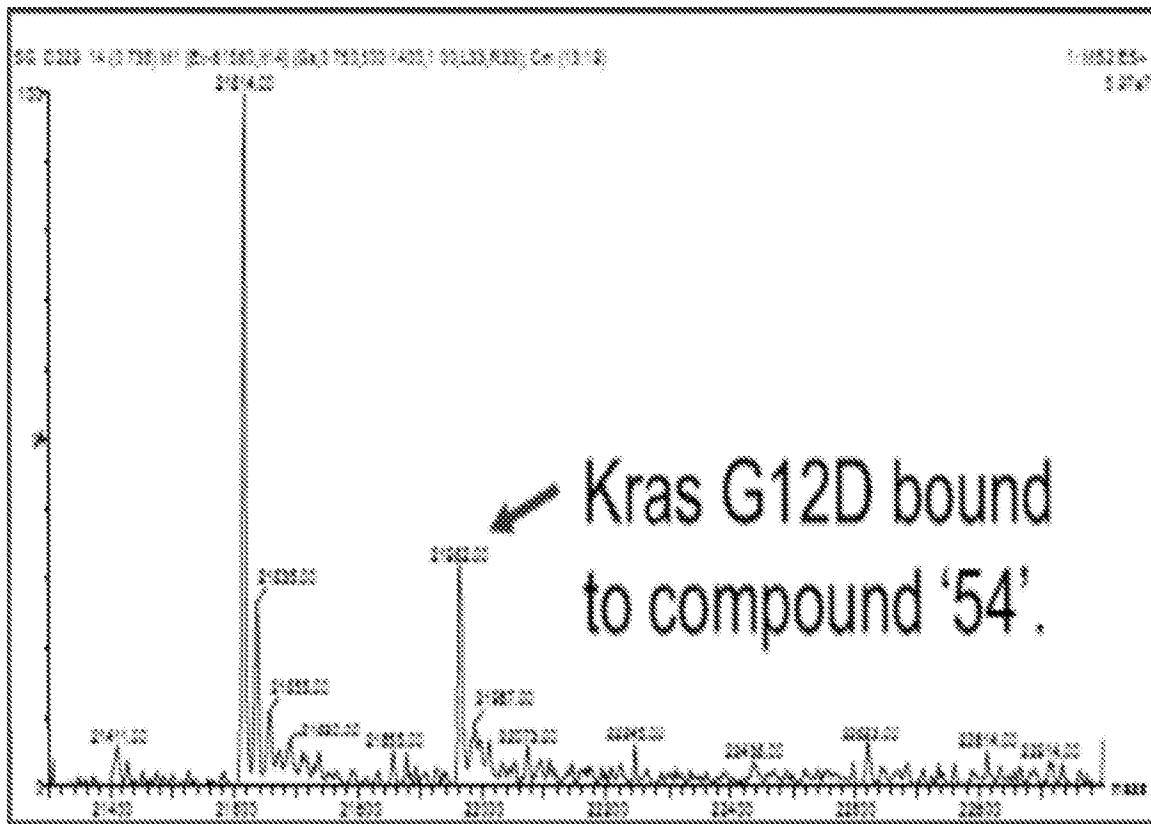
FIG. 15D

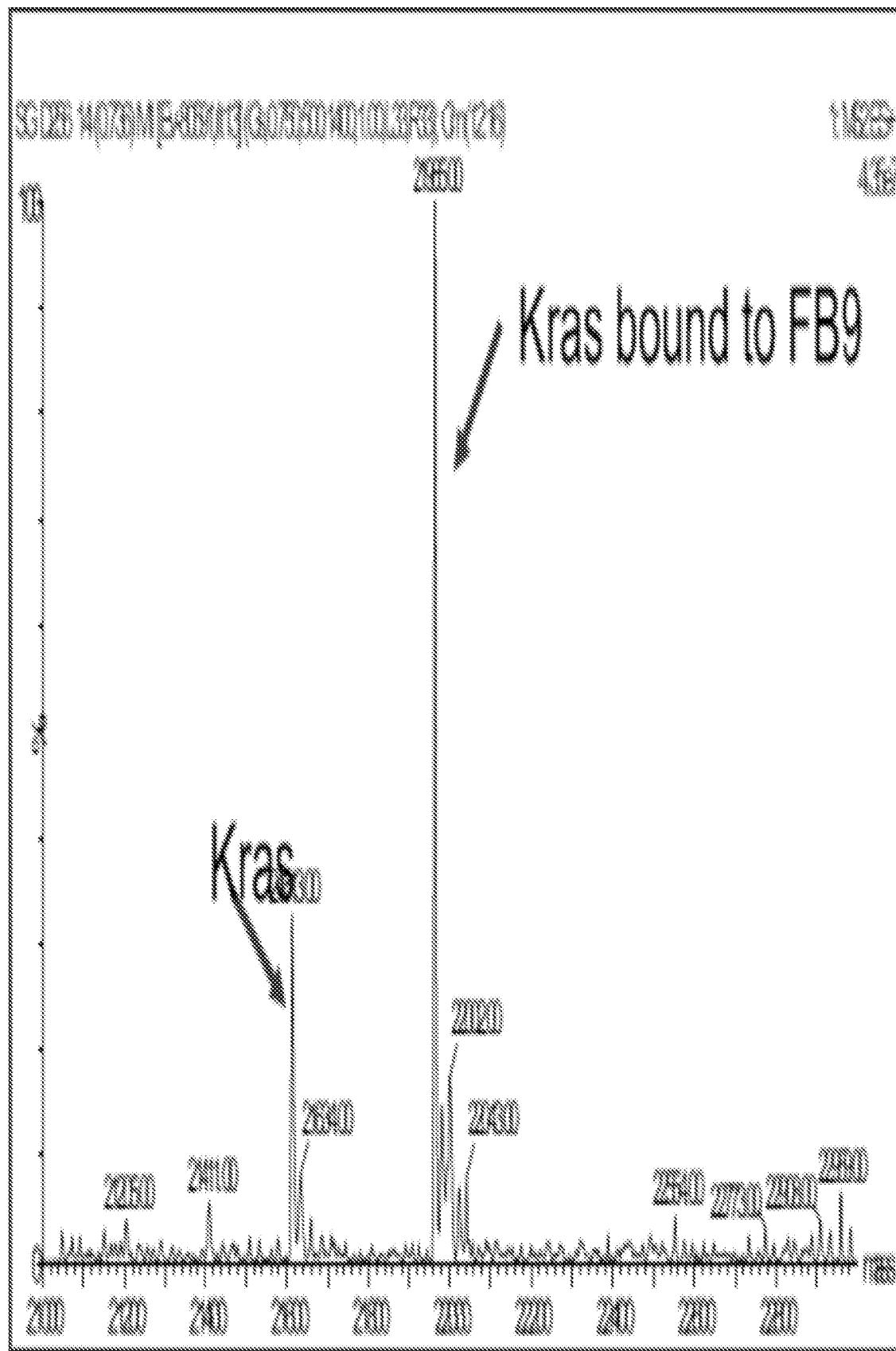
FIG. 16A

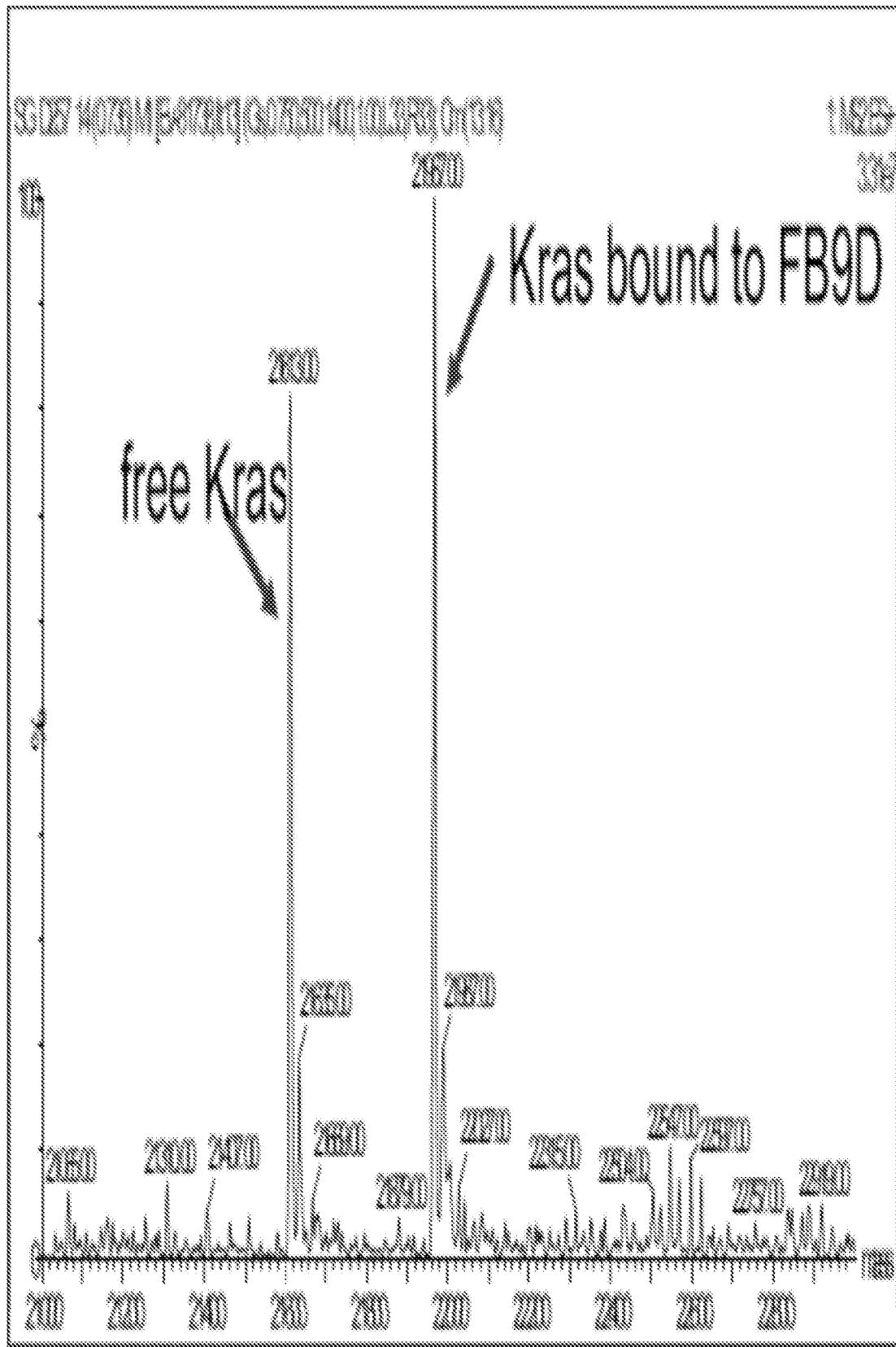
FIG. 16B

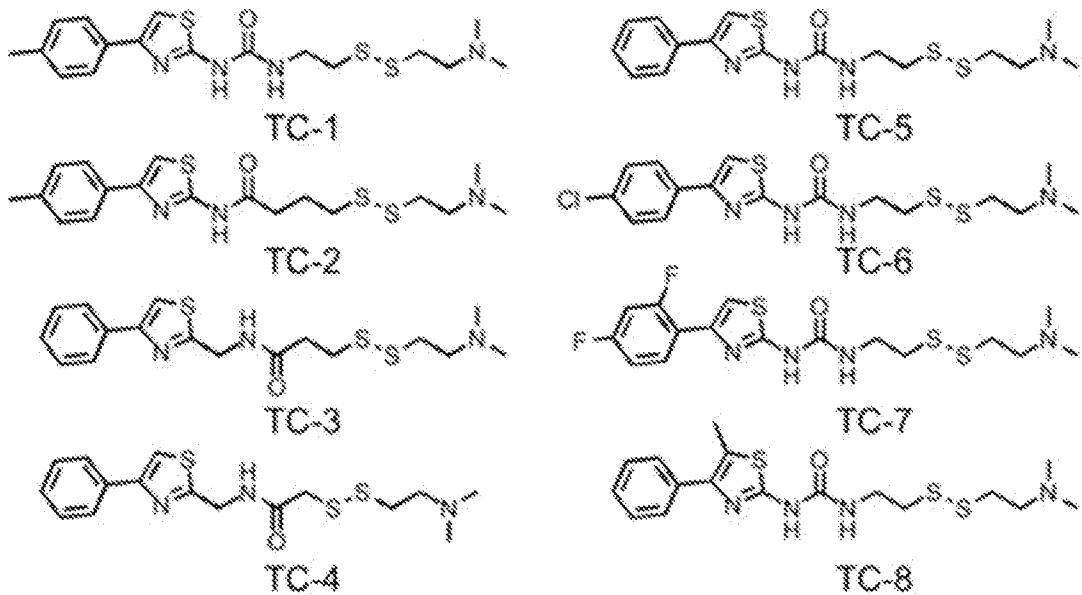
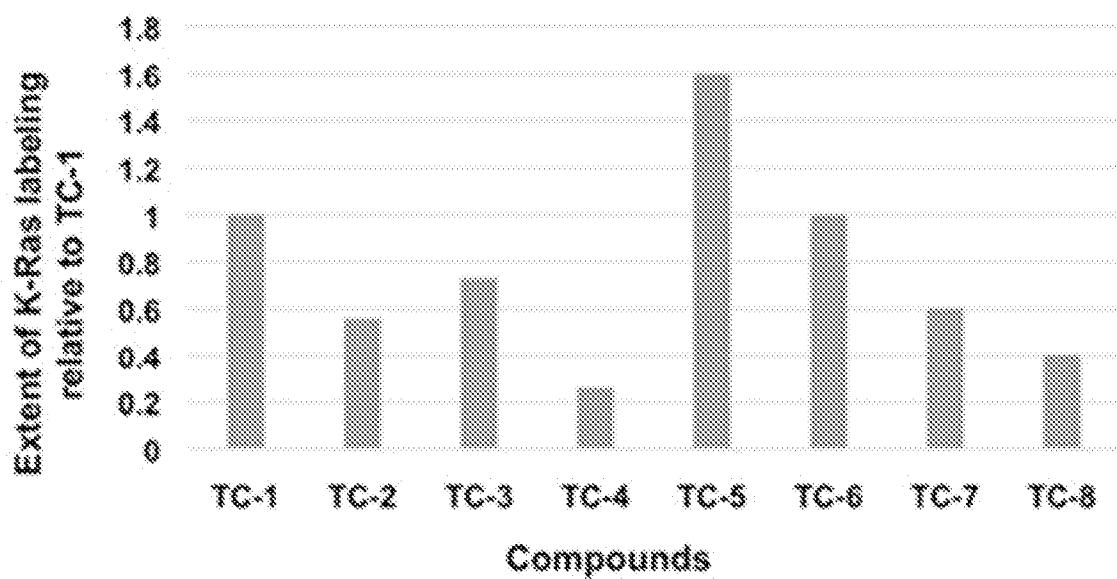
FIG. 17A**FIG. 17B**

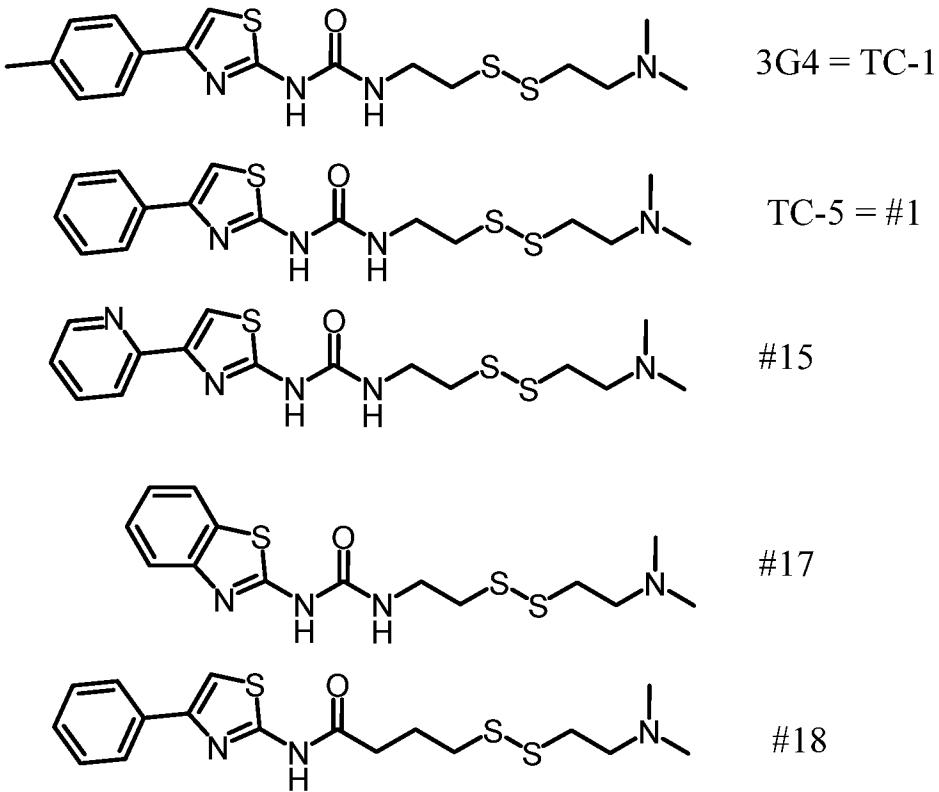
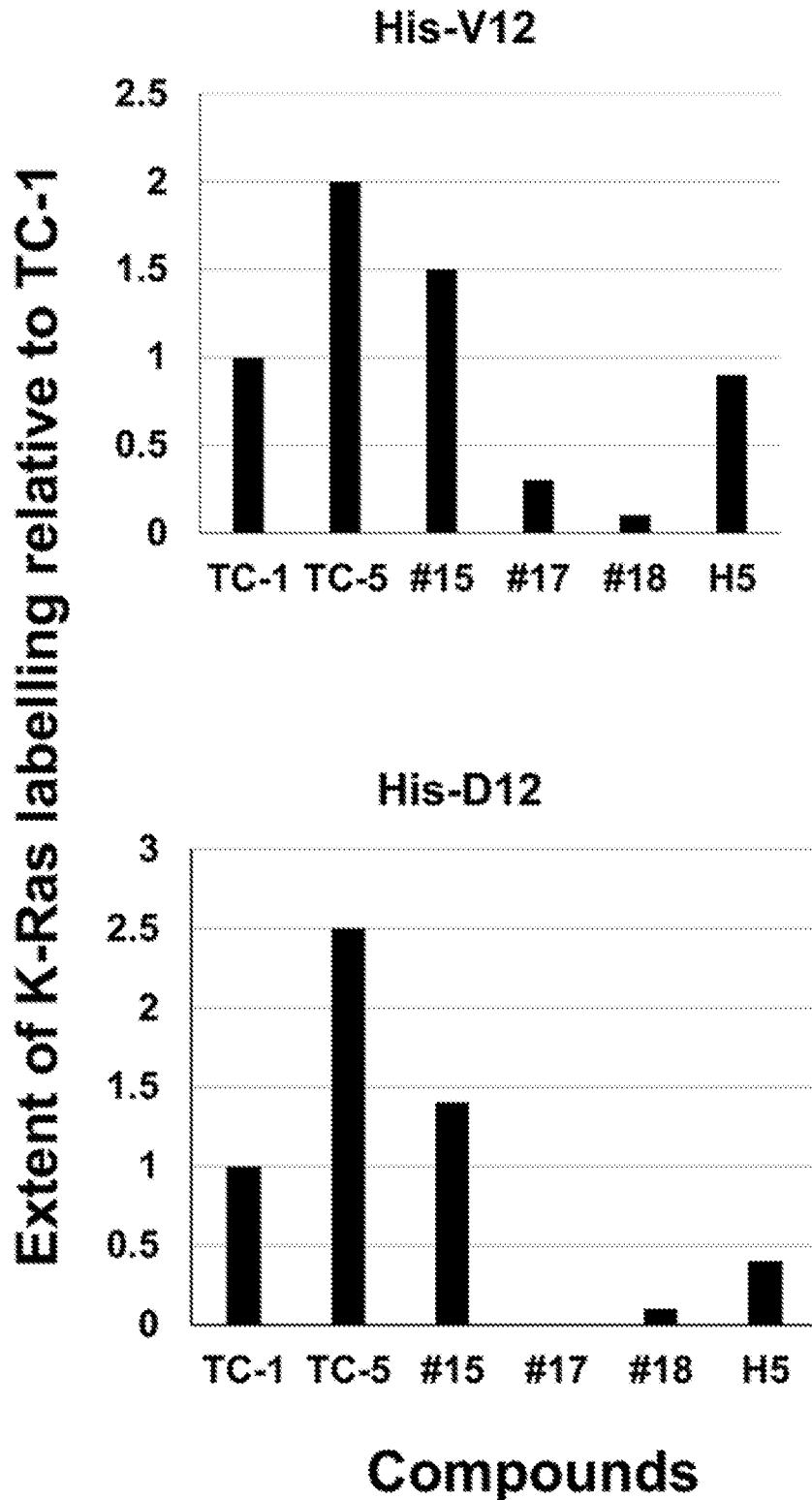
FIG. 18A

FIG. 18B

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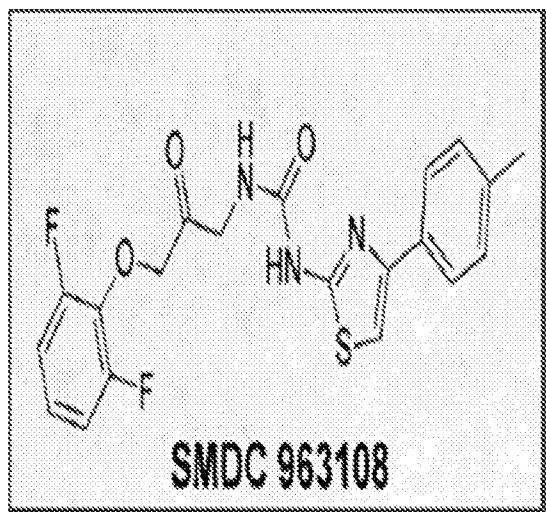
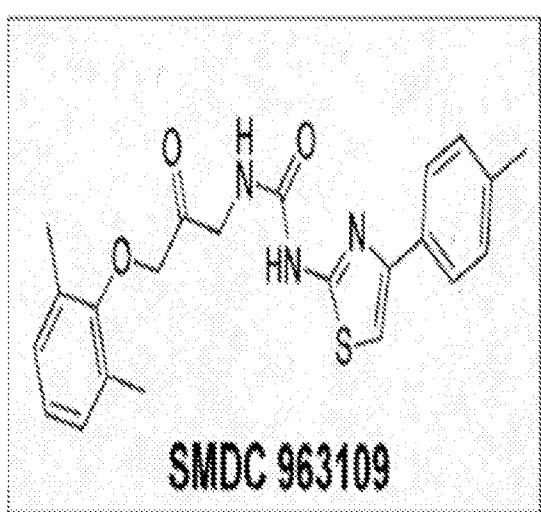
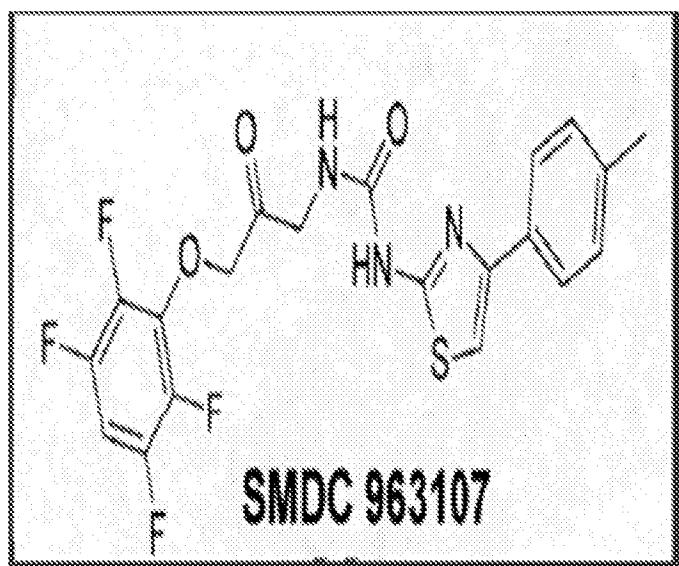
FIG. 19A**FIG. 19B****FIG. 19C**

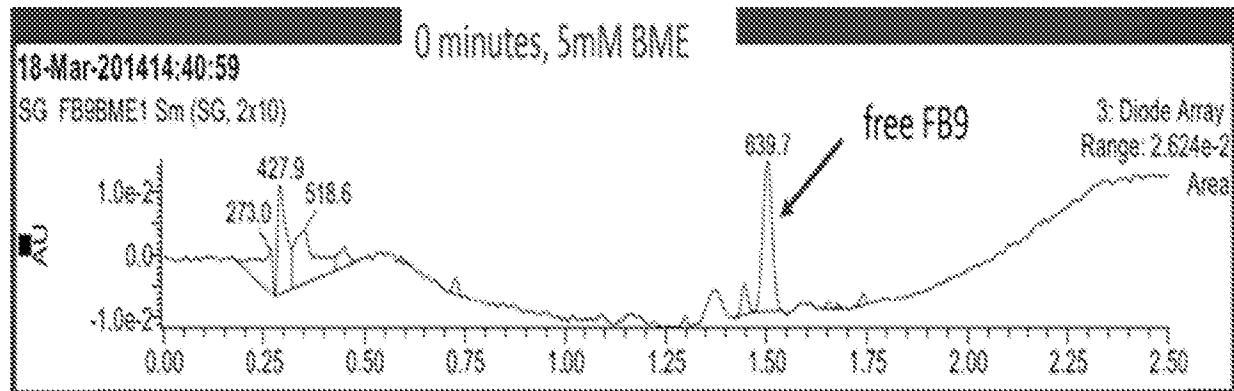
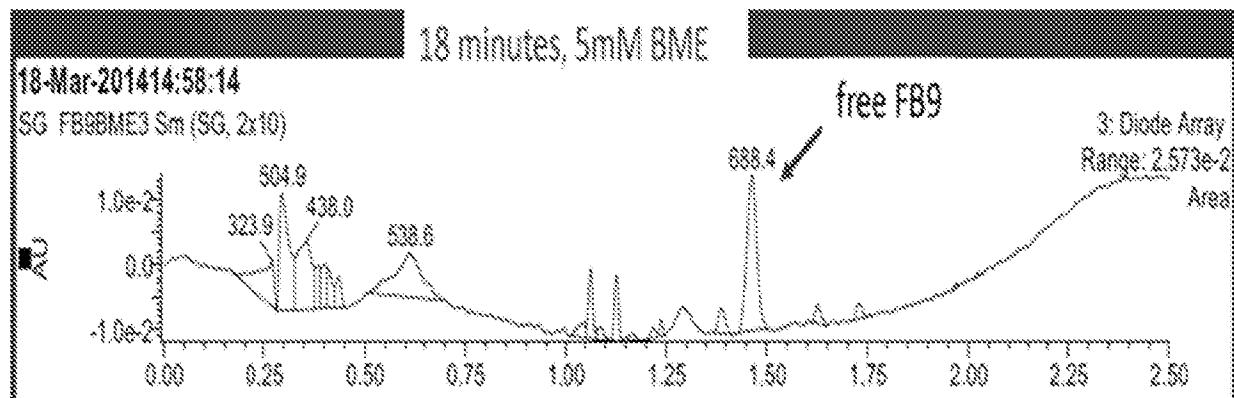
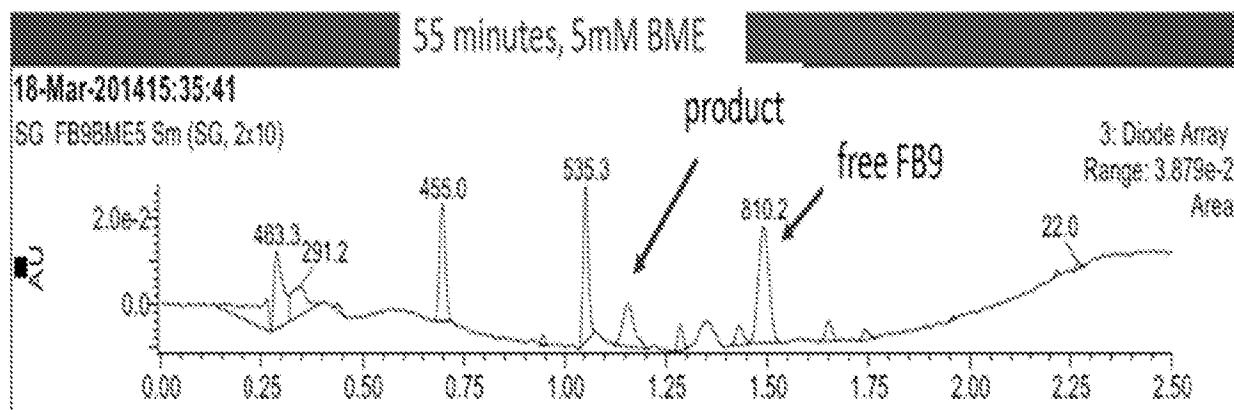
FIG. 20A**FIG. 20B****FIG. 20C**

FIG. 21A

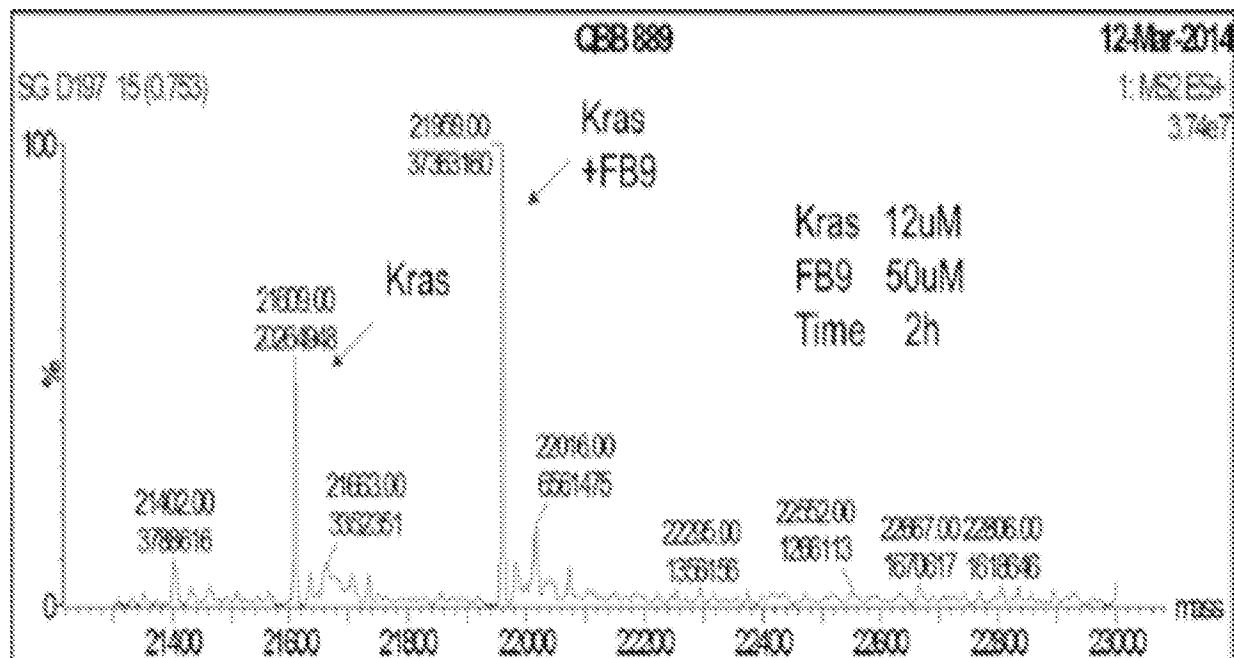


FIG. 21B

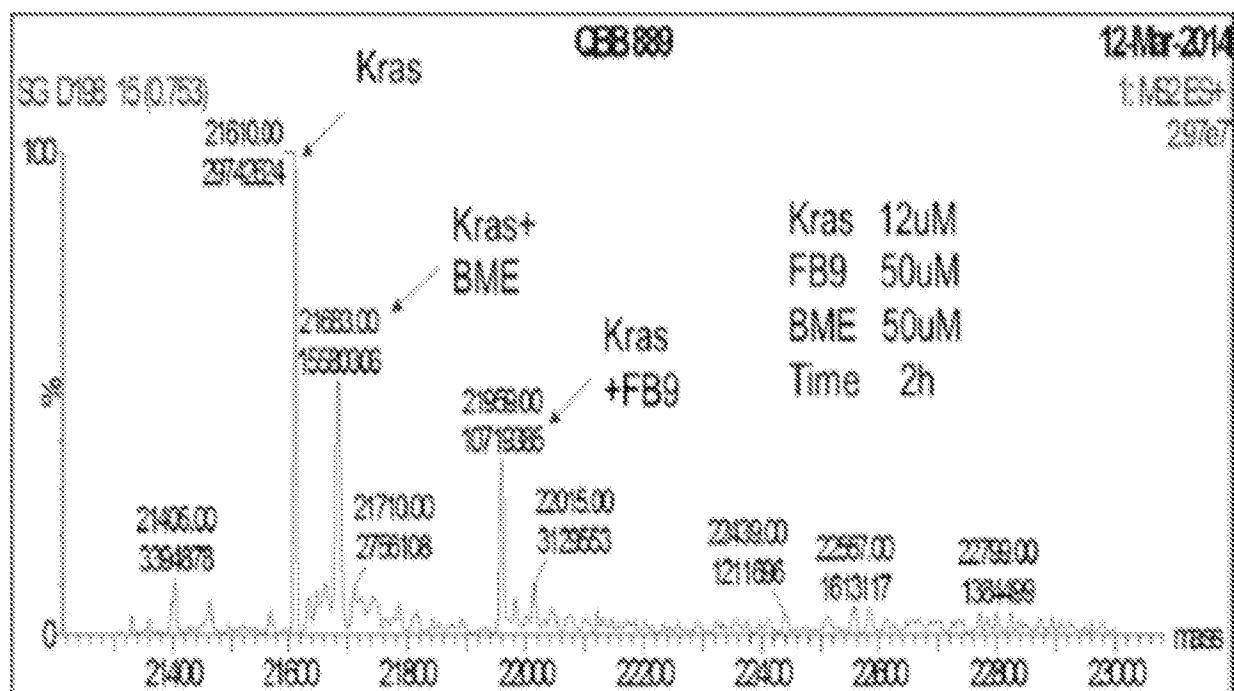


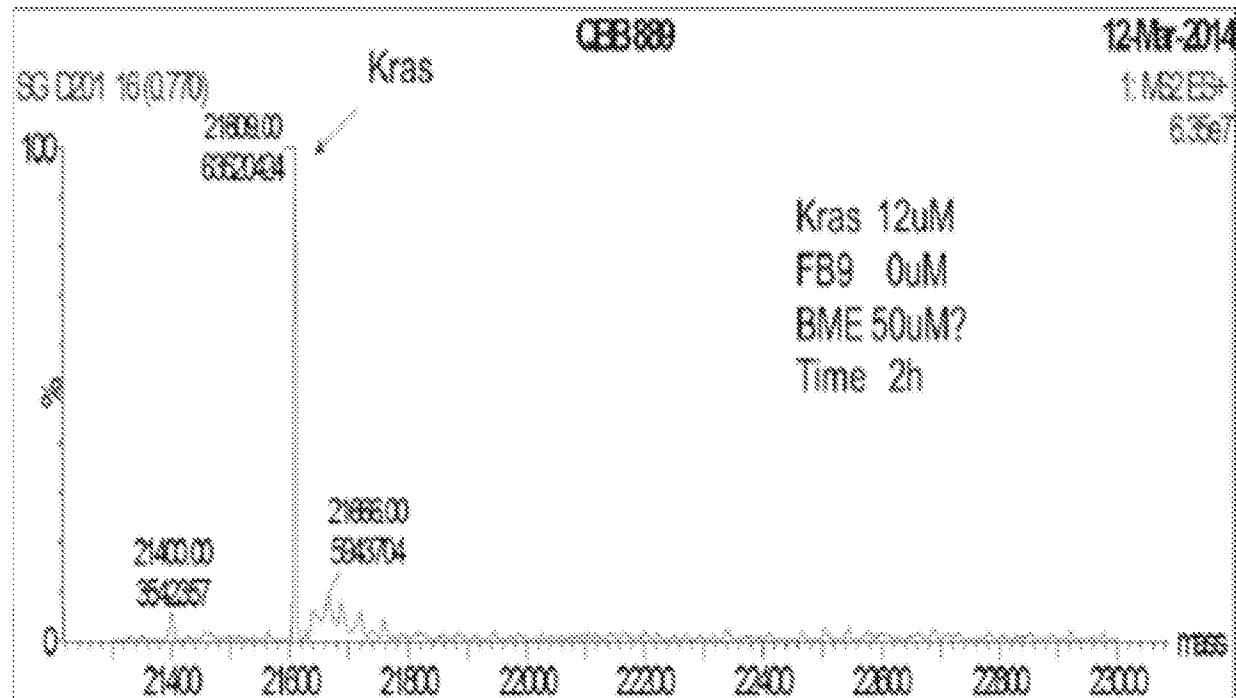
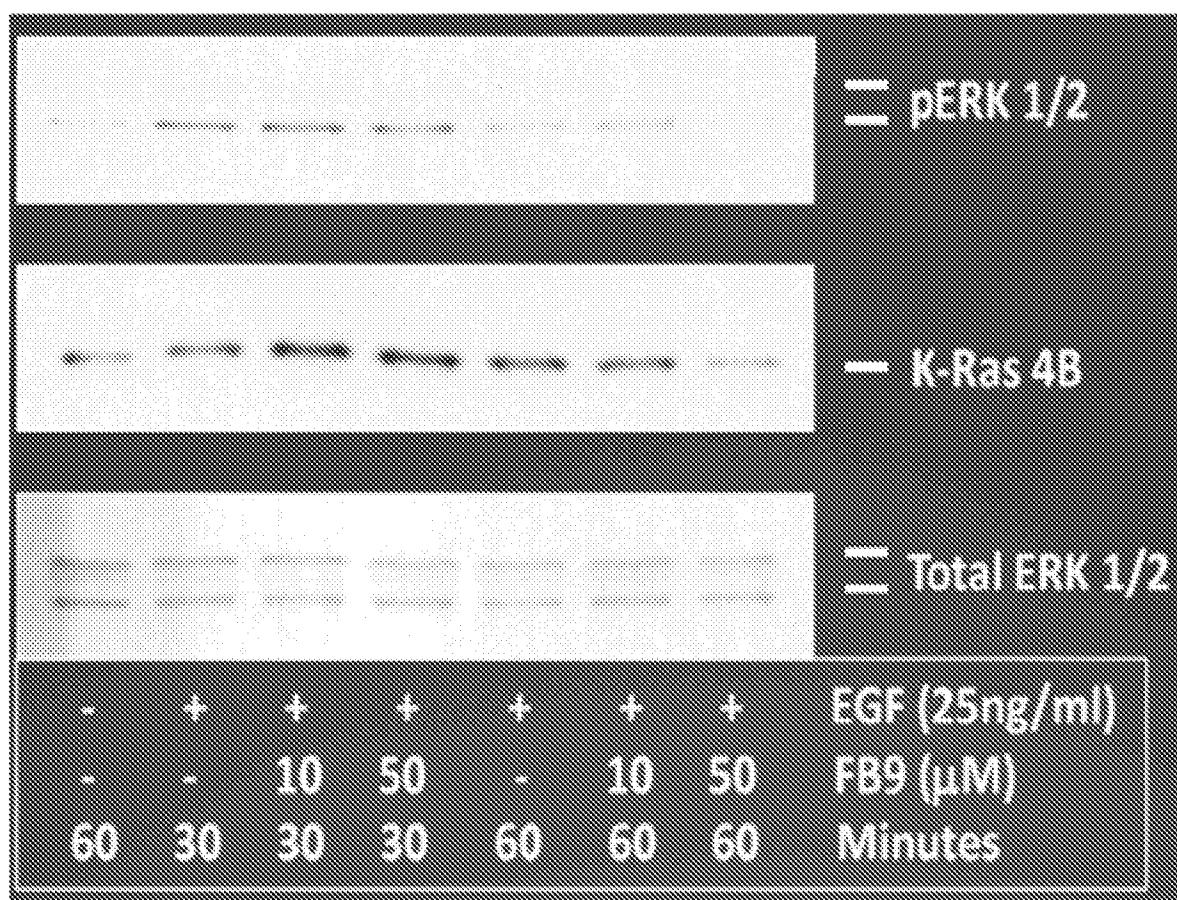
FIG. 21C**FIG. 22**

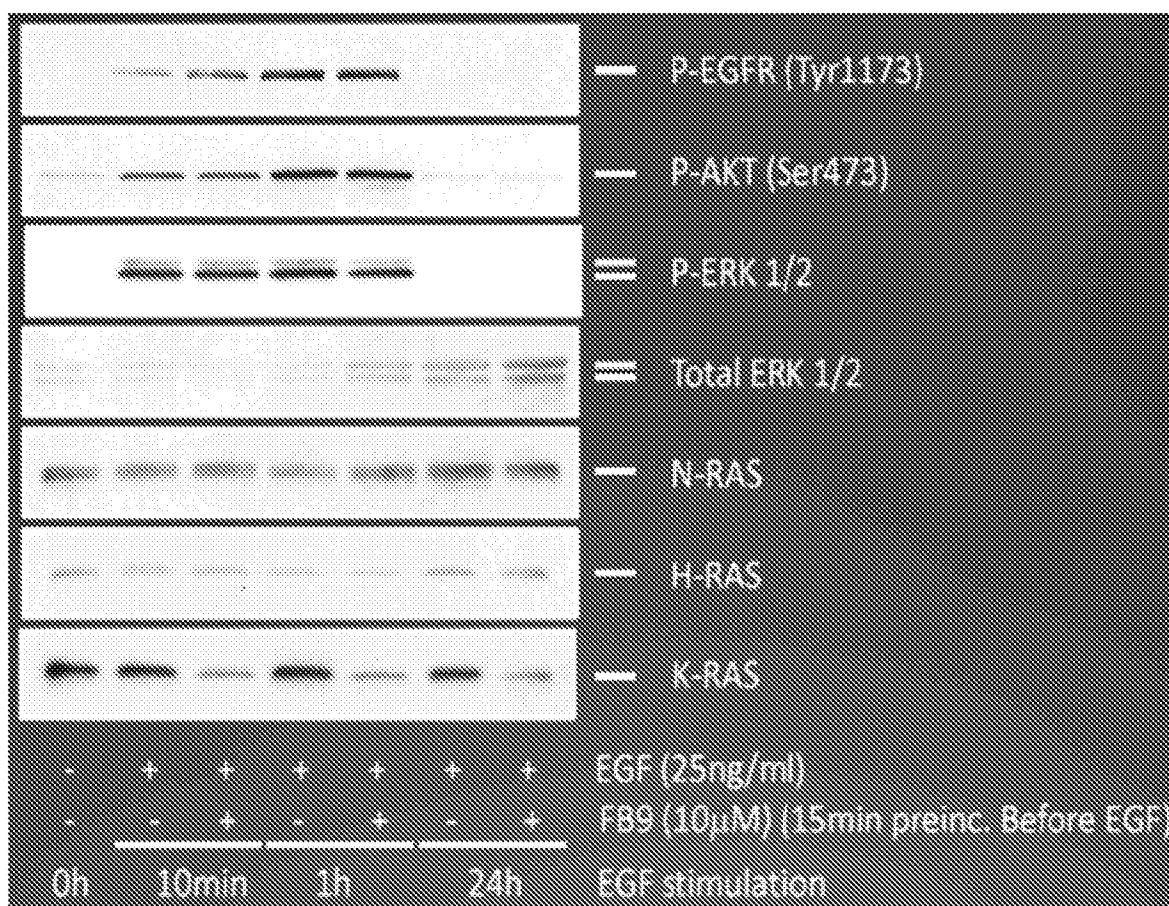
FIG. 23

FIG. 24

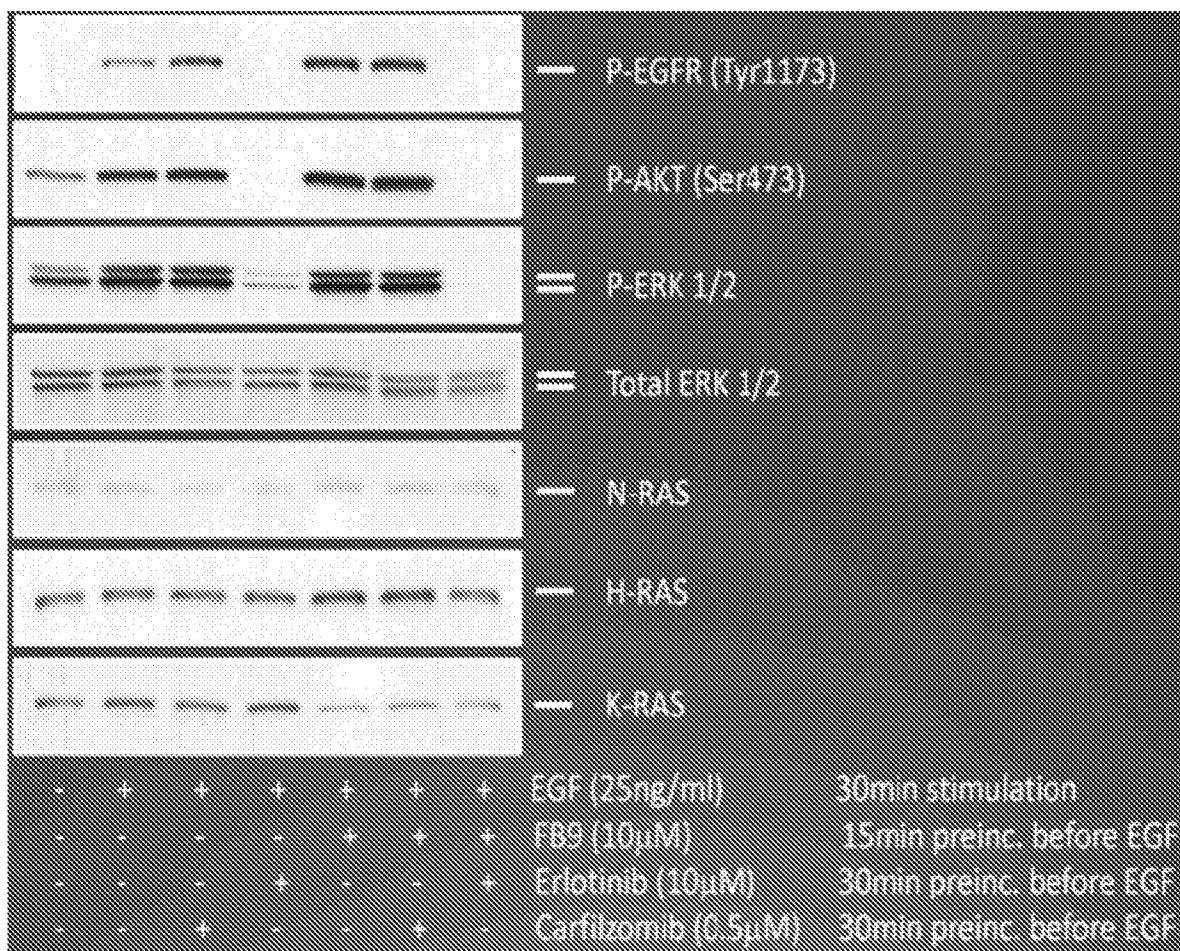


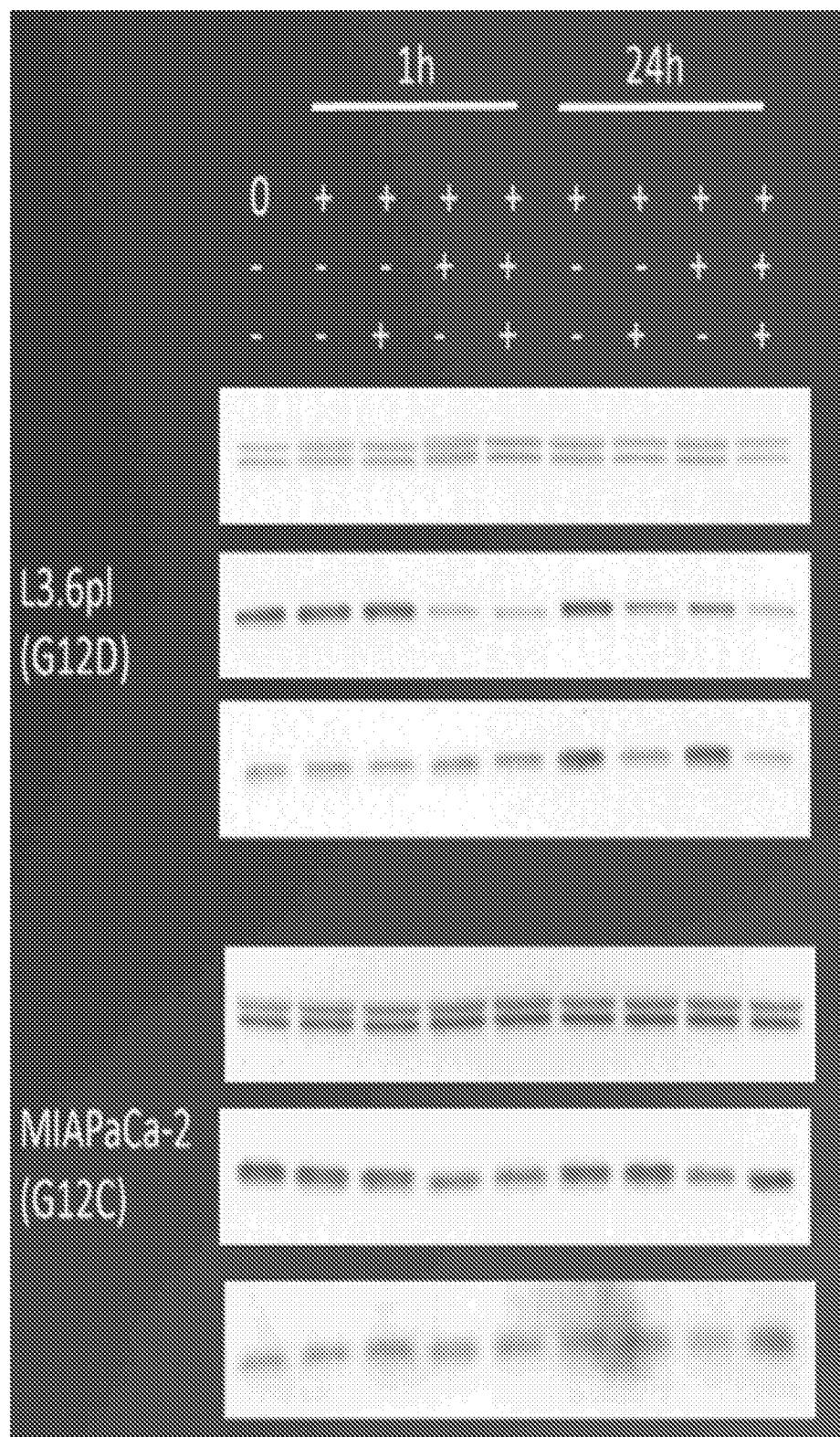
FIG. 25A

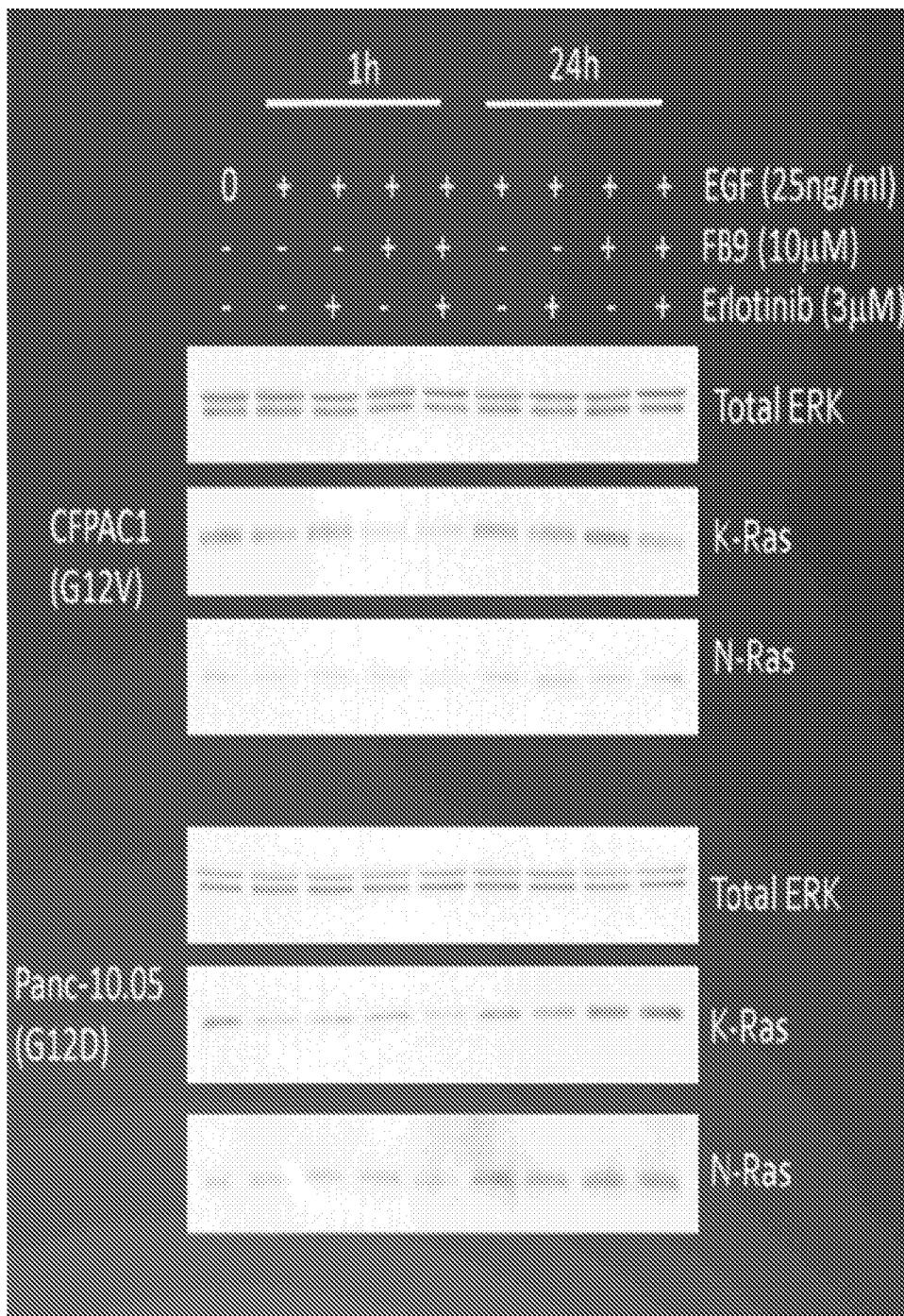
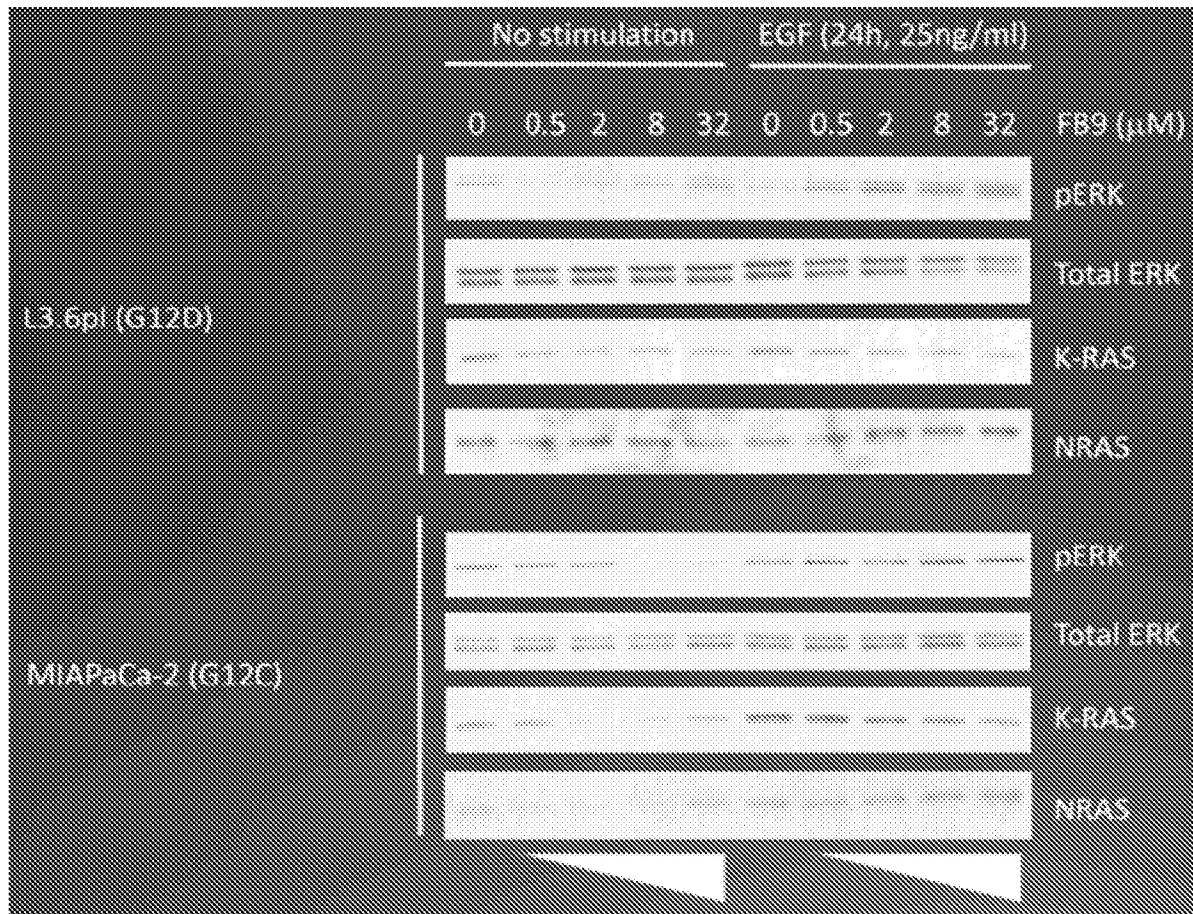
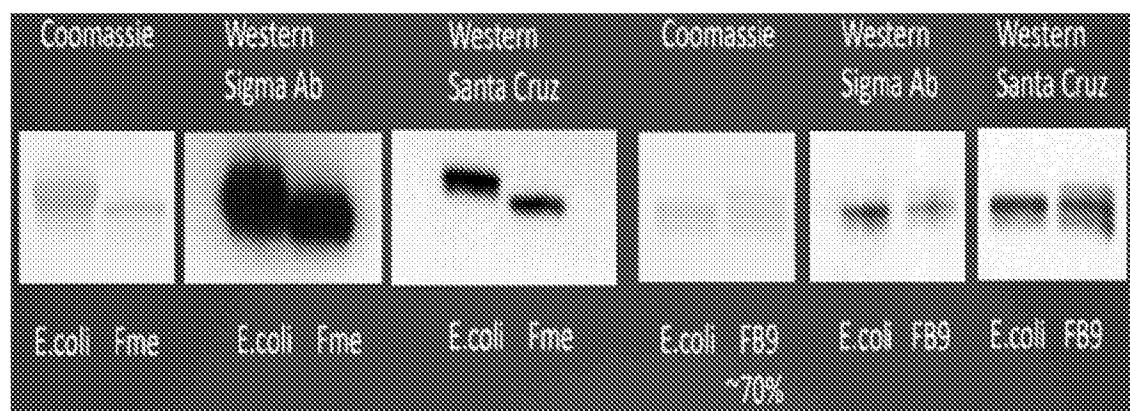
FIG. 25B

FIG. 26**FIG. 27**

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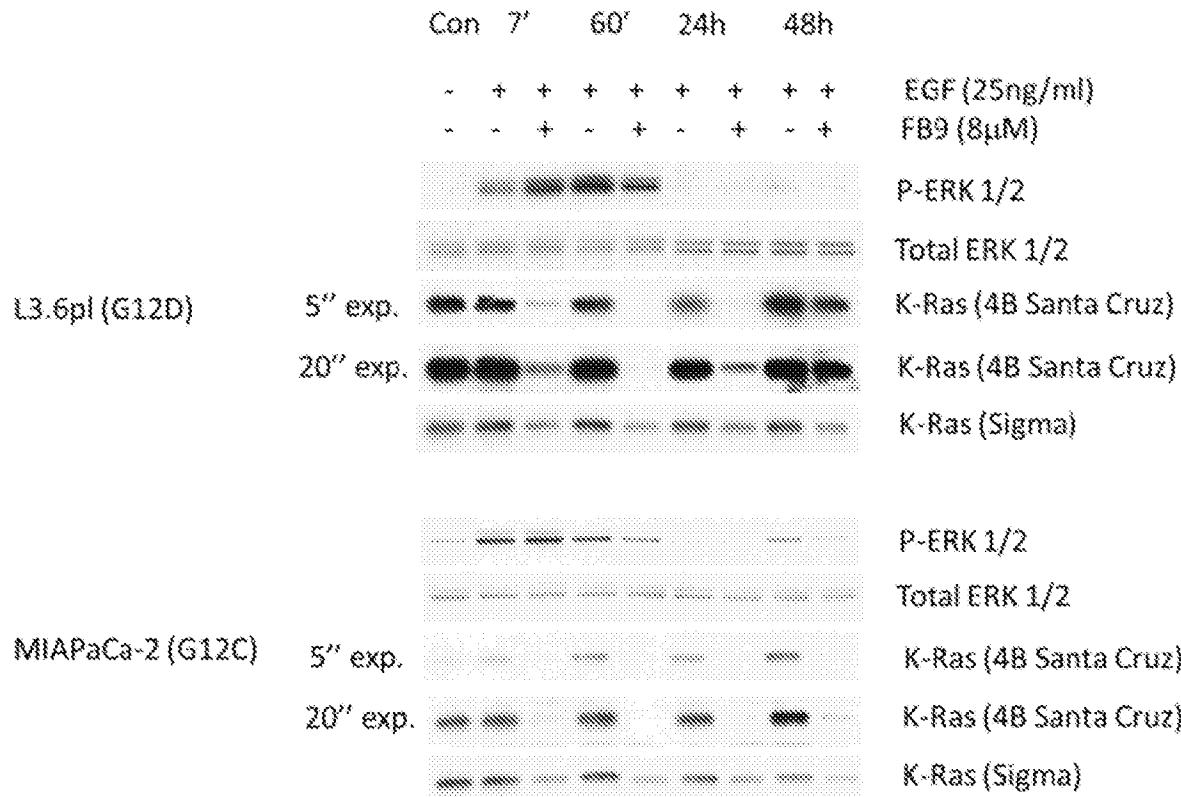
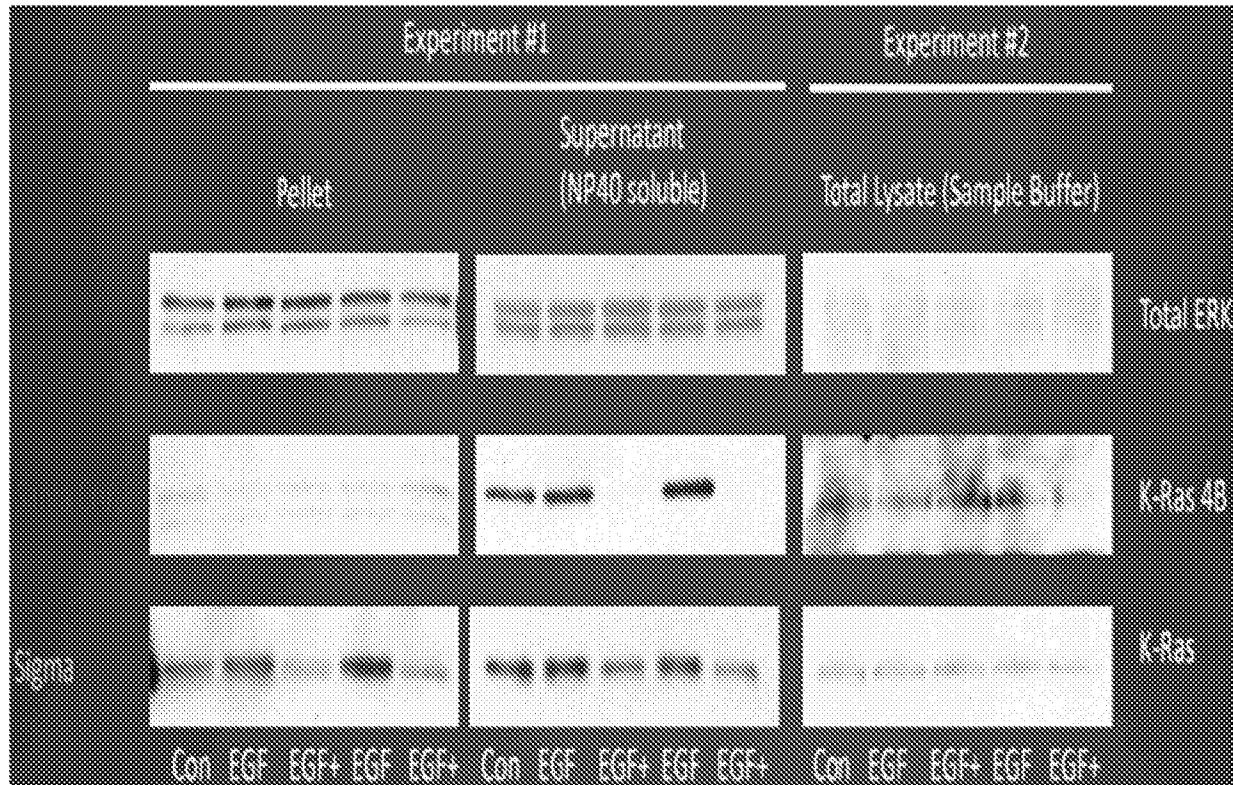
FIG. 28**FIG. 29**

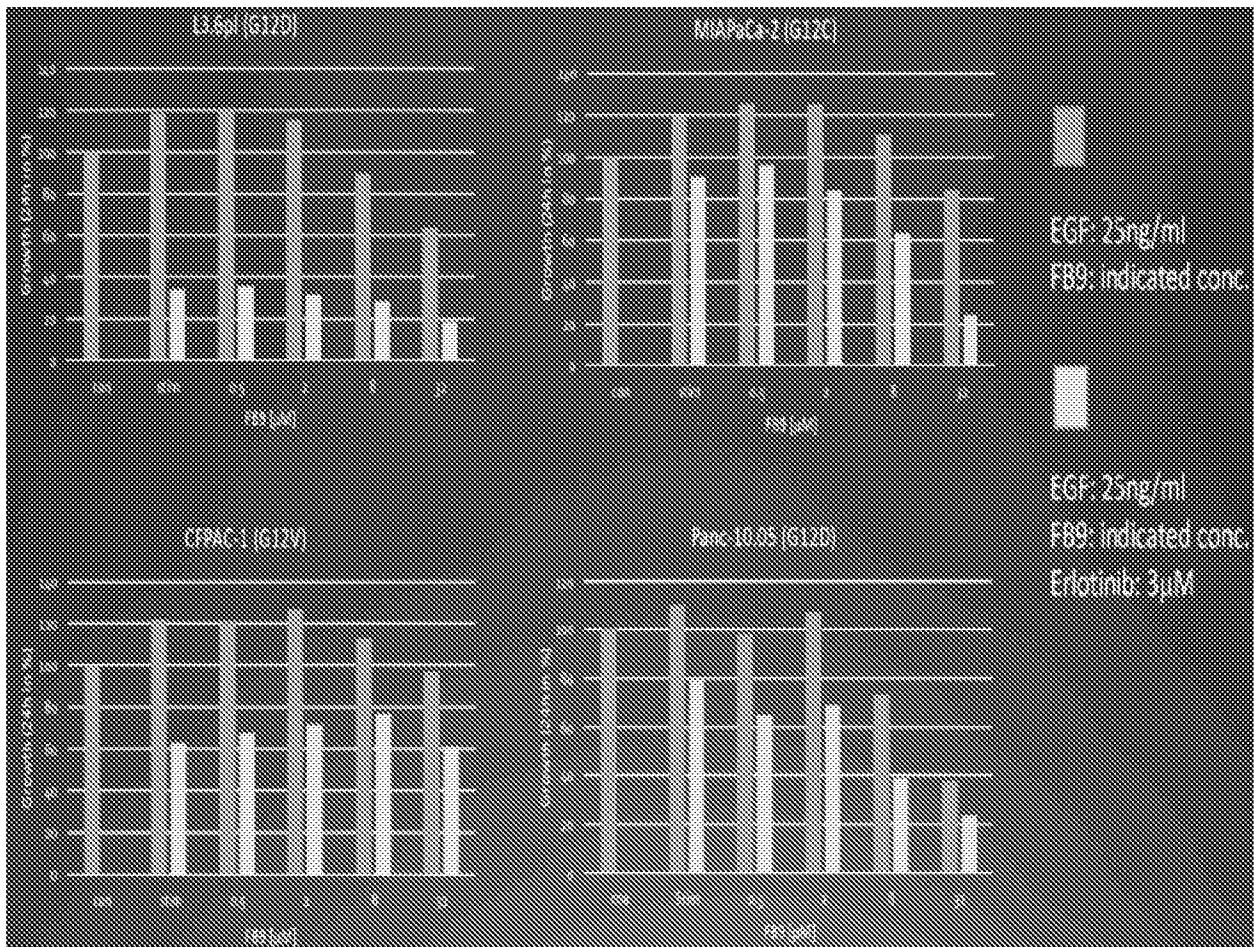
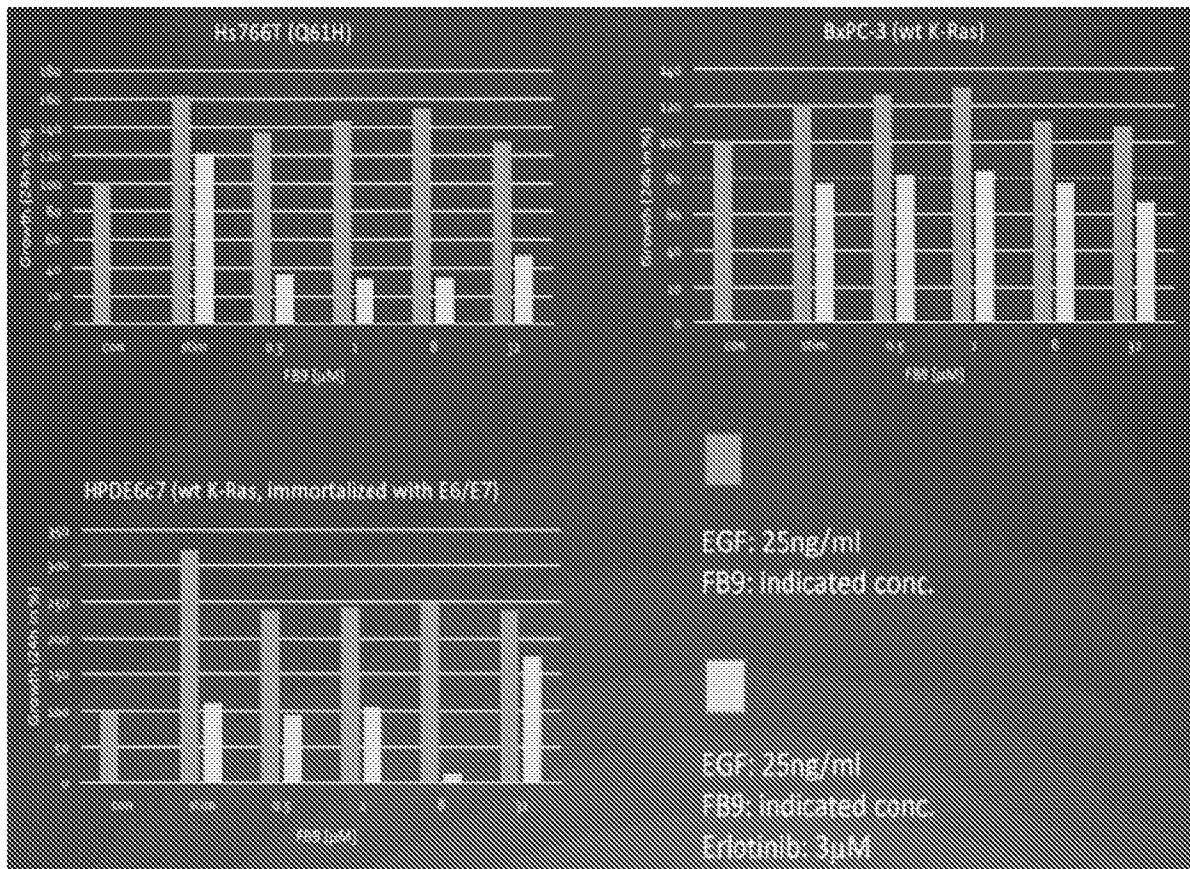
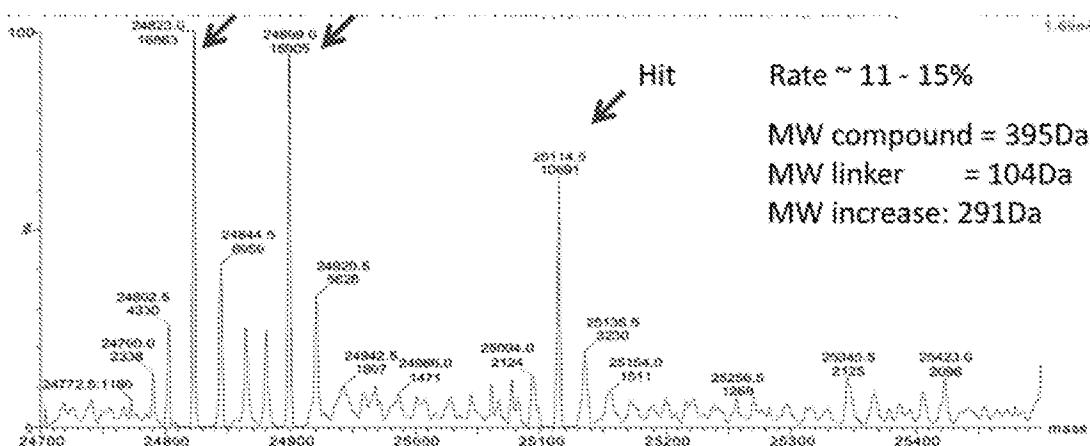
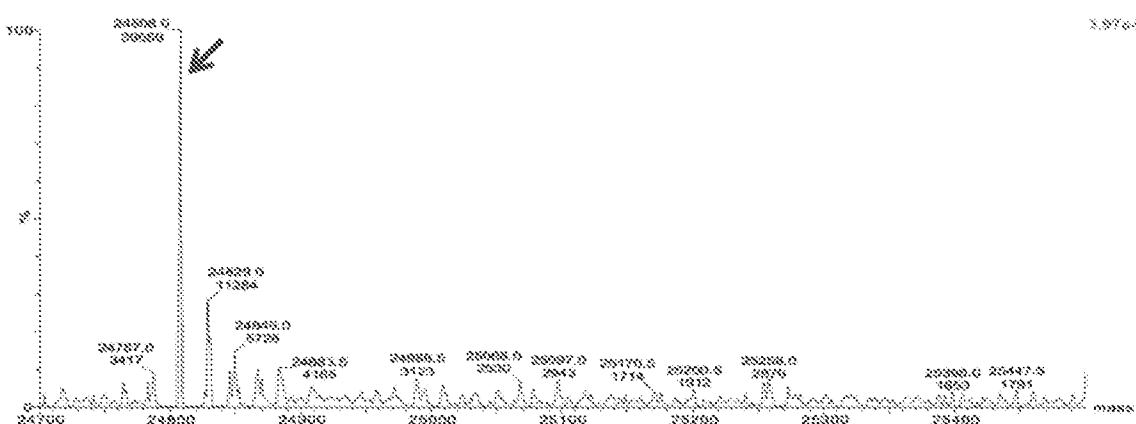
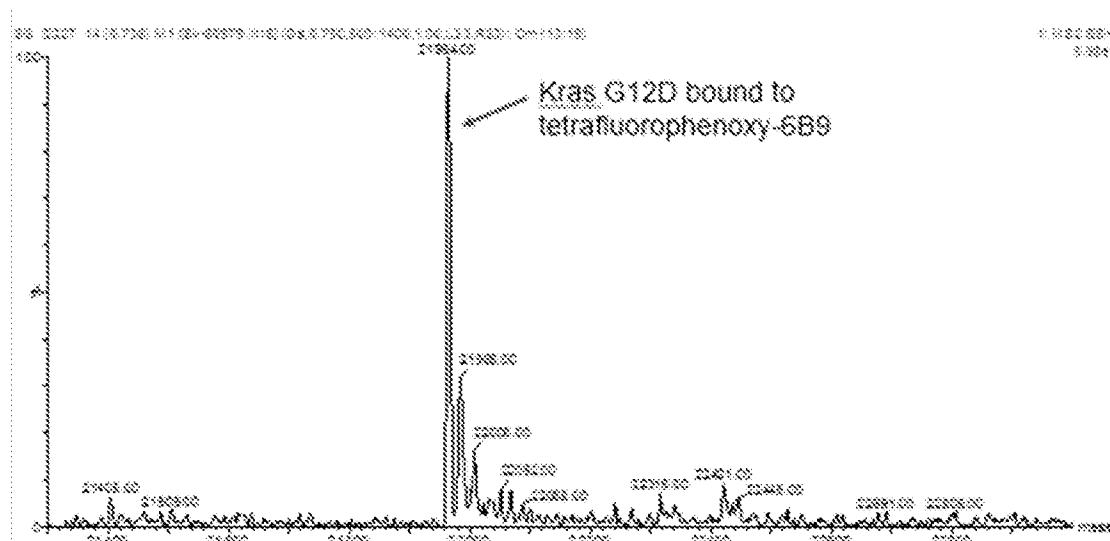
FIG. 30

FIG. 31

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FIG. 32A**K-Ras 4B wild type C-terminus: Compound 3G4****FIG. 32B****K-Ras 4B mutant C-terminus (C185S): Compound 3G4****FIG. 33**

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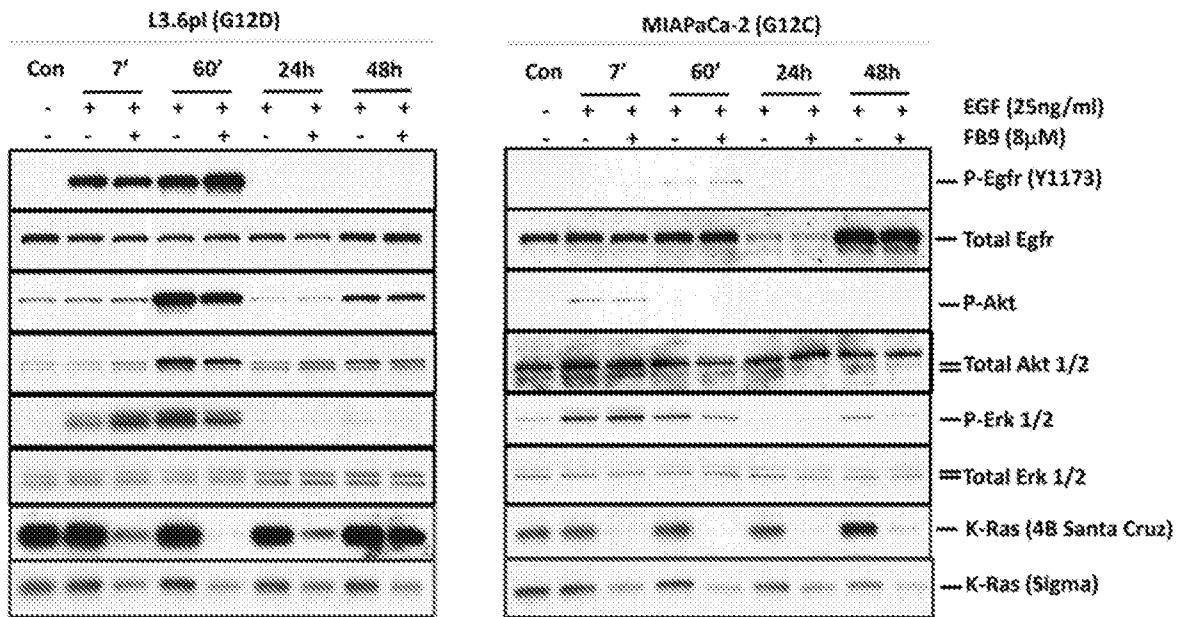
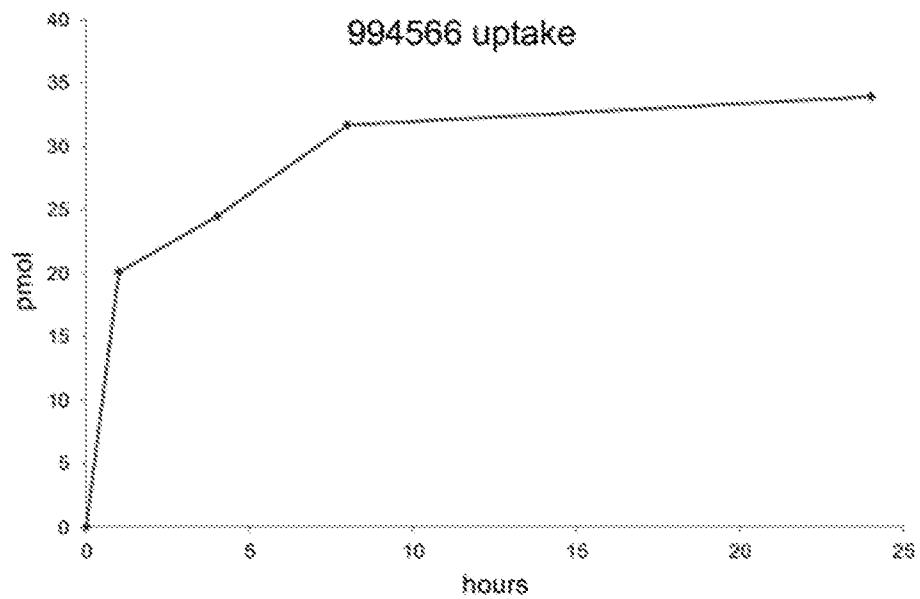
FIG. 34**FIG. 35**

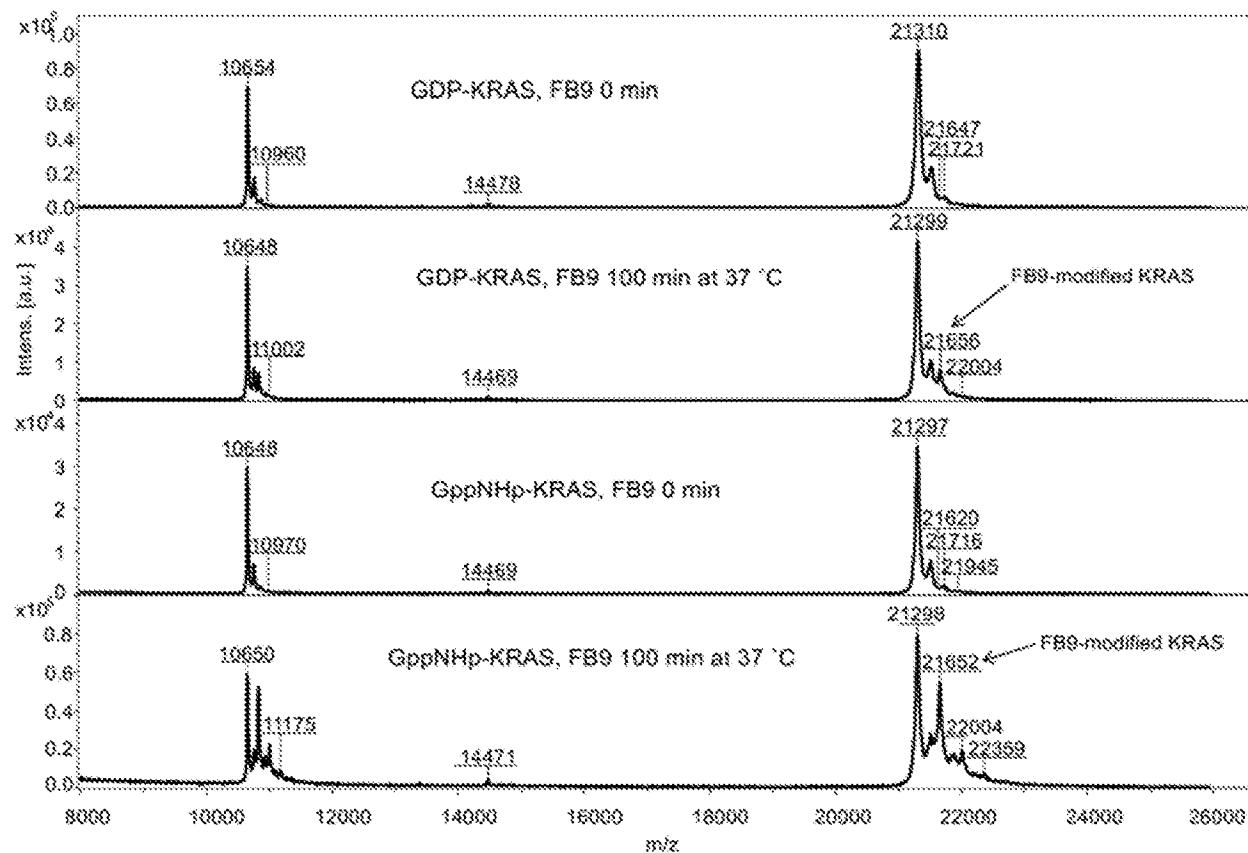
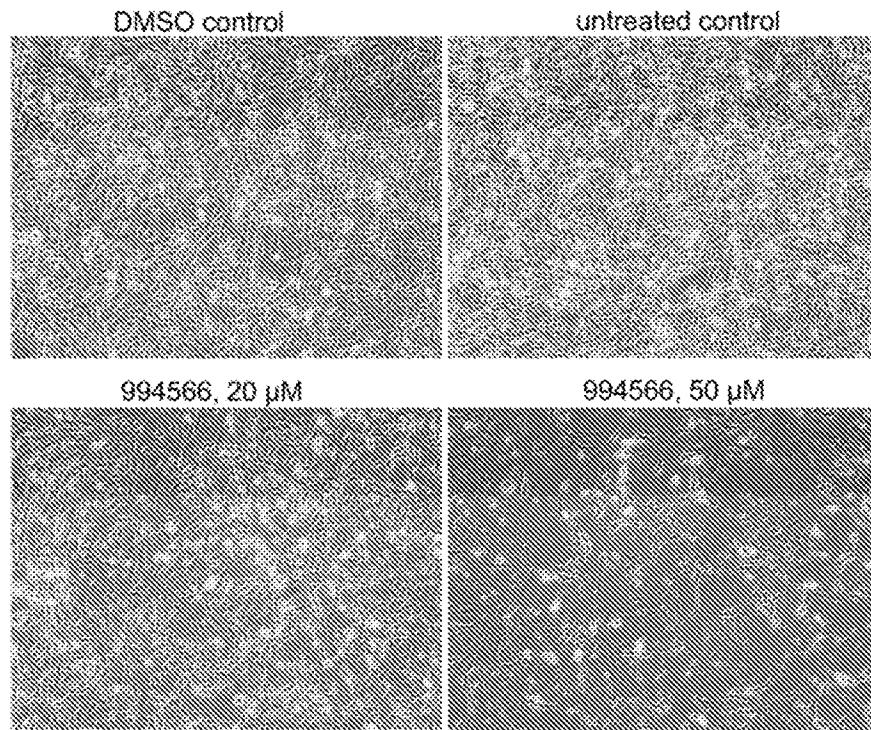
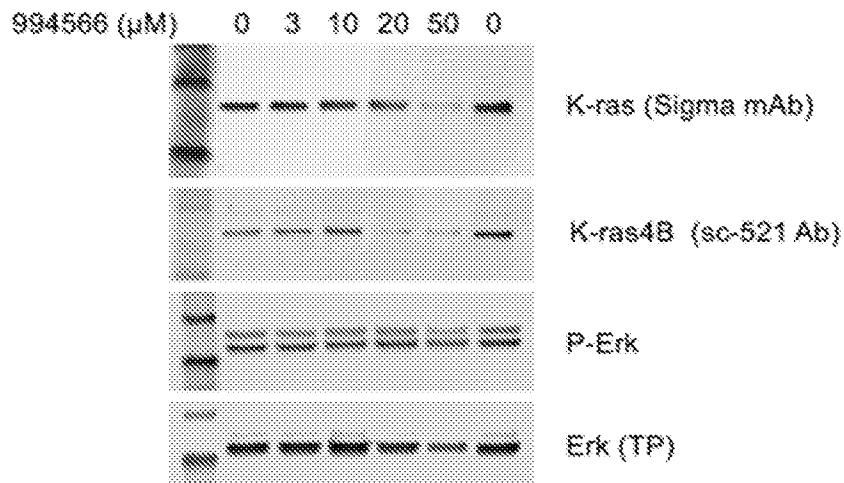
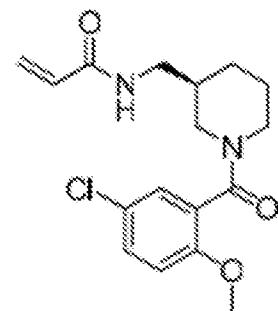
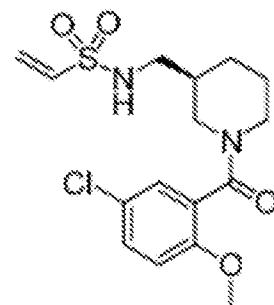
FIG. 36**FIG. 37**

FIG. 38A**FIG. 38B**

Molecular Weight: 336.81
SMDC 994565
45.2 mg



Molecular Weight: 372.87
SMDC 994566
24.3 mg

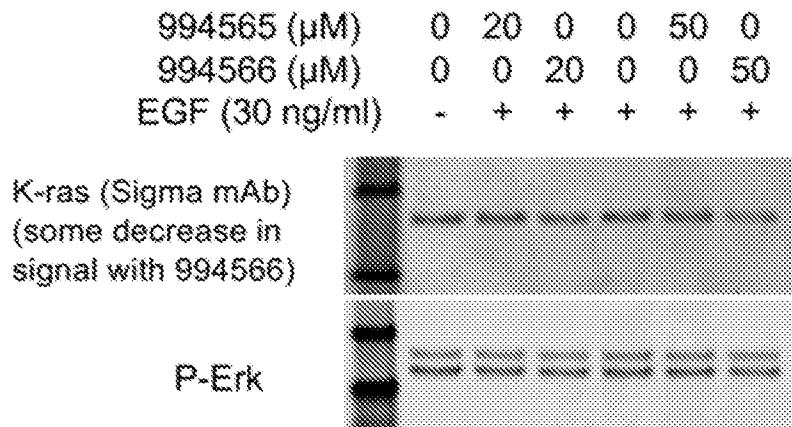
FIG. 39

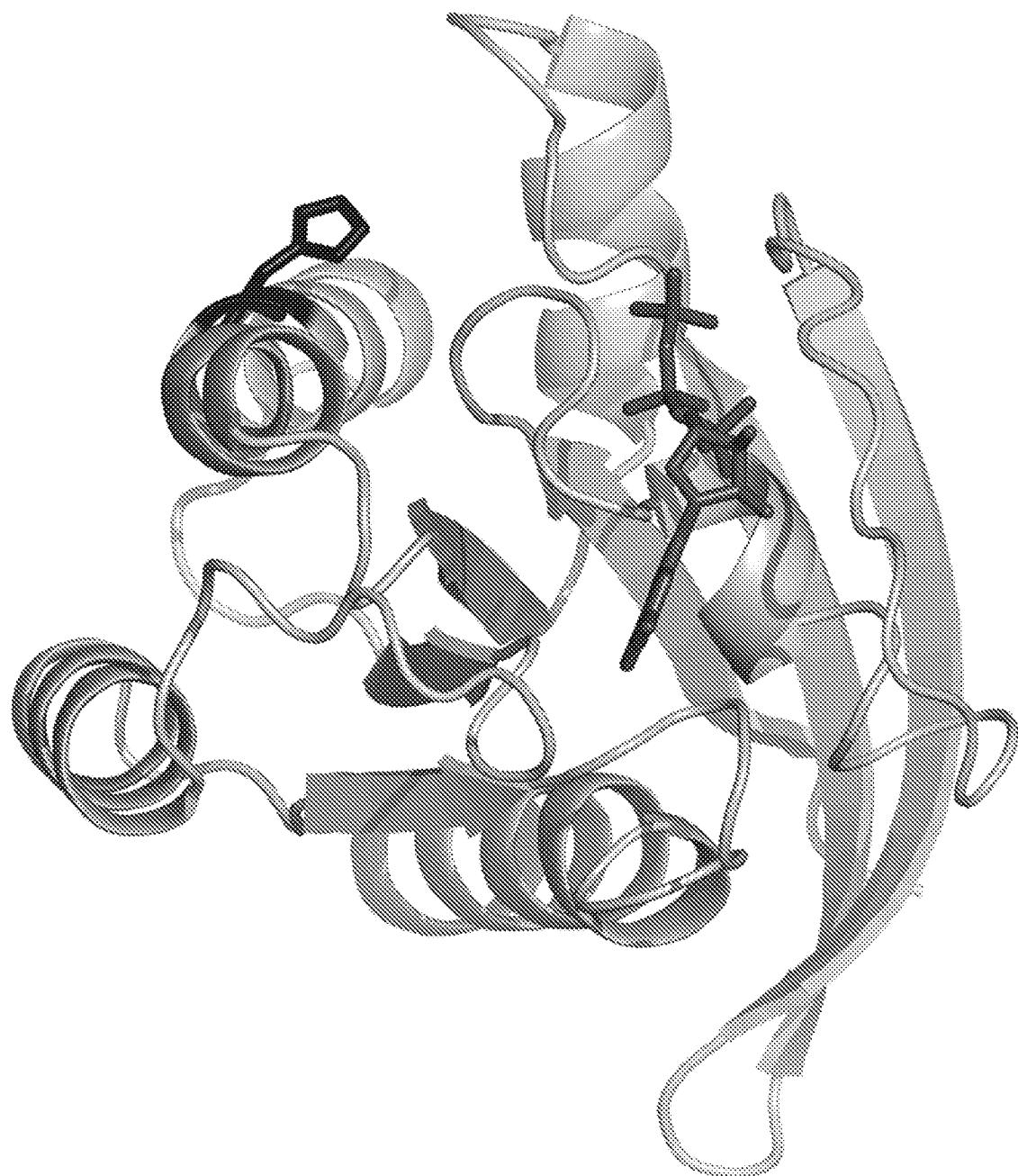
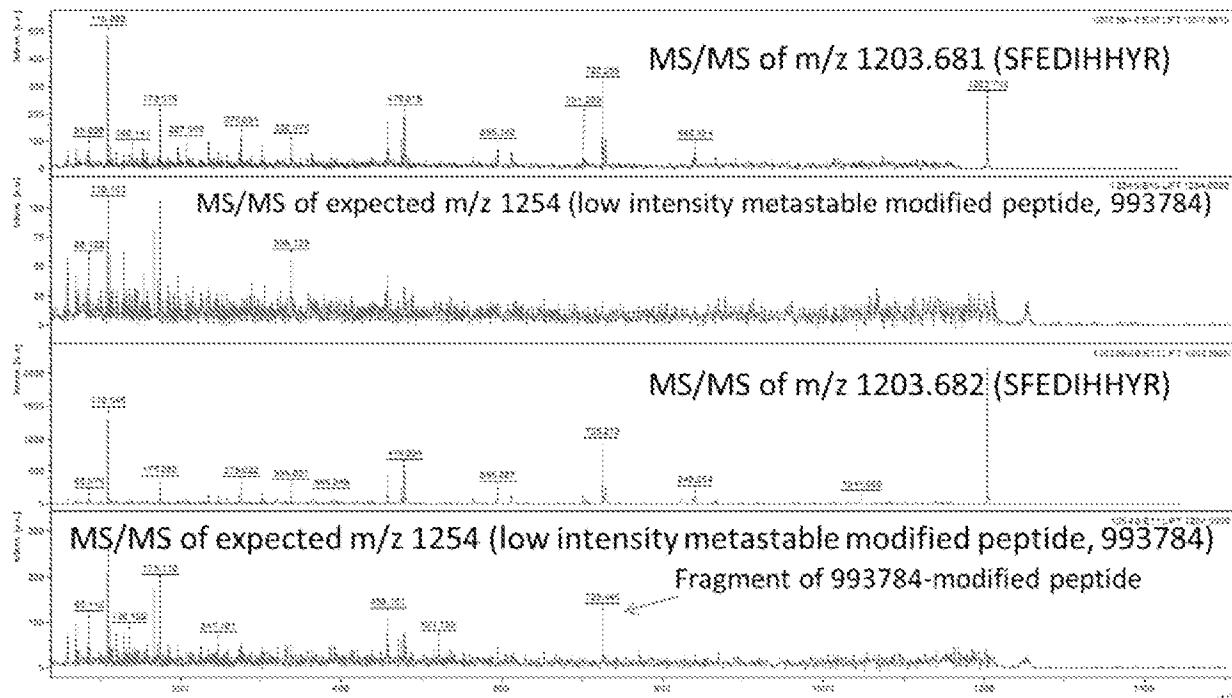
FIG. 40

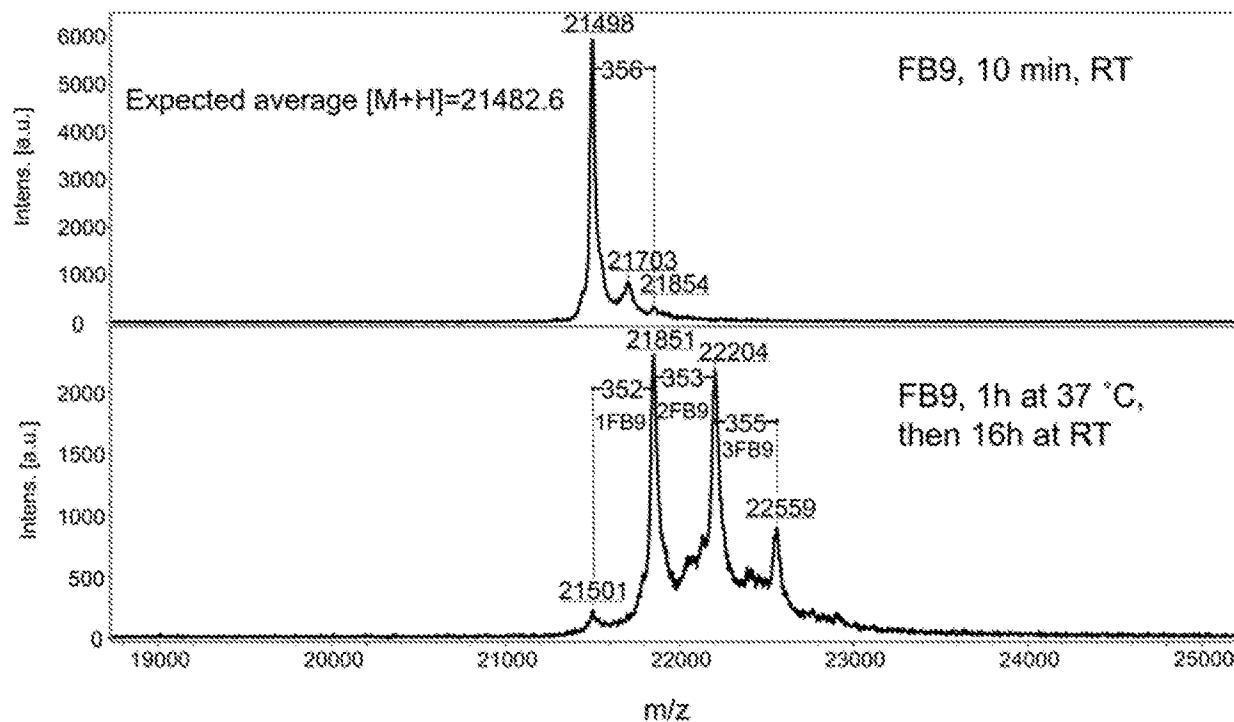
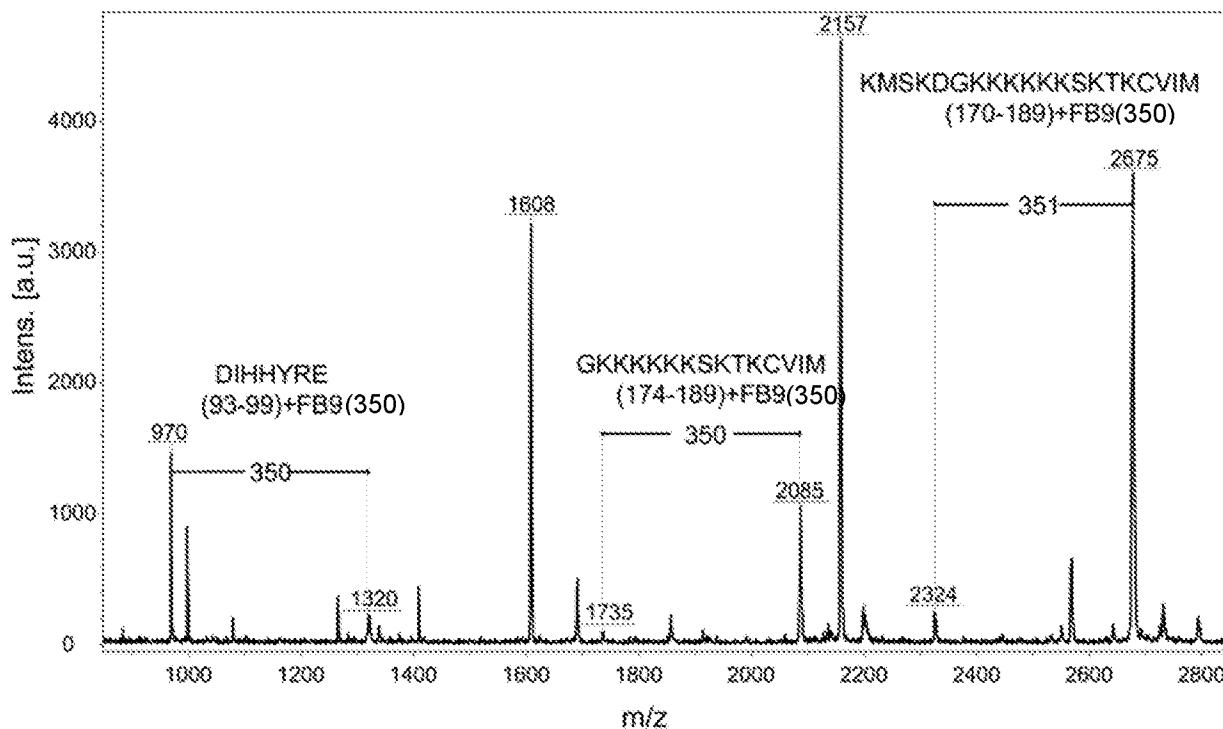
FIG. 41**FIG. 42**

Full-size KRAS (G-Hs.KRAS4b, 1-188); RPX150917.19; RP1150917140242
Average [M+H]⁺ 21482.5940

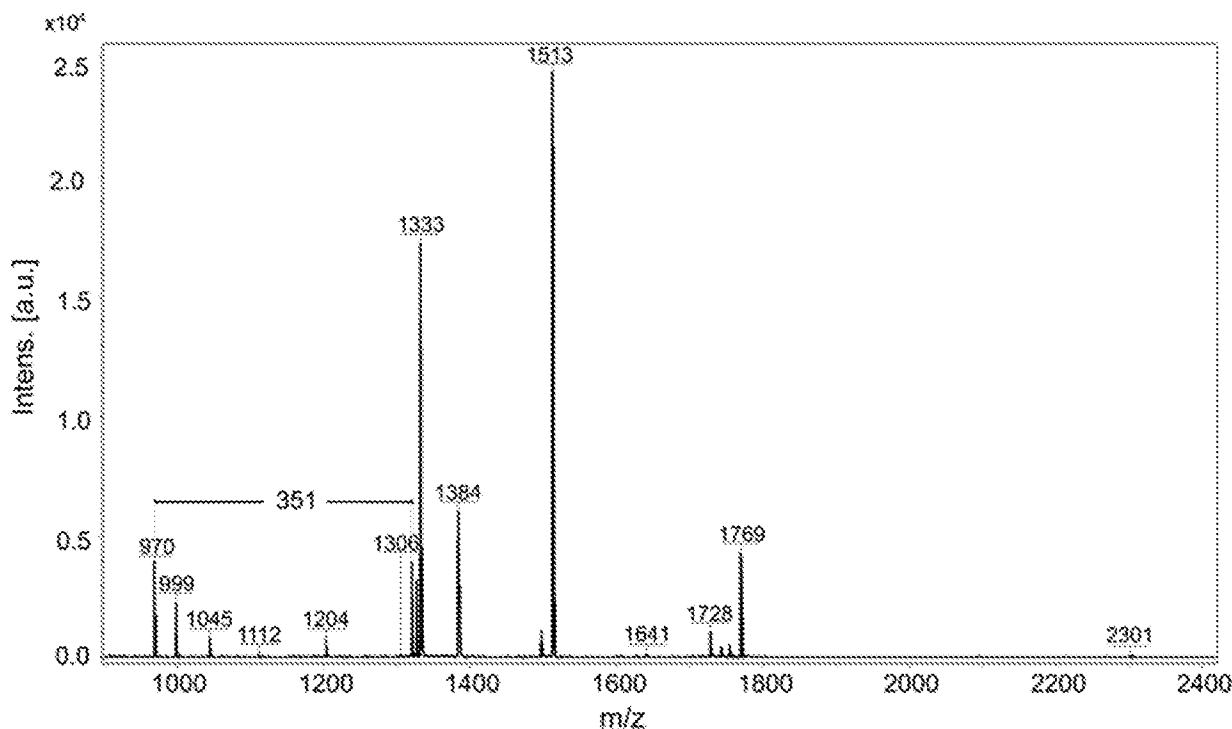
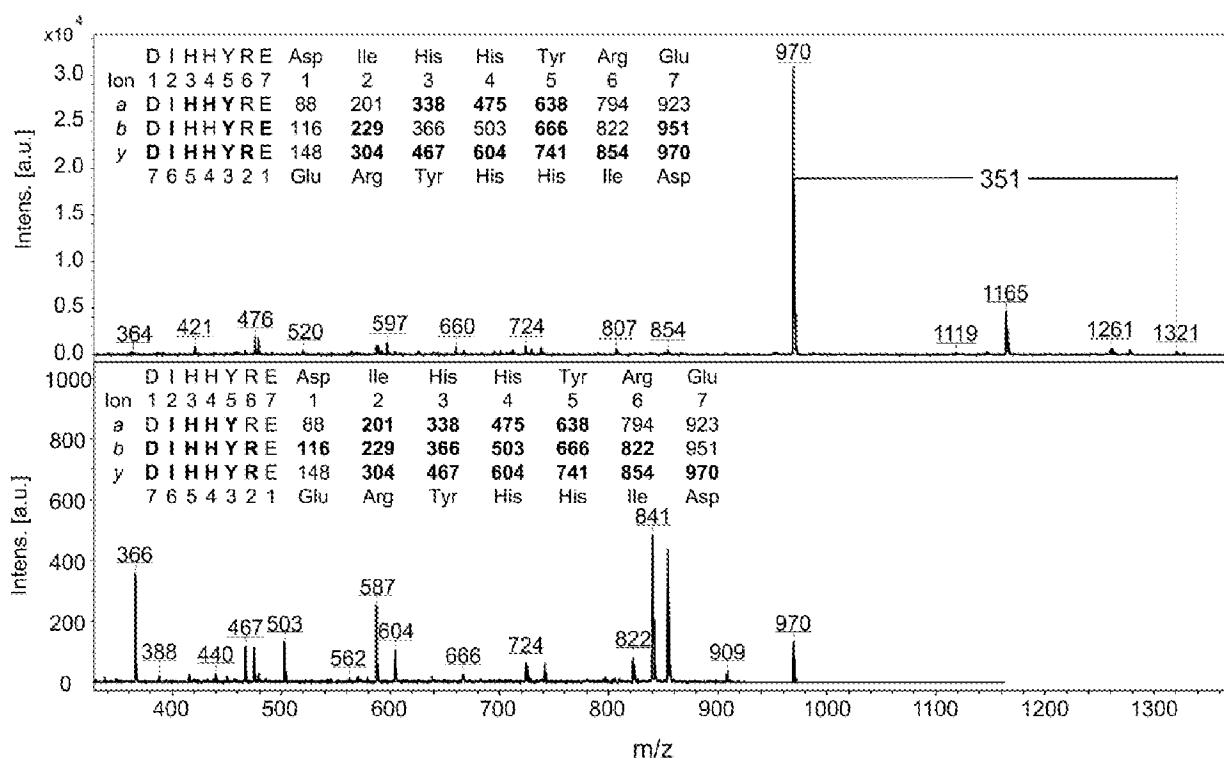
GMTEYKLVVVGAGGVGKSLTIQLIQNHVDEYDPTIEDSYRKQVVIDGETCLLDILDTAGQEEYS
AMRDQYMRTGEGLCVFAINNTKSFEDIHHYREQIKRVKDSEDVPMVLGNKCDLPSRTVDTK
QAQDLARSYGIPPIETSAKTRQGVDDAFYTLVREIRKHKEKMSKGKKKKSKTKCIVM

10	20	30	40	50	60
GTTTGTATLUVV GAGGGVGGKSLTIQLIQNHVDEYDPTIEDSYRKQVVIDGETCLLDILDTAGQEEYS					
70	80	90	100	110	120
AQQEYDQYMRTGEGLCVFAINNTKSFEDIHHYREQIKRVKDSEDVPMVLGNKCDLPSRTVDTK					
130	140	150	160	170	180
QAQDLARSYGIPPIETSAKTRQGVDDAFYTLVREIRKHKEKMSKGKKKKSKTKCIVM					
KAKTPKCVIM					

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FIG. 43**FIG. 44**

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FIG. 45A**FIG. 45B**

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FIG. 46A

Farnesylated carboxymethylated KRAS4b GG-HsKRAS-4b,
RP1151105092454 Average [M+H]⁺ 21283.35

GGTEYKLVVVGAGGVGKSALTIQLIQNHFVDEYDPTIEDSYRKQVVIDGET
CLLDILDTAGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIK
RVKDSEDVPMVLVGNKCDLPSRTVDTKQAQDLARSYGIPFIETSAKTRQG
VDDAFYTLVREIRKHKEKMSKGKKKKKSHTKC-farnMe

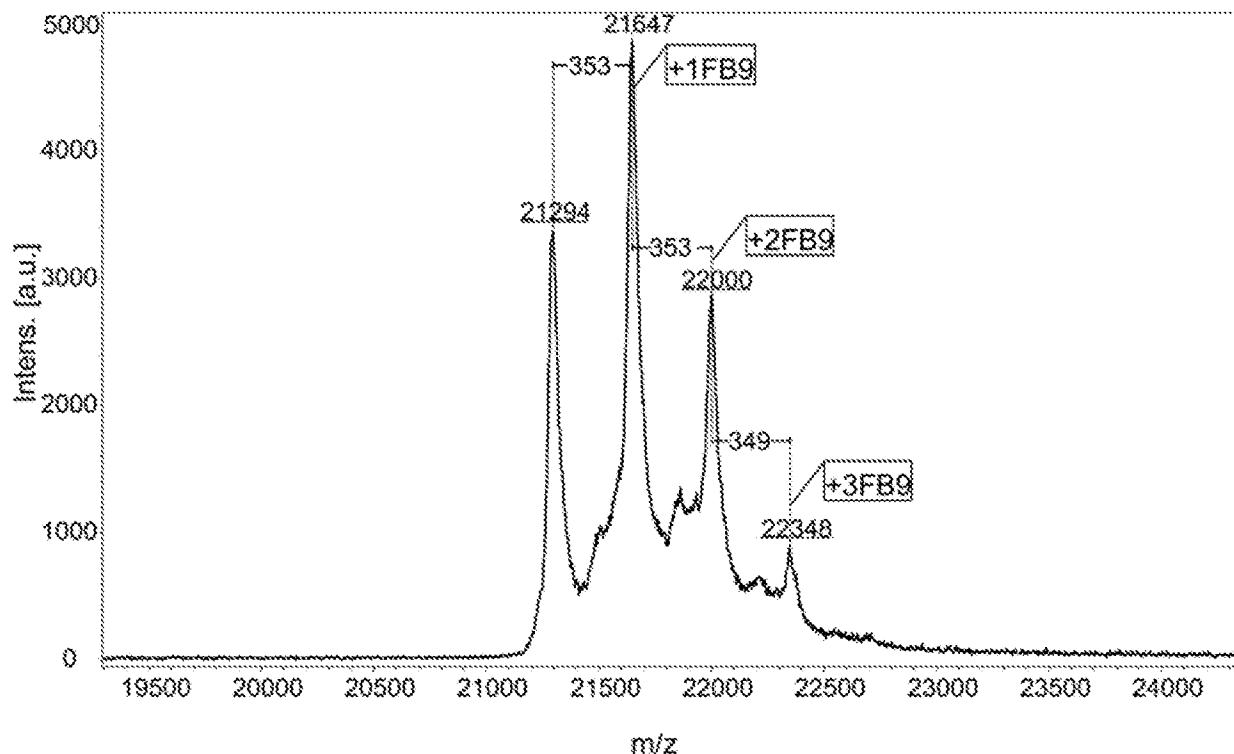
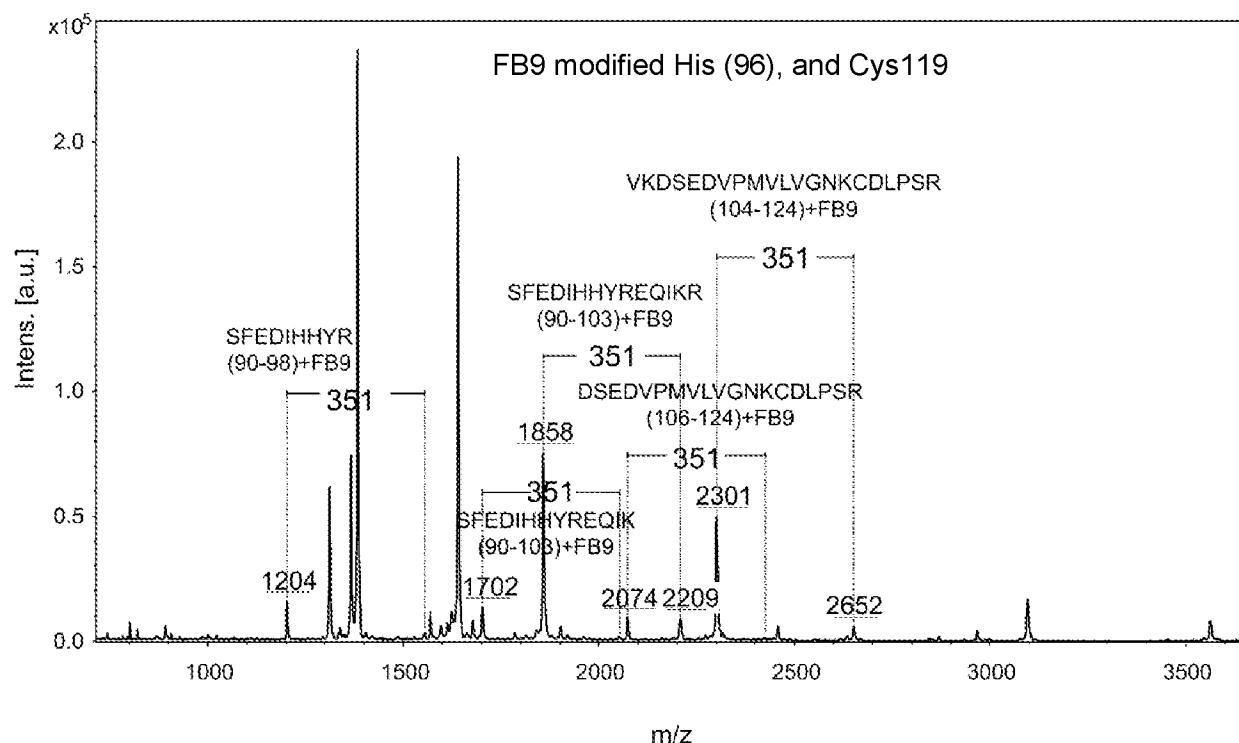
FIG. 46B

FIG. 47

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031344

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/44; A61K 31/445; A61K 31/451; A61K 31/4462 (2016.01)

CPC - A61K 31/44; A61K 31/445; C07D 213/75; C07D 401/12 (2016.05)

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)

IPC - A61K 31/44; A61K 31/445; A61K 31/451; A61K 31/4462

CPC - A61K 31/44; A61K 31/445; C07D 213/75; C07D 401/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

IPC(8) - A61K 31/44; A61K 31/445; A61K 31/451; A61K 31/4462 (2016.01); CPC - A61K 31/44; A61K 31/445; C07D 213/75; C07D 401/12 (2016.05); USPC - 514/317; 546/194; 546/309 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, STN, PubChem, Google Patents, Google Scholar

Search terms used: benzamide cycloalkyl heterocycloalkyl cycloheteroalkyl electrophilic K Ras

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,475,109 A (SELNICK et al) 12 December 1995 (12.12.1995) entire document	1, 2, 5, 11, 14-18, 20, 21, 23, 25, 38 ----- 39, 41, 42
X	US 2007/0112000 A1 (BARTON et al) 17 May 2007 (17.05.2007) entire document	1, 3, 7, 8, 13
X	STRATMANN et al. Welwitindolinones, Unusual Alkaloids from the Blue-Green Algae Hapalosiphon welwitschii and Westiella intricata. Relationship to Fischerindoles and Hapalinodoles. Journal of the American Chemical Society, 116(22), 9935-9942, 1994. supporting information. [retrieved on 11 July 2016]. Retrieved from the Internet. < http://pubs.acs.org/doi/suppl/10.1021/ja00101a015/suppl_file/ja00101a015_si_001.pdf > entire document	1, 4, 6
X	PUBCHEM, Substance Record for SID 110091647 Create Date: 2011-02-25. [retrieved on 08 July 2016]. retrieved from the internet: < https://pubchem.ncbi.nlm.nih.gov/substance/110091647 >. entire document	1, 9
X	PUBCHEM, Substance Record for SID 74797094 Create Date: 2009-06-11. [retrieved on 08 July 2016]. retrieved from the internet: < https://pubchem.ncbi.nlm.nih.gov/substance/74797094 >. entire document	1, 10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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- "P" document published prior to the international filing date but later than the priority date claimed

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- "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
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- "&" document member of the same patent family

Date of the actual completion of the international search

12 July 2016

Date of mailing of the international search report

19 AUG 2016

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031344

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. forming part of the international application as filed:
 in the form of an Annex C/ST.25 text file.
 on paper or in the form of an image file.
 - b. furnished together with the international application under PCT Rule 13*ter*. 1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. furnished subsequent to the international filing date for the purposes of international search only:
 in the form of an Annex C/ST.25 text file (Rule 13*ter*. 1(a)).
 on paper or in the form of an image file (Rule 13*ter*. 1(b) and Administrative Instructions, Section 713).
2. In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031344

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUBCHEM, Substance Record for SID 223343680 Create Date: 2014-11-10. [retrieved on 08 July 2016], retrieved from the internet: < https://pubchem.ncbi.nlm.nih.gov/substance/223343680 >. entire document	1, 12, 19
Y	US 2014/0288045 A1 (ARAXES PHARMA LLC) 25 September 2014 (25.09.2014) entire document	39, 41, 42
A	US 2015/087628 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 26 March 2015 (26.03.2015) entire document	1-53

摘要

本文尤其提供了用于抑制 K-Ras 和治疗癌症的方法和化合物。