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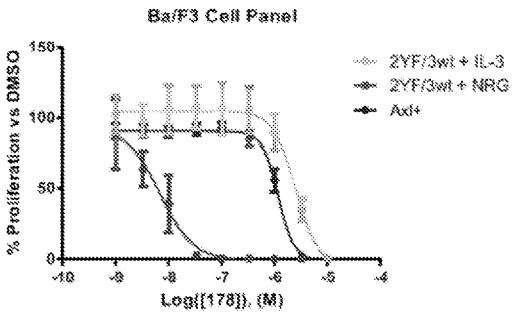
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(54) Title: ERBB INHIBITORS AND USES THEREOF

FIG. 5B



(57) Abstract: Described herein, *inter alia*, are compositions of ErbB modulators and methods of using the same.

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ErbB INHIBITORS AND USES THEREOF

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/324,864, filed April 19, 2016, which is incorporated herein by reference in 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 48536-586001WO_ST25.txt, created April 19, 2017, 33,272 bytes, machine format IBM-PC, MS Windows operating system, is hereby incorporated by reference.

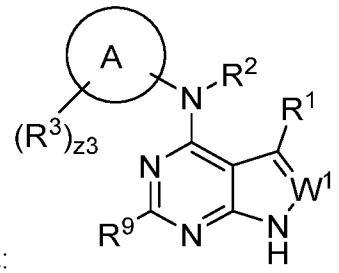
BACKGROUND

[0003] Signaling from the epidermal growth factor receptor (EGFR or HER) family of receptor tyrosine kinases (RTK) is dependent on a well-orchestrated series of interactions between family members to form either homo- or heterodimers. This dimerization process allows the intracellular kinase domains to form an asymmetric dimer in which the C-terminal domain of the activator kinase binds to the N-terminal portion of the receiver kinase to stabilize it in an active conformation. The receiver kinase then phosphorylates tyrosine residues on the C-terminal tails of the kinases to recruit and activate downstream signaling components, most notably those involved in pro-growth and survival pathways. Because of this, the improper activation of the EGFR family of kinases, either by mutation or overexpression, is observed in a variety of cancers. Interestingly, cell culture studies suggest that rather than causing escape from the biological mechanism of regulation, oncogenic activation alters the equilibrium between active and in-active states to favor the improper dimerization and activation of these receptors. This dependence on dimerization is particularly evident in HER2 overexpressing breast cancers that are dependent on the presence of HER3. Within the EGFR family, HER2 and HER3 are unique. HER3 is classified as a pseudokinase with only residual kinase activity, whereas HER2 has no known activating ligand but is constitutively able to dimerize with other active family members. In this way HER2 and HER3 together form a functional RTK unit, with HER3 responding to activating ligands such as neuregulin (NRG), HER2 providing the intracellular kinase activity, and both intracellular domains providing phosphorylation sites. Additionally, HER2 and HER3 are each other's preferred heterodimerization partners and also form the most mitogenic complex

among all possible EGFR family dimers. Because of this co-dependence, HER3 is important for the formation, proliferation, and survival of HER2 overexpressing tumors. Disclosed herein, inter alia, are solutions to these and other problems in the art.

BRIEF SUMMARY OF THE INVENTION

[0004] In an aspect is provided a compound having the formula:



(I).

[0005] Ring A is aryl or heteroaryl. W^1 is N or C(H). R^1 is hydrogen, $-L^1-L^2-E$, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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. The symbol z3 is an integer from 0 to 4. L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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. L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or

substituted or unsubstituted heteroarylene. R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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. E is an electrophilic moiety. Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. R^{9A} and R^{9B} 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^3, X^6, X^7, and X^9 is independently –F, -Cl, -Br, or –I. The symbols n3, n6, n7, and n9 are independently an integer from 0 to 4. The symbols m3, m6, m7, m9, v3, v6, v7, and v9 are independently an integer from 1 to 2.

[0006] In another aspect is provided a pharmaceutical composition including a pharmaceutically acceptable excipient and a compound, or pharmaceutically acceptable salt thereof, as described herein, including embodiments.

[0007] In an aspect is provided a method of treating cancer in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein.

[0008] In an aspect is provided a method of treating a disease associated with EGFR activity, HER2 activity, HER3 activity, HER4 activity, c-MET activity, PI3K activity, MEK activity, MAPK activity, RAF activity, BRAF activity, AKT activity, RAS activity, KRAS activity, heregulin activity, or neuregulin activity in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0009] In an aspect is provided a method of treating psoriasis, eczema, or atherosclerosis, in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein.

[0010] In an aspect is provided a method of inhibiting an ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) activity, the method including contacting ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) with an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0011] In an aspect is provided a method of inhibiting HER2 activity, the method including contacting HER2 with an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0012] In an aspect is provided a method of inhibiting EGFR activity, the method including contacting EGFR with an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0013] In an aspect is provided an EGFR protein covalently bonded to a compound (e.g., a compound described herein, an EGFR inhibitor).

[0014] In an aspect is provided a HER2 protein covalently bonded to a compound (e.g., a compound described herein, a HER2 inhibitor).

[0015] In an aspect is provided an ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) protein covalently bonded to a compound (e.g., a compound described herein, an ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) inhibitor).

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIGS. 1A-1E. NRG rescues HER2 over-expressing cancer cells from HER2 inhibitors. FIG. 1A: 72h Proliferation of SK-BR-3 and BT-474 cells treated with a dose-response of lapatinib in the presence or absence of NRG (mean±SD, n=3). FIG. 1B: Same experiment as

depicted in FIG. 1A, but with the inhibitor TAK-285. FIG. 1C: The ability of NRG to rescue SK-BR-3 and BT-474 cell proliferation from HER2 inhibitors is dose dependent. Cells were treated with 1μM of the indicated inhibitor in the presence of varying concentrations of NRG, and proliferation was read out after 72h (mean±SD, n=3). FIG. 1D: HER2/HER3 signaling was evaluated over a time-course in SK-BR-3 cells treated with either lapatinib, NRG, or both. The addition of NRG rescues p-HER3 and all downstream signaling at all time points examined. FIG. 1E: Cartoon schematic of the EGFR family kinase domain asymmetric dimer. The C-terminal domain of the 'activator' kinase (right) interacts with the N-terminal portion of the 'receiver' kinase (left). This interaction stabilizes the active conformation of the receiver kinase identified by the 'in' conformation of the receiver kinase's α-C helix and the ordered extension of the activation loop. The activator kinase retains the inactive conformation.

[0017] FIGS. 2A-2D. Lapatinib is unable to bind to the active HER2/HER3 heterodimer. FIG. 2A: SK-BR-3 or MCF-7 cells were serum starved for 24 h and then either treated with lapatinib alone for 15 min – followed by a 15 min NRG stimulation (15 min pre-treat), or were treated with lapatinib and NRG together for 15 min (simultaneous addition). The reduced efficacy of lapatinib when simultaneously added with NRG indicates a reduced ability to bind active HER2 in HER2/HER3 heterodimers. FIG. 2B: NRG rescues the 72h proliferation of CW-2 cells, which contain an activating mutation in HER3 (E928G), from HER2 inhibitors (mean±SD, n=3). FIG. 2C: CW-2 cells treated with a dose response of lapatinib in the presence or absence of NRG for 1h show that NRG rescues HER2/HER3 signaling. FIG. 2D: NCI-H1781 cells were treated with a dose response of lapatinib, and signaling was evaluated after 15 min. The short treatment time shows lapatinib does not efficiently bind to HER2 mutants biased towards the active conformation.

[0018] FIGS. 3A-3D. Design and execution of a high-throughput screen identifies a novel HER2/HER3 inhibitor. FIG. 3A: 2YF/3wt cells were incubated in the presence or absence of NRG for 48h and proliferation was assessed by CellTiter-Glo (mean±SD, n=1). FIG. 3B: 48h proliferation curves of the Ba/F3 panel show they can separate out compounds that specifically inhibit signaling at the HER2/HER3 level (lapatinib) from those that hit downstream (PIK-93) (mean±SD, for lapatinib n=3, for PIK-93 n=1). FIG. 3C: Structure and proliferation curves for hit compound 1 (also referred herein as compound 185) against the Ba/F3 cell line panel (mean±SD, n=3). FIG. 3D: Structure and proliferation curves for compound 2 (also referred to herein as compound 55A) against the panel of Ba/F3 cell lines (mean±SD, n=3).

[0019] FIGS. 4A-4F. Compound 2 is a selective Type I inhibitor for HER2. FIG. 4A: *In vitro* kinase assay of the HER2 kinase domain against lapatinib and compound 2 (mean±SD, n=3). FIG. 4B: Thermal stabilization of the HER3 kinase domain by either compound 2 or ATP as determined by Thermofluor (mean±SD, n=3). FIGS. 4C-4D: The crystal structure of either erlotinib (FIG. 4C) or 2 (FIG. 4D) bound to EGFR V924R. The kinase domain in complex with compound 2 has been stabilized in the active confirmation by drug binding, despite the mutation – as evidenced by the ordered extension of the activation loop and the inward positioning of the α-C helix. FIG. 4E: Magnified view of the EGFR V924R active site when bound to compound 2 shows the proximity of the β3 lysine (K721) and the glutamate (E738) in the α-C helix, which are positioned so as to make a predicted hydrogen bond. FIG. 4F: Table of IC_{50} values for NRG stimulated HER2YF/HER3 heterodimers +/- the gatekeeper mutations (mean±SD, n=3). The large shift in potency is only seen when compound 2 is unable to bind to HER2, indicating that its cytotoxicity is due to HER2 inhibition.

[0020] FIGS. 5A-5D. A Type I inhibitor of HER2 is insensitive to the presence of NRG. FIG. 5A: Chemical structure of compound 3 (also referred to herein as compound 178). FIG. 5B: Proliferation curves for compound 3 against the Ba/F3 cell line panel (mean±SD, n=3). FIG. 5C: 72h proliferation curves of SK-BR-3 and BT-474 cells treated with a dose response of compound 3 in the presence or absence of NRG indicates that compound 3 is insensitive to the presence of NRG in HER2 overexpressing cell lines (mean±SD, n=3). FIG. 5D: The same assay in FIG. 2A was performed with compound 3 in SK-BR-3 cells.

[0021] FIGS. 6A-6H. Compound 3 inhibits the active HER2/HER3 heterodimer in multiple oncogenic settings. FIG. 6A:72h proliferation of CW-2 cells against compound 3 in the presence or absence of NRG (mean±SD, n=3). FIG. 6B: CW-2 cells treated with a dose response of compound 3 in the presence or absence of NRG for 1h. FIG. 6C: 72h proliferation of NCI-H1781 cells shows that they are sensitive to compound 3 but not to DFG in/α-C out inhibitors (mean±SD, n=3). FIG. 6D: NCI-H1781 cells were treated with a dose response of 3 and signaling was evaluated after 15 min. FIG. 6E: 72h proliferation curves of CHL-1 cells treated with the indicated inhibitors (mean±SD, n=3). FIG. 6F: The growth of CHL-1 cells treated with a dose response of either lapatinib (left) or compound 3 (right) was monitored over 96h using the IncuCyte Zoom. Confluence measurements show that compound 3 is more effective at reducing the growth of CHL-1 cells (mean±SD, n=2). FIG. 6G: HER2/HER3 signaling was evaluated in CHL-1 cells treated with a dose response of either lapatinib or compound 3 for 24h. Compound 3 is better able to inhibit p-HER3 and thus the PI3K/Akt pathway. FIG. 6H: CHL-1 cells were

treated with either DMSO or 500 nM lapatinib for 24h. The cells were then washed and treated with a dose response of either lapatinib or compound 3 for an additional 24h. Signaling shows compound 3 is better able to inhibit feedback activated HER2/HER3 signaling in CHL-1 cells.

[0022] FIGS. 7A-7C. FIGS. 7A-7B: Compound 3 was biased towards inhibition of the mutationally activated forms of EGFR in HCC 827 and NCI-H1650 cells, with near complete inhibition of multiple phosphosites on EGFR at less than 10 nM, while leaving the same phosphosites on wt EGFR relatively unaffected up to 1 μM. Consistent with the resistance seen in the HER2 gatekeeper mutant Ba/F3 cells, mutation of the EGFR gatekeeper to methionine in NCI-H1975 cells caused a shift in the ability of compound 3 to inhibit both signaling and proliferation, although the p-845 site showed inhibition at concentrations less than 1 μM, making compound 3 one of the more potent selective and reversible inhibitors of this mutant in a cell line to be reported. The preferential inhibition of the mutationally activated EGFR by compound 3 was also seen in proliferation assays and is in stark contrast to lapatinib's profile against these cells (FIG. 7C).

[0023] FIG. 8. SK-BR-3 cells were treated with DMSO or 1 μM lapatinib in the presence or absence of NRG for 1h. HER3 is the only member of the EGFR family who remains activated in the presence of both NRG and lapatinib. HER4 was undetectable in this cell line.

[0024] FIG. 9. NRG pre-treatment rescues HER2/HER3 signaling from lapatinib. SK-BR-3 cells were serum starved for 24h and then either treated with NRG or vehicle for 15 min followed by a dose response of lapatinib for 15 min and signaling was analyzed by western blot.

[0025] FIG. 10. 48h proliferation curves of the 2YF/3wt Ba/F3 cell line in the presence of either NRG or IL-3 (mean ± SD, n=1).

[0026] FIG. 11. Compound 2 binds to the active site of HER3. 1μM of The HER3 intracellular domain (665-1323) was concentrated on vesicles and incubated with 200μM ATP in the presence of varying concentrations of compound 2. HER3 kinase activity inhibition was evaluated by western blotting for autophosphorylation of HER3.

[0027] FIGS. 12A-12B. Mutation of the gatekeeper residue of HER2 or HER3 to Methionine reduces the binding affinity of compound 2. FIG. 12A. HEK-293T cells were transfected with either wt HER2 or HER2 T798M, which were then treated with a dose response of lapatinib or compound 2 (1nM - 10μM). FIG. 12B. Stabilization of either wt or T787M HER3 kinase

domain by compound 2 compared to DMSO as determined by thermofluor (mean value ± SD, n=2).

[0028] FIG. 13. In vitro kinase assay of the HER2 kinase domain against compound 3 (mean ± SD, n=3).

[0029] FIG. 14. SK-BR-3 cells treated with a dose response of compound 3 in the presence or absence of NRG for 1h.

[0030] FIGS. 15A-15C. NRG rescues HER2 overexpressing cell lines from type 1.5 inhibitors but not compound 3. FIG. 15A. BT-474 cells were treated with the indicated concentrations of drugs in the presence or absence of NRG for 72h. Cell death was determined using CellTox green with the Incucyte Zoom data are represented as mean values ± SD (n=3). FIG. 15B. Same experiment as in FIG. 15A, but with SK-BR-3 cells. c. Cells were treated with 1 μM of the indicated inhibitor in the presence of varying concentrations of NRG. The lapatininb data is reproduced from FIG. 1C (mean value ± SD, n=3).

[0031] FIG. 16. SK-BR-3 cells were treated with NRG +/- 1 uM of compound 3 for 1h. HER3 was purified by immunoprecipitation and analyzed for the presence of HER2.

[0032] FIG. 17. MCF-7 cells were serum starved for 24 h and then either treated with compound 3 for 15 min followed by a 15 min NRG stimulation (15 min pre-treat), or compound 3 and NRG were added simultaneously for 15 min (simultaneous addition). Compound 3 shows little to no shift in its ability to inhibit signaling +/- pre-incubation indicating it can bind to the actively signaling HER2/HER3 heterodimer.

[0033] FIG. 18. SK-BR-3 cells were serum starved for 24h and then either treated with NRG or vehicle for 15 min followed by a dose response of compound 3 for 15 min and signaling was analyzed by western blot.

[0034] FIGS. 19A-19D. NRG rescues HER3 mutant driven Ba/F3 cells. 48h proliferation of 2YF/HER3E928G (2YF/3EG) Ba/F3 cells treated with a dose response of (FIG. 19A) lapatinib, (FIG. 19B) TAK-285, or (FIG. 19C) compound 3 in the presence or absence of NRG. The large shift in the ability to inhibit proliferation by the current HER2 drugs shows that HER3 mutants could be rescued from the effects of HER2 drugs by NRG in a manner similar to HER2 over expressing cells (mean value ± SD, n=3). FIG. 19D. Table of IC50 values for the 2YF/3EG cell lines (nM±SD, n=3).

[0035] FIGS. 20A-20B. FaDu cells are more sensitive to compound 3 compared to lapatinib. FIG 20A. 72h Proliferation of FaDu cells shows compound 3 is more effective than current HER2 inhibitors (mean value ± SD, n=3). FIG. 20B. HER2/HER3 signaling was evaluated in FaDu cells treated with a dose response of either lapatinib or compound 3 for 24h. Compound 3 is better able to inhibit pHER3 and its downstream signaling pathways.

[0036] FIG. 21. Pharmacokinetics of compound 3. Plasma concentration of compound 3 following a single administration of 2mg/kg by IV or IP. Also shown are the pharmacokinetic (PK) parameters of compound 3.

[0037] FIGS. 22A-22H. Screening assays of compounds 184 (FIG. 22A), 185 (FIG. 22B), 189A (FIG. 22C), 189B (FIG. 22D), 190A (FIG. 22E), 190C (FIG. 22F), 190D (FIG. 22G), and 191A (FIG. 22H).

[0038] FIGS. 23A-23H. Screening assays of compounds 191B (FIG. 23A), 191D (FIG. 23B), 191E (FIG. 23C), 191F (FIG. 23D), 191H (FIG. 23E), 5-001A (FIG. 23F), 5-001B (FIG. 23G), and 5-004 (FIG. 23H).

[0039] FIGS. 24A-24H. Screening assays of compounds 6 (FIG. 24A), 13 (FIG. 24B), 39A (FIG. 24C), 39B (FIG. 24D), 39C (FIG. 24E), 39D (FIG. 24F), 41A (FIG. 24G), and 41B (FIG. 24H).

[0040] FIGS. 25A-25H. Screening assays of compounds 42 (FIG. 25A), 43 (FIG. 25B), 45A (FIG. 25C), 45B (FIG. 25D), 45C (FIG. 25E), 45D (FIG. 25F), 45E (FIG. 25G), and 45F (FIG. 25H).

[0041] FIGS. 26A-26D. Screening assays of compounds 53B (FIG. 26A), 55A (FIG. 26B), 57A (FIG. 26C), and 57B (FIG. 26D).

[0042] FIGS. 27A-27D. Screening assays of compounds 65 (FIG. 27A), 66A (FIG. 27B), 66B (FIG. 27C), and 66C (FIG. 27D).

[0043] FIGS. 28A-28H. Screening assays of compounds 144A (FIG. 28A), 144B (FIG. 28B), 147 (FIG. 28C), 152 (FIG. 28D), 153 (FIG. 28E), 154A (FIG. 28F), 154B (FIG. 28G), and 154C (FIG. 28H).

[0044] FIGS. 29A-29D. Screening assays of compounds 170 (FIG. 29A), 171 (FIG. 29B), 172 (FIG. 29C), and 173B (FIG. 29D).

[0045] FIGS. 30A-30B. Screening assays of compounds 178 (FIG. 30A) and 176 (FIG. 30B).

[0046] FIGS. 31A-31D. Screening assays of compounds CJN-08-089 (FIG. 31A), CJN-08-090 (FIG. 31B), CJN-08-091 (FIG. 31C), and CJN-08-092 (FIG. 31D). Compounds CJN-08-089, CJN-08-090, CJN-08-091, and CJN-08-092 may also be referred to herein as 8-089, 8-090, 8-091, and 8-092 respectively. Compounds CJN-08-089, CJN-08-090, CJN-08-091, and CJN-08-092 may also be referred to herein as 8089, 8090, 8091, and 8092 respectively

[0047] FIGS. 32A-32D. Screening assays of compounds 89 (FIG. 32A), 90 (FIG. 32B), 91 (FIG. 32C), and 92 (FIG. 32D).

[0048] FIGS. 33A-33C. Screening assays and nonlinear fits of compounds CJN-08-095 (FIG. 33A), CJN-08-096 (FIG. 33B), and CJN-08-097 (FIG. 33C). Compounds CJN-08-095, CJN-08-096, and CJN-08-097 may also be referred to herein as 08-095, 08-096, and 08-097. Compounds CJN-08-095, CJN-08-096, and CJN-08-097 may also be referred to herein as 8095, 8096, and 8097.

[0049] FIGS. 34A-34C. Screening assays of compounds 95 (FIG. 34A), 96 (FIG. 34B), and 97 (FIG. 34C).

[0050] FIGS. 35A-35B. Screening assays and nonlinear fits of compounds CJN-08-104A (FIG. 35A) and CJN-08-104B (FIG. 35B).

[0051] FIG. 37. Average IC50 assay results from 6 compounds, 45A, 45E, 53B, 55A, 57A, and 57B, compared to lapatinib.

[0052] FIGS. 38A-38B. Average IC50 assay results from 9 compounds, 45E, 57A, 57B, 144A, 144B, 147, 153, 154B, and 155, over a wide range 0 to 1500 nM (FIG. 38A) and over a restricted range 0-300 nM (FIG. 38B).

[0053] FIG. 39. Summary of average IC50 assay results in various cell lines for the following compounds: 178, 8096, 8134, 8164, 8168A, 8168B, 8168C, 8177, 8179, 8184, 8168 dasatinib, sapitinib, XL-880, and 8185. For the analysis of human cell line proliferation and determination of the IC50, the indicated cell lines were first transduced with a lentivirus encoding a nuclear localized mRuby. The cells were selected with puro for 4 days and were then routinely passaged in media containing ¼ the amount of puro used for the selection. The cells were then seeded in clear bottom black 384 well plates and allowed to attach to the plates for 24 h in media with no puro. After 24h media containing drug or drug + growth factor (if indicated) was added on top (1:1 seed media to new media) and the cell growth was monitored for 72h using the incucyte zoom in both the phase and fluorescent channel (384 whole well scan). The Essen software was

then used to analyze the images and count the number of cells/well using the fluorescent nuclei. After 72h the counts were exported to excel and the number of cells/well was normalized to time 0. These values were then entered into prism (technical triplicate) and used to calculate the area under the curve. This AUC was normalized to the DMSO control on the plate. The process was repeated either 1 or 2 times depending on the compound and cell condition, the averages of these biological triplicate or duplicate values were then analyzed to determine the IC50.

[0054] FIG. 40. The cell viability across different cell lines for compound 8156. Compound 8156 has a MW of 428.44, LogP of 3; tPSA of 116.54, and a CLogP of 3.48644.

DETAILED DESCRIPTION

[0055] Herein we identify novel HER2/HER3 inhibitors that preferentially target the active state of the heterodimer. An inhibitor described herein is capable of potently inhibiting signaling from the HER2/HER3 heterodimer regardless of the activating oncogenic mechanism.

A. **Definitions**

[0056] 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.

[0057] 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., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0058] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched non-cyclic carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). 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, 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), 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-). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an alkynyl moiety. An alkyl moiety may be fully saturated.

[0059] 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, $-CH_2CH_2CH_2CH_2-$. 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 in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0060] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched non-cyclic 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, 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, and 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. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P).

[0061] 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, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. 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 $-SO_2R'$. 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.

[0062] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, non-aromatic cyclic versions of "alkyl" and "heteroalkyl," respectively, wherein the carbons making up the ring or rings do not necessarily need to be bonded to a hydrogen due to all carbon valencies participating in bonds with non-hydrogen atoms. 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, 3-hydroxy-cyclobut-3-enyl-1,2, dione, 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. A heterocycloalkyl moiety may include one ring heteroatom (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include two optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include three optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include four optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include five optionally different ring heteroatoms (e.g., O, N, S, Si, or P). A heterocycloalkyl moiety may include up to 8 optionally different ring heteroatoms (e.g., O, N, S, Si, or P).

[0063] 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(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0064] 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.

[0065] 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, 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. Non-limiting examples of aryl and heteroaryl groups include pyridinyl, pyrimidinyl, thiophenyl, thienyl, furanyl, indolyl, benzoxadiazolyl, benzodioxolyl, benzodioxanyl, thianaphthanyl, pyrrolopyridinyl, indazolyl, quinolinyl, quinoxalinyl,

pyridopyrazinyl, quinazolinonyl, benzoisoxazolyl, imidazopyridinyl, benzofuranyl, benzothienyl, benzothiophenyl, phenyl, naphthyl, biphenyl, pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furylthienyl, pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, isoquinolyl, thiadiazolyl, oxadiazolyl, pyrrolyl, diazolyl, triazolyl, tetrazolyl, benzothiadiazolyl, isothiazolyl, pyrazolopyrimidinyl, pyrrolopyrimidinyl, benzotriazolyl, benzoxazolyl, or quinolyl. The examples above may be substituted or unsubstituted and divalent radicals of each heteroaryl example above are non-limiting examples of heteroarylene. A heteroaryl moiety may include one ring heteroatom (e.g., O, N, or S). A heteroaryl moiety may include two optionally different ring heteroatoms (e.g., O, N, or S). A heteroaryl moiety may include three optionally different ring heteroatoms (e.g., O, N, or S). A heteroaryl moiety may include four optionally different ring heteroatoms (e.g., O, N, or S). A heteroaryl moiety may include five optionally different ring heteroatoms (e.g., O, N, or S). An aryl moiety may have a single ring. An aryl moiety may have two optionally different rings. An aryl moiety may have three optionally different rings. An aryl moiety may have four optionally different rings. A heteroaryl moiety may have one ring. A heteroaryl moiety may have two optionally different rings. A heteroaryl moiety may have three optionally different rings. A heteroaryl moiety may have four optionally different rings. A heteroaryl moiety may have five optionally different rings.

[0066] A fused ring heterocyloalkyl-aryl is an aryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-heteroaryl is a heteroaryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-cycloalkyl is a heterocycloalkyl fused to a cycloalkyl. A fused ring heterocycloalkyl-heterocycloalkyl is a heterocycloalkyl fused to another heterocycloalkyl. Fused ring heterocycloalkyl-aryl, fused ring heterocycloalkyl-heteroaryl, fused ring heterocycloalkyl-cycloalkyl, or fused ring heterocycloalkyl-heterocycloalkyl may each independently be unsubstituted or substituted with one or more of the substitutents described herein.

[0067] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0068] The term "alkylsulfonyl," as used herein, means a moiety having the formula $-S(O_2)-R'$, where R' is a substituted or unsubstituted alkyl group as defined above. R' may have a specified number of carbons (e.g., "C_1-C_4 alkylsulfonyl").

[0069] Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0070] 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', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', –NR'NR"R"', –ONR'R", –NR'C=(O)NR"NR"'R"", -CN, -NO_2, 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 of the invention 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., -CF_3 and -CH_2CF_3) and acyl (e.g., -C(O)CH_3, -C(O)CF_3, -C(O)CH_2OCH_3, and the like).

[0071] 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', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', –NR'NR"R"', –ONR'R", –NR'C=(O)NR"NR"'R"", -CN, -NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, 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 of the invention 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.

[0072] 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.

[0073] 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-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, 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 -$S(O)_2$NR'-. The substituents 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.

[0074] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include, oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0075] A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CF_3, -CCl_3, -CBr_3, -CI_3, -CHF_2, -$CHCl_2$, -$CHBr_2$, -CHI_2, -CH_2F, -CH_2Cl, -CH_2Br, -CH_2I, -OCF_3, -$OCCl_3$, -$OCBr_3$, -OCI_3, -$OCHF_2$, -$OCHCl_2$, -$OCHBr_2$, -$OCHI_2$, -OCH_2F, -OCH_2Cl, -OCH_2Br, -OCH_2I, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, 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:

(i) oxo, halogen, -CF_3, -CCl_3, -CBr_3, -CI_3, -CHF_2, -$CHCl_2$, -$CHBr_2$, -CHI_2, -CH_2F, -CH_2Cl, -CH_2Br, -CH_2I, -OCF_3, -$OCCl_3$, -$OCBr_3$, -OCI_3, -$OCHF_2$, -$OCHCl_2$, -$OCHBr_2$, -$OCHI_2$, -OCH_2F, -OCH_2Cl, -OCH_2Br, -OCH_2I, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, 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:

(a) oxo, halogen, -CF_3, -CCl_3, -CBr_3, -CI_3, -CHF_2, -$CHCl_2$, -$CHBr_2$, -CHI_2, -CH_2F, -CH_2Cl, -CH_2Br, -CH_2I, -OCF_3, -$OCCl_3$, -$OCBr_3$, -OCI_3, -$OCHF_2$, -$OCHCl_2$, -$OCHBr_2$, -$OCHI_2$, -OCH_2F, -OCH_2Cl, -OCH_2Br, -OCH_2I, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, 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: oxo, halogen, -CF_3, -CCl_3, -CBr_3, -CI_3, -CHF_2, -$CHCl_2$, -$CHBr_2$, -CHI_2, -CH_2F, -CH_2Cl, -CH_2Br, -CH_2I, -OCF_3, -$OCCl_3$, -$OCBr_3$, -OCI_3, -$OCHF_2$, -$OCHCl_2$, -$OCHBr_2$, -$OCHI_2$, -OCH_2F, -OCH_2Cl, -OCH_2Br, -OCH_2I, -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, -$NHSO_2H$, -NHC(O)H, -

NHC(O)-OH, -NHOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

[0076] 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 C_1-C_{20} 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 C_3-C_8 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 C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0077] 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 C_1-C_8 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 C_3-C_7 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 C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0078] 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.

[0079] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} 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 C_3-C_8 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 C_6-C_{10} 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 C_1-C_{20} 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 C_3-C_8 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 C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0080] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 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 C_3-C_7 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 C_6-C_{10} 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 C_1-C_8 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 C_3-C_7 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 C_6-C_{10} 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.

[0081] 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, 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, e.g.*, Berge *et al.*, *Journal of Pharmaceutical Science* 66:1-19 (1977)). 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. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present invention. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

[0082] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

[0083] 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 differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0084] Provided herein are agents (e.g. compounds, drugs, therapeutic agents) that may be in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under select physiological conditions to provide the final agents (e.g. compounds, drugs, therapeutic agents). Additionally, prodrugs can be converted to agents (e.g. compounds, drugs, therapeutic agents) by chemical or biochemical methods in an *ex vivo* environment. Prodrugs described herein include compounds that readily undergo chemical changes under select physiological conditions to provide agents (e.g. compounds, drugs, therapeutic agents) to a biological system (e.g. in a subject, in a cancer cell, in the extracellular space near a cancer cell).

[0085] 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 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.

[0086] As used herein, the term "salt" refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts.

[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 which 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 ^{13}C- or ^{14}C-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 (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0094] The symbol "〰" denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0095] 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 C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls. 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.

[0096] Descriptions 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 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.

[0097] 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 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, and/or a psychiatric evaluation. For example, certain methods herein treat diseases associated with ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) activity. Certain methods described herein may treat diseases associated with ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) activity (e.g., cancer) by inhibiting ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) activity. For example, certain methods herein treat cancer. For example certain methods herein treat cancer by decreasing a symptom of cancer. Symptoms of cancer would be known or may be determined by a person of ordinary skill in the art. The term "treating" and conjugations thereof, include prevention of an injury, pathology, condition, or disease. In embodiments, treating does not include preventing.

[0098] An "effective amount" is an amount sufficient to accomplish a stated purpose (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce protein function, reduce one or more symptoms of a disease or condition). 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 or prodrug is an amount of a drug or prodrug that, when administered to a subject, will have the intended prophylactic effect, e.g., 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. 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 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).

[0099] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. cancer) means that the disease 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. 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 disease associated with ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) activity may be treated with an agent (e.g. compound as described herein) effective for decreasing the level of ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) activity.

[0100] "Control" or "control experiment" or "standard control" 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.

[0101] "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, that 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. 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. In some embodiments contacting includes allowing a compound described herein to interact with a protein (e.g., ErbB/HER (e.g., EGFR, HER2, HER3, or HER4)) or enzyme.

[0102] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor (e.g. antagonist) interaction means negatively affecting (e.g. decreasing) the level of activity or function of the protein relative to the level of 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. Thus, inhibition may include, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein.

[0103] As defined herein, the term "activation", "activate", "activating" and the like in reference to a protein-activator (e.g. agonist) interaction means positively affecting (e.g. increasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the activator (e.g. compound described herein). Thus, activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease. Activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein.

[0104] The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule relative to a standard control (e.g., such as the absence of the modulator). In embodiments, a modulator is an anti-cancer agent. In embodiments, a modulator is an ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) antagonist. In embodiments, a modulator is an ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) agonist.

[0105] "Anti-cancer agent" or "anti-cancer drug" 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 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, anti-androgens (e.g., Casodex, Flutamide, MDV3100, or ARN-509), 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, 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., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethlymelamine, 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), pyrimidine analogs (e.g., fluorouracil, floxouridine, 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.*), 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. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002), mTOR inhibitors, antibodies (e.g., rituxan), 5-aza-2'-deoxycytidine, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), bortezomib, trastuzumab, anastrozole; angiogenesis inhibitors; antiandrogen, antiestrogen; antisense oligonucleotides; apoptosis gene modulators; apoptosis regulators; arginine deaminase; BCR/ABL antagonists; beta lactam derivatives; bFGF inhibitor; bicalutamide; camptothecin derivatives; casein kinase inhibitors (ICOS); clomifene analogues; cytarabine dacliximab; dexamethasone; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; finasteride; fludarabine; fluorodaunorunicin hydrochloride; gadolinium texaphyrin; gallium nitrate; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam;

immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; matrilysin inhibitors; matrix metalloproteinase inhibitors; MIF inhibitor; mifepristone; mismatched double stranded RNA; monoclonal antibody,; mycobacterial cell wall extract; nitric oxide modulators; oxaliplatin; panomifene; pentrozole; phosphatase inhibitors; plasminogen activator inhibitor; platinum complex; platinum compounds; prednisone; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; ribozymes; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; stem cell inhibitor; stem-cell division inhibitors; stromelysin inhibitors; synthetic glycosaminoglycans; tamoxifen methiodide; telomerase inhibitors; thyroid stimulating hormone; translation inhibitors; tyrosine kinase inhibitors; urokinase receptor antagonists; steroids (*e.g.,* dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethlystilbestrol, 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 (*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 ^{111}In, ^{90}Y, or ^{131}I, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, 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 (Iressa ™), erlotinib (Tarceva ™), cetuximab (Erbitux™), 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, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, pyrrolo benzodiazepines (e.g. tomaymycin), carboplatin, CC-1065 and CC-1065 analogs including amino-CBIs, nitrogen

mustards (such as chlorambucil and melphalan), dolastatin and dolastatin analogs (including auristatins: eg. monomethyl auristatin E), anthracycline antibiotics (such as doxorubicin, daunorubicin, etc.), duocarmycins and duocarmycin analogs, enediynes (such as neocarzinostatin and calicheamicins), leptomycin derivaties, maytansinoids and maytansinoid analogs (e.g. mertansine), methotrexate, mitomycin C, taxoids, vinca alkaloids (such as vinblastine and vincristine), epothilones (e.g. epothilone B), camptothecin and its clinical analogs topotecan and irinotecan, or the like.

[0106] "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.

[0107] "Patient" or "subject in need thereof" or "subject" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a compound or pharmaceutical composition or by a method, as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human. In some embodiments, a subject is human.

[0108] "Disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with a compound, pharmaceutical composition, or method provided herein. In some embodiments, the disease is a disease having the symptom of cell hyperproliferation. In some embodiments, the disease is a disease having the symptom of an aberrant level of ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) activity. In some embodiments, the disease is a cancer. 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 lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including AML, ALL, and CML), or multiple myeloma. In embodiments, the disease is brain cancer. In embodiments, the disease is neuroblastoma. In embodiments, the disease is glioblastoma.

[0109] 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 cancer of the prostate, 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 may 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 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.

[0110] 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 leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, 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, 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.

[0111] 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.

[0112] 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, subungal melanoma, or superficial spreading melanoma.

[0113] 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 adenomatosum, 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, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni 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, 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 carcinoma villosum.

[0114] 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.

[0115] 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 herein), results in reduction of the disease or one or more disease symptoms.

[0116] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, about 60% identity, preferably 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%,

90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher identity over a specified region when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (*see, e.g.*, NCBI web site or the like). Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the compliment of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 10 amino acids or 20 nucleotides in length, or more preferably over a region that is 10-50 amino acids or 20-50 nucleotides in length. As used herein, percent (%) amino acid sequence identity is defined as the percentage of amino acids in a candidate sequence that are identical to the amino acids in a reference sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared can be determined by known methods.

[0117] For sequence comparisons, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Preferably, default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0118] A “comparison window”, as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 10 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the

search for similarity method of Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (*see, e.g., Current Protocols in Molecular Biology* (Ausubel *et al.*, eds. 1995 supplement)).

[0119] Twenty amino acids are commonly found in proteins. Those amino acids can be grouped into nine classes or groups based on the chemical properties of their side chains. Substitution of one amino acid residue for another within the same class or group is referred to herein as a "conservative" substitution. Conservative amino acid substitutions can frequently be made in a protein without significantly altering the conformation or function of the protein. Substitution of one amino acid residue for another from a different class or group is referred to herein as a "non-conservative" substitution. In contrast, non-conservative amino acid substitutions tend to modify conformation and function of a protein. **Example of amino acid classification:**

Small/Aliphatic residues:	Gly, Ala, Val, Leu, Ile
Cyclic Imino Acid:	Pro
Hydroxyl-containing Residues:	Ser, Thr
Acidic Residues:	Asp, Glu
Amide Residues:	Asn, Gln
Basic Residues:	Lys, Arg
Imidazole Residue:	His
Aromatic Residues:	Phe, Tyr, Trp
Sulfur-containing Residues:	Met, Cys

[0120] In some embodiments, the conservative amino acid substitution comprises substituting any of glycine (G), alanine (A), isoleucine (I), valine (V), and leucine (L) for any other of these aliphatic amino acids; serine (S) for threonine (T) and vice versa; aspartic acid (D) for glutamic acid (E) and vice versa; glutamine (Q) for asparagine (N) and vice versa; lysine (K) for arginine (R) and vice versa; phenylalanine (F), tyrosine (Y) and tryptophan (W) for any other of these aromatic amino acids; and methionine (M) for cysteine (C) and vice versa. Other substitutions can also be considered conservative, depending on the environment of the particular amino acid and its role in the three- dimensional structure of the protein. For example, glycine (G) and alanine (A) can frequently be interchangeable, as can alanine (A) and valine (V). Methionine (M), which is relatively hydrophobic, can frequently be interchanged with leucine and isoleucine, and sometimes with valine. Lysine (K) and arginine (R) are frequently interchangeable in locations in which the significant feature of the amino acid residue is its

charge and the differing pKs of these two amino acid residues are not significant. Still other changes can be considered "conservative" in particular environments (see, e.g., BIOCHEMISTRY at pp. 13-15, 2nd ed. Lubert Stryer ed. (Stanford University); Henikoff et al., *Proc. Nat'l Acad. Sci. USA* (1992) 89:10915-10919; Lei et al., *J. Biol. Chem.* (1995) 270(20):11882-11886).

[0121] "Polypeptide," "peptide," and "protein" are used herein interchangeably and mean any peptide-linked chain of amino acids, regardless of length or post-translational modification. As noted below, the polypeptides described herein can be, e.g., wild-type proteins, biologically-active fragments of the wild-type proteins, or variants of the wild- type proteins or fragments. Variants, in accordance with the disclosure, can contain amino acid substitutions, deletions, or insertions. The substitutions can be conservative or non-conservative.

[0122] Following expression, the proteins can be isolated. The term "purified" or "isolated" as applied to any of the proteins described herein refers to a polypeptide that has been separated or purified from components (e.g., proteins or other naturally-occurring biological or organic molecules) which naturally accompany it, e.g., other proteins, lipids, and nucleic acid in a cell expressing the proteins. Typically, a polypeptide is purified when it constitutes at least 60 (e.g., at least 65, 70, 75, 80, 85, 90, 92, 95, 97, or 99) %, by weight, of the total protein in a sample.

[0123] 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 a particular amino acid in an ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) when the selected residue occupies the same essential spatial or other structural relationship as particular amino acid in an ErbB/HER (e.g., EGFR, HER2, HER3, or HER4). In some embodiments, where a selected protein is aligned for maximum homology with the human ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) protein, the position in the aligned selected protein aligning with a particular reside is said to correspond to that particular reside. 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 ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) protein and the overall structures compared. In this case, an amino acid that occupies the same essential position as a particular reside in the structural model is said to correspond to the particular reside.

[0124] "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, hydroxymethycellulose, 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 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.

[0125] 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 lozenges can be used as solid dosage forms suitable for oral administration.

[0126] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, 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 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 administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent). The compound 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 compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation, to increase degradation of a prodrug and release of the drug, detectable agent). 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. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.,* by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0127] Pharmaceutical compositions provided by the present invention include compositions wherein the active ingredient (e.g. compounds described herein, including embodiments or examples) is contained in a therapeutically effective amount, *i.e.*, in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia,* on the condition being treated. When administered in methods to treat a disease, such compositions will contain an amount of active ingredient effective to achieve the desired result, e.g., reducing, eliminating, or slowing the progression of disease symptoms (e.g.

symptoms of cancer or aberrant ErbB/HER (e.g., EGFR, HER2, HER3, or HER4) activity). Determination of a therapeutically effective amount of a compound of the invention is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein.

[0128] The dosage and frequency (single or multiple doses) administered to a mammal can vary depending upon a variety of factors, for example, whether the mammal suffers from another disease, and its route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated (e.g. symptoms of cancer), kind of concurrent treatment, complications from the disease being treated or other health-related problems. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds of Applicants' invention. Adjustment and manipulation of established dosages (e.g., frequency and duration) are well within the ability of those skilled in the art.

[0129] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0130] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0131] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. 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.

[0132] Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0133] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

[0134] 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.

[0135] 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. In some embodiments, the compounds described herein may be combined with treatments for cancer such as radiation or surgery.

[0136] As used herein, the term "about" means a range of values including the specified value, which a person of ordinary skill in the art would consider reasonably similar to the specified value. In embodiments, about means within a standard deviation using measurements generally acceptable in the art. In embodiments, about means a range extending to +/- 10% of the specified value. In embodiments, about includes the specified value.

[0137] The term "Receptor tyrosine-protein kinase erbB-3", "human epidermal growth factor receptor 3 "ERBB3", or "HER3" refers to a pseudokinase (reduced activity or inactive kinase) that is a member of the epidermal growth factor receptor (EGFR/ERBB) family of receptor tyrosine kinases. The term "HER3" may refer to the nucleotide sequence or protein sequence of human HER3 (e.g., Entrez 2065, Uniprot P21860, RefSeq NM_001982, or RefSeq NP_001973)

and homologs thereof. The term "HER3" includes both the wild-type form of the nucleotide sequences or proteins as well as any mutants thereof. In some embodiments, "HER3" is wild-type HER3 receptor. In some embodiments, "HER3" is one or more mutant forms. The term "HER3" XYZ refers to a nucleotide sequence or protein of a mutant HER3wherein the Y numbered amino acid of HER3 that normally has an X amino acid in the wildtype, instead has a Z amino acid in the mutant. In embodiments, an HER3 is the human HER3. In embodiments, the HER3 has the nucleotide sequence corresponding to reference number GI:317171925. In embodiments, the HER3 has the nucleotide sequence corresponding to RefSeq NM_001982.3. In embodiments, the HER3 has the protein sequence corresponding to reference number GI:54792100. In embodiments, the HER3 has the protein sequence corresponding to RefSeq NP_001973.2. In embodiments, the HER3 has the following amino acid sequence:

MRANDALQVLGLLFSLARGSEVGNSQAVCPGTLNGLSVTGDAENQYQTLYKLYERCEVVMGNLEIVLTGH
NADLSFLQWIREVTGYVLVAMNEFSTLPLPNLRVVRGTQVYDGKFAIFVMLNYNTNSSHALRQLRLTQLT
EILSGGVYIEKNDKLCHMDTIDWRDIVRDRDAEIVVKDNGRSCPPCHEVCKGRCWGPGSEDCQTLTKTIC
APQCNGHCFGPNPNQCCHDECAGGCSGPQDTDCFACRHFNDSGACVPRCPQPLVYNKLTFQLEPNPHTKY
QYGGVCVASCPHNFVVDQTSCVRACPPDKMEVDKNGLKMCEPCGGLCPKACEGTGSGSRFQTVDSSNIDG
FVNCTKILGNLDFLITGLNGDPWHKIPALDPEKLNVFRTVREITGYLNIQSWPPHMHNFSVFSNLTTIGG
RSLYNRGFSLLIMKNLNVTSLGFRSLKEISAGRIYISANRQLCYHHSLNWTKVLRGPTEERLDIKHNRPR
RDCVAEGKVCDPLCSSGGCWGPGPGQCLSCRNYSRGGVCVTHCNFLNGEPREFAHEAECFSCHPECQPME
GTATCNGSGSDTCAQCAHFRDGPHCVSSCPHGVLGAKGPIYKYPDVQNECRPCHENCTQGCKGPELQDCL
GQTLVLIGKTHLTMALTVIAGLVVIFMMLGGTFLYWRGRRIQNKRAMRRYLERGESIEPLDPSEKANKVL
ARIFKETELRKLKVLGSGVFGTVHKGVWIPEGESIKIPVCIKVIEDKSGRQSFQAVTDHMLAIGSLDHAH
IVRLLGLCPGSSLQLVTQYLPLGSLLDHVRQHRGALGPQLLLNWGVQIAKGMYYLEEHGMVHRNLAARNV
LLKSPSQVQVADFGVADLLPPDDKQLLYSEAKTPIKWMALESIHFGKYTHQSDVWSYGVTVWELMTFGAE
PYAGLRLAEVPDLLEKGERLAQPQICTIDVYMVMVKCWMIDENIRPTFKELANEFTRMARDPPRYLVIKR
ESGPGIAPGPEPHGLTNKKLEEVELEPELDLDLDLEAEEDNLATTTLGSALSLPVGTLNRPRGSQSLLSP
SSGYMPMNQGNLGESCQESAVSGSSERCPRPVSLHPMPRGCLASESSEGHVTGSEAELQEKVSMCRSRSR
SRSPRPRGDSAYHSQRHSLLTPVTPLSPPGLEEEDVNGYVMPDTHLKGTPSSREGTLSSVGLSSVLGTEE
EDEDEEYEYMNRRRRHSPPHPPRPSSLEELGYEYMDVGSDLSASLGSTQSCPLHPVPIMPTAGTTPDEDY
EYMNRQRDGGGPGGDYAAMGACPASEQGYEEMRAFQGPGHQAPHVHYARLKTLRSLEATDSAFDNPDYWH
SRLFPKANAQRT
(SEQ ID NO:1)

[0138] In embodiments, the HER3 is a mutant HER3. In embodiments, the mutant HER3 is associated with a disease that is not associated with wildtype HER3. In embodiments, the HER3 includes at least one amino acid mutation (e.g., 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 mutations) compared to the sequence above. In embodiments, the HER3 is a variant of the sequence above, including a shorter variant or mutated variant. In embodiments, the mutant HER3 is a splice variant. In embodiments, the mutant HER3 is a splice variant with aberrant activity relative to the widtype HER3. In embodiments, the mutant HER3 is a truncated splice variant with aberrant activity relative to the widtype HER3. In embodiments, the mutant HER3 is a splice variant lacking a portion of the

wildtype HER3 with aberrant activity relative to the widtype HER3. In embodiments, the HER3 is described in Cancer Cell (2013) May 13 23, 603-617, which is herein incorporated in its entirety for all purposes.

[0139] The term "Receptor tyrosine-protein kinase erbB-2", "human epidermal growth factor receptor 2 ", "CD340", "ERBB2", "neu", "HER2/neu", or "HER2" refers to a member of the epidermal growth factor receptor (EGFR/ERBB) family of receptor tyrosine kinases. The term "HER2" may refer to the nucleotide sequence or protein sequence of human HER2 (e.g., Entrez 2064, Uniprot P04626, RefSeq NM_004448, or RefSeq NP_004439) and homologs thereof. The term "HER2" includes both the wild-type form of the nucleotide sequences or proteins as well as any mutants thereof. In some embodiments, "HER2" is wild-type HER2 receptor. In some embodiments, "HER2" is one or more mutant forms. The term "HER2" XYZ refers to a nucleotide sequence or protein of a mutant HER2 wherein the Y numbered amino acid of HER2 that normally has an X amino acid in the wildtype, instead has a Z amino acid in the mutant. In embodiments, an HER2 is the human HER2. In embodiments, the HER2 has the nucleotide sequence corresponding to reference number GI:584277099. In embodiments, the HER2 has the nucleotide sequence corresponding to RefSeq NM_004448.3. In embodiments, the HER2 has the protein sequence corresponding to reference number GI:54792096. In embodiments, the HER2 has the protein sequence corresponding to RefSeq NP_004439.2. In embodiments, the HER2 has the following amino acid sequence:

MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNAS
LSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLREL
QLRSLTEILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPMCKGSRCWGESSE
DCQSLTRTVCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFE
SMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARVCYGLGMEHL
REVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWPDSLP
DLSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLALIHHNTHLCFVHTVPWDQLFRNPH
QALLHTANRPEDECVGEGLACHQLCARGHCWGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHC
LPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGACQPCPINC
THSCVDLDDKGCPAEQRASPLTSIISAVVGILLVVVLGVVFGILIKRRQQKIRKYTMRRLLQETELVEPL
TPSGAMPNQAQMRILKETELRKVKVLGSGAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDE
AYVMAGVGSPYVSRLLGICLTSTVQLVTQLMPYGCLLDHVRENRGRLGSQDLLNWCMQIAKGMSYLEDVR
LVHRDLAARNVLVKSPNHVKITDFGLARLLDIDETEYHADGGKVPIKWMALESILRRRFTHQSDVWSYGV
TVWELMTFGAKPYDGIPAREIPDLLEKGERLPQPPICTIDVYMIMVKCWMIDSECRPRFRELVSEFSRMA
RDPQRFVVIQNEDLGPASPLDSTFYRSLLEDDDMGDLVDAEEYLVPQQGFFCPDPAPGAGGMVHHRHRSS
STRSGGGDLTLGLEPSEEEAPRSPLAPSEGAGSDVFDGDLGMGAAKGLQSLPTHDPSPLQRYSEDPTVPL
PSETDGYVAPLTCSPQPEYVNQPDVRPQPPSPREGPLPAARPAGATLERPKTLSPGKNGVVKDVFAFGGA
VENPEYLTPQGGAAPQPHPPPAFSPAFDNLYYWDQDPPERGAPPSTFKGTPTAENPEYLGLDVPV
(SEQ ID NO:2)

[0140] In embodiments, the HER2 is a mutant HER2. In embodiments, the mutant HER2 is associated with a disease that is not associated with wildtype HER2. In embodiments, the HER2

includes at least one amino acid mutation (e.g., 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 mutations) compared to the sequence above. In embodiments, the HER2 is a variant of the sequence above, including a shorter variant or mutated variant. In embodiments, the mutant HER2 is a splice variant. In embodiments, the mutant HER2 is a splice variant with aberrant activity relative to the widtype HER2. In embodiments, the mutant HER2 is a truncated splice variant with aberrant activity relative to the widtype HER2. In embodiments, the mutant HER2 is a splice variant lacking a portion of the wildtype HER2 with aberrant activity relative to the widtype HER2.

[0141] The term "epidermal growth factor receptor", "ErbB1", and "EGFR" refer to a member of the epidermal growth factor receptor (EGFR/ERBB) family of receptor tyrosine kinases. The term "EGFR" may refer to the nucleotide sequence or protein sequence of human EGFR (e.g., Entrez 1956, Uniprot P00533, RefSeq NM_05228, or RefSeq NP_005219) and homologs thereof. The term "EGFR" includes both the wild-type form of the nucleotide sequences or proteins as well as any mutants thereof. In some embodiments, "EGFR" is wild-type EGFR receptor. In some embodiments, "EGFR" is one or more mutant forms. The term "EGFR" XYZ refers to a nucleotide sequence or protein of a mutant EGFR wherein the Y numbered amino acid of EGFR that normally has an X amino acid in the wildtype, instead has a Z amino acid in the mutant. In embodiments, an EGFR is the human EGFR. In embodiments, the EGFR has the nucleotide sequence corresponding to reference number GI:41327737. In embodiments, the EGFR has the nucleotide sequence corresponding to RefSeq NM_005228.3. In embodiments, the EGFR has the protein sequence corresponding to reference number GI:29725609. In embodiments, the EGFR has the protein sequence corresponding to RefSeq NP_005219.2. In embodiments, the EGFR has the following amino acid sequence:

MRPSGTAGAALLALLAALCPASRALEEKKVCQGTSNKLTQLGTFEDHFLSLQRMFNNCEVVLGNLEITYV
QRNYDLSFLKTIQEVAGYVLIALNTVERIPLENLQIIRGNMYYENSYALAVLSNYDANKTGLKELPMRNL
QEILHGAVRFSNNPALCNVESIQWRDIVSSDFLSNMSMDFQNHLGSCQKCDPSCPNGSCWGAGEENCQKL
TKIICAQQCSGRCRGKSPSDCCHNQCAAGCTGPRESDCLVCRKFRDEATCKDTCPPLMLYNPTTYQMDVN
PEGKYSFGATCVKKCPRNYVVTDHGSCVRACGADSYEMEEDGVRKCKKCEGPCRKVCNGIGIGEFKDSLS
INATNIKHFKNCTSISGDLHILPVAFRGDSFTHTPPLDPQELDILKTVKEITGFLLIQAWPENRTDLHAF
ENLEIIRGRTKQHGQFSLAVVSLNITSLGLRSLKEISDGDVIISGNKNLCYANTINWKKLFGTSGQKTKI
ISNRGENSCKATGQVCHALCSPEGCWGPEPRDCVSCRNVSRGRECVDKCNLLEGEPREFVENSECIQCHP
ECLPQAMNITCTGRGPDNCIQCAHYIDGPHCVKTCPAGVMGENNTLVWKYADAGHVCHLCHPNCTYGCTG
PGLEGCPTNGPKIPSIATGMVGALLLLLVVALGIGLFMRRRHIVRKRTLRRLLQERELVEPLTPSGEAPN
QALLRILKETEFKKIKVLGSGAFGTVYKGLWIPEGEKVKIPVAIKELREATSPKANKEILDEAYVMASVD
NPHVCRLLGICLTSTVQLITQLMPFGCLLDYVREHKDNIGSQYLLNWCVQIAKGMNYLEDRRLVHRDLAA
RNVLVKTPQHVKITDFGLAKLLGAEEKEYHAEGGKVPIKWMALESILHRIYTHQSDVWSYGVTVWELMTF
GSKPYDGIPASEISSILEKGERLPQPPICTIDVYMIMVKCWMIDADSRPKFRELIIEFSKMARDPQRYLV
IQGDERMHLPSPTDSNFYRALMDEEDMDDVVDADEYLIPQQGFFSSPSTSRTPLLSSLSATSNNSTVACI
DRNGLQSCPIKEDSFLQRYSSDPTGALTEDSIDDTFLPVPEYINQSVPKRPAGSVQNPVYHNQPLNPAPS
RDPHYQDPHSTAVGNPEYLNTVQPTCVNSTFDSPAHWAQKGSHQISLDNPDYQQDFFPKEAKPNGIFKGS
TAENAEYLRVAPQSSEFIGA

(SEQ ID NO:3)

[0142] In embodiments, the EGFR is a mutant EGFR (e.g., exon 20 mutant). In embodiments, the mutant EGFR is associated with a disease that is not associated with wildtype EGFR. In embodiments, the EGFR includes at least one amino acid mutation (e.g., 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 mutations) compared to the sequence above. In embodiments, the EGFR is a variant of the seqeuence above, including a shorter variant or mutated variant. In embodiments, the mutant EGFR is a splice variant. In embodiments, the mutant EGFR is a splice variant with aberrant activity relative to the widtype EGFR. In embodiments, the mutant EGFR is a truncated splice variant with aberrant activity relative to the widtype EGFR. In embodiments, the mutant EGFR is a splice variant lacking a portion of the wildtype EGFR with aberrant activity relative to the widtype EGFR.

[0143] The term "ligand" is used in accordance with its plain ordinary meaning and refers to a molecule (e.g., compound as described herein) capable of binding to another molecule (e.g., protein, receptor, enzyme, target, or cell). In embodiments, a ligand is a modulator, inhibitor, activator, agonist, or antagonist.

[0144] The terms "analog" or "analogue" are used in accordance with their plain ordinary meaning in Chemistry and refers to a compound having a structure (e.g., chemical structure) similar to another compound (reference compound, compound described herein) but differing in one or more components (e.g., different substituent(s), addition of substituent(s), removal of substituent(s)).

[0145] The term "derivative" is used in accordance with its plain ordinary meaning in chemistry and refers to a compound that is derived (e.g., a product made from a reactant) from a similar compound by a chemical or physical process.

[0146] The term "HER2 activity" is used in accordance with its plain ordinary meaning and refers to the function or activity of the HER2 protein. Examples of HER2 activity include dimerization (e.g., heterodimerization). In embodiments, HER2 activity is increasing or activating activity of a protein interacting with HER2 (e.g., PI3K activity, MEK activity, MAPK activity, RAF activity, BRAF activity, AKT activity, RAS activity, or KRAS activity). In embodiments HER2 activity is activation or increasing of activity of a signaling pathway by

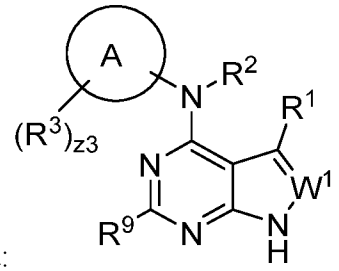
HER2 or activation of a component of a signaling pathway by HER2 (e.g., directly or through intervening components of the signaling pathway). In embodiments HER2 activity is activation of kinase activity of a protein that interacts (e.g., directly contacting HER3 or interactions with HER2 through intermediates) with HER2 (e.g., EGFR, HER3, HER4, c-MET, PI3K, MEK, MAPK, RAF, BRAF, AKT, RAS, or KRAS).

[0147] The term "EGFR activity" is used in accordance with its plain ordinary meaning and refers to the function or activity of the EGFR protein. Examples of EGFR activity include dimerization (e.g., heterodimerization) or activation of the activity of a protein upon dimerization of EGFR (e.g., HER2 activity, HER3 activity, HER4 activity, or c-MET activity). In embodiments, EGFR activity is increasing or activating activity of a protein interacting with EGFR (e.g., PI3K activity, MEK activity, MAPK activity, RAF activity, BRAF activity, AKT activity, RAS activity, or KRAS activity). In embodiments EGFR activity is activation or increasing of activity of a signaling pathway by EGFR or activation of a component of a signaling pathway by EGFR (e.g., directly or through intervening components of the signaling pathway). In embodiments HER2 activity is activation of kinase activity of a protein that interacts (e.g., directly contacting EGFR or interactions with EGFR through intermediates) with EGFR (e.g., HER2, HER3, HER4, c-MET, PI3K, MEK, MAPK, RAF, BRAF, AKT, RAS, or KRAS).

[0148] The term "active conformation" when referring to the ERBB (e.g., HER2 or EGFR) protein, is the protein conformation in which the protein has kinase activity (e.g., an increased kinase activity relative to an inactive conformation or basal activity when not activated (e.g., by ligand binding or dimerization)). The active conformation may be characterized by, for example, the "in conformation" of the α-C helix, which allows formation of the characteristic salt-bridge between a β3 lysine and an α-C glutamate or formation of an ordered extension of the activation loop (e.g., in HER2) or a correspondingly similar conformational change in EGFR, HER2, HER3, or HER4.

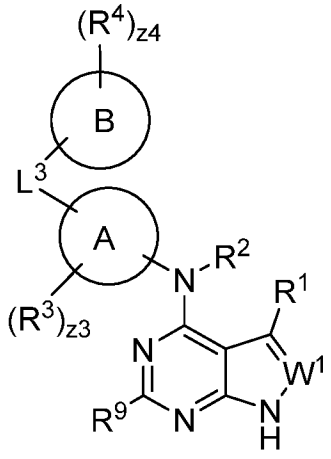
[0149] A "covalent cysteine modifier moiety" as used herein refers to a substituent that is capable of reacting with the sulfhydryl functional group of a cysteine amino acid (e.g. cysteine 797 of human EGFR or cysteine 805 of human HER2) to form a covalent bond. Thus, the covalent cysteine modifier moiety is typically electrophilic.

B. Compounds

[0150] In an aspect is provided a compound having the formula:  (I).

[0151] Ring A is aryl or heteroaryl. W^1 is N or C(H). R^1 is hydrogen, $-L^1-L^2-E$, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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. The symbol z3 is an integer from 0 to 4. L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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. L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)$

O)R^{7C}, -C(O)-OR^{7C}, -C(O)N$R^{7A}R^{7B}$, -OR^{7D}, -N$R^{7A}SO_2R^{7D}$, -NR^{7A}C(O)R^{7C}, -NR^{7A}C(O)OR^{7C}, -NR^{7A}OR^{7C}, 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^9 is hydrogen, halogen, -CX^9_3, -CHX^9_2, -CH_2X^9, -OCX^9_3, -OCH_2X^9, -OCHX^9_2, -CN, -$SO_{n9}R^{9D}$, -$SO_{v9}NR^{9A}R^{9B}$, -NHC(O)N$R^{9A}R^{9B}$, -N$(O)_{m9}$, -N$R^{9A}R^{9B}$, -C(O)R^{9C}, -C(O)-OR^{9C}, -C(O)N$R^{9A}R^{9B}$, -OR^{9D}, -N$R^{9A}SO_2R^{9D}$, -NR^{9A}C(O)R^{9C}, -NR^{9A}C(O)OR^{9C}, -NR^{9A}OR^{9C}, 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. E is an electrophilic moiety. Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, -CX_3, -CN, -COOH, -$CONH_2$, -CHX_2, -CH_2X, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. R^{9A} and R^{9B} 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^3, X^6, X^7, and X^9 is independently –F, -Cl, -Br, or –I. The symbols n3, n6, n7, and n9 are independently an integer from 0 to 4. The symbols m3, m6, m7, m9, v3, v6, v7, and v9 are independently an integer from 1 to 2.

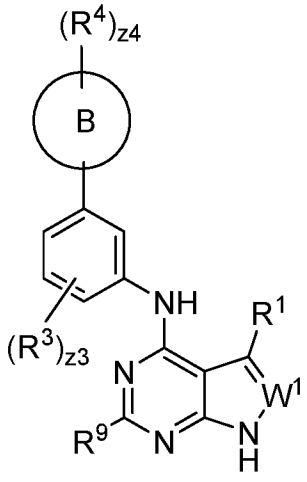


[0152] In embodiments, the compound has the formula: (II), wherein R^1, R^2, R^3, R^9, Ring A, W^1, and z3 are as described herein.

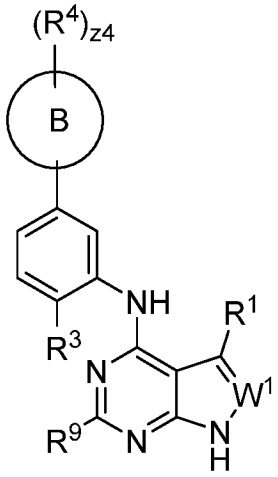
[0153] Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. L^3 is a bond, $-S(O)_2-$, $-NR^8-$, -O-, -S-, -C(O)-, $-C(O)NR^8-$, $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-NHC(O)NR^8-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0154] R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, 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^8 is independently hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, -CN, $-SO_{n8}R^{8D}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-C(O)R^{8C}$, $-C(O)-OR^{8C}$, $-C(O)NR^{8A}R^{8B}$, $-OR^{8D}$, $-NR^{8A}SO_2R^{8D}$, $-NR^{8A}C(O)R^{8C}$, $-NR^{8A}C(O)OR^{8C}$, $-NR^{8A}OR^{8C}$, 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. The symbol z4 is an integer from 0 to 5. Each R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{8A}, R^{8B}, R^{8C}, and R^{8D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or

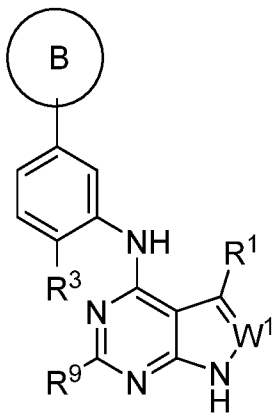
substituted or unsubstituted heteroaryl. Each X^4 and X^8 is independently –F, -Cl, -Br, or –I. The symbols n4 and n8 are independently an integer from 0 to 4. The symbols m4, m8, v4, and v8, are independently an integer from 1 to 2.



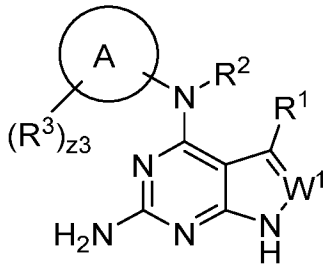
[0155] In embodiments, the compound has the formula: (III), wherein R^1, R^2, R^3, R^4, R^9, Ring B, W^1, z3, and z4 are as described herein.



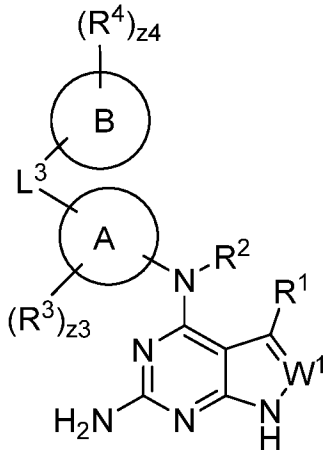
[0156] In embodiments, the compound has the formula: (IV), wherein R^1, R^3, R^4, R^9, Ring B, W^1, and z4 are as described herein.



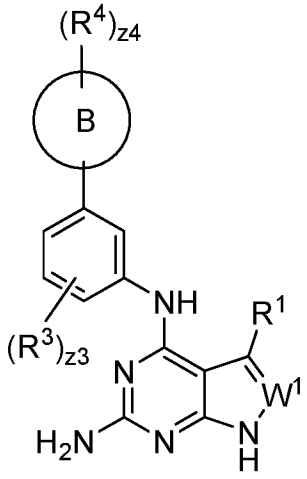
[0157] In embodiments, the compound has the formula: (V), wherein R^1, R^3, R^9, Ring B, and W^1 are as described herein.



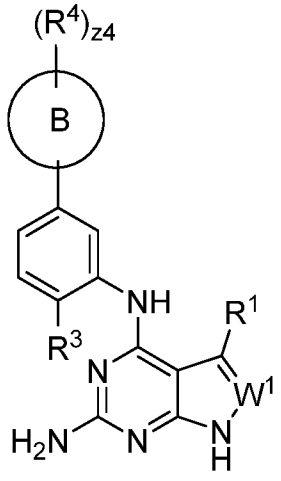
[0158] In embodiments, the compound has the formula: (IA), wherein R^1, R^2, R^3, Ring A, W^1, and z3 are as described herein.

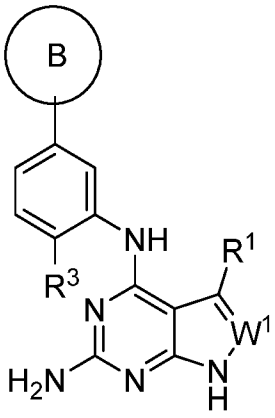


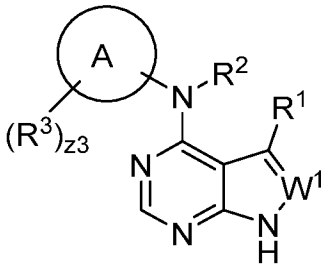
[0159] In embodiments, the compound has the formula: (IIA), wherein R^1, R^2, R^3, R^4, L^3, Ring A, Ring B, W^1, z3, and z4 are as described herein.

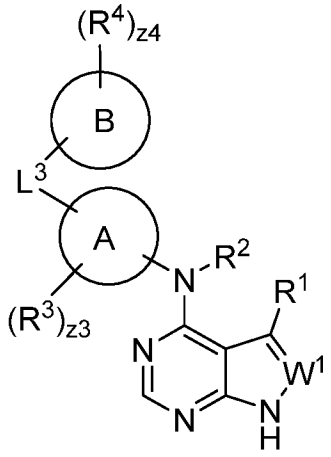


[0160] In embodiments, the compound has the formula: (IIIA), wherein R^1, R^3, R^4, Ring B, W^1, z3, and z4 are as described herein.

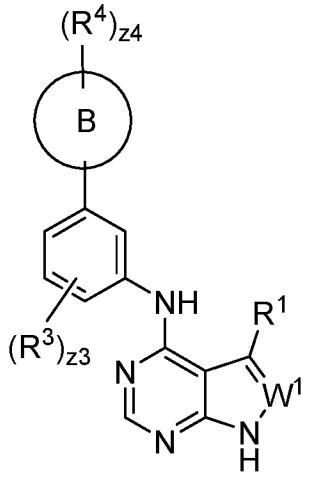
[0161] In embodiments, the compound has the formula:  (IVA), wherein R^1, R^3, R^4, Ring B, W^1, and z4 are as described herein.

[0162] In embodiments, the compound has the formula:  (VA), wherein R^1, R^3, Ring B, and W^1 are as described herein.

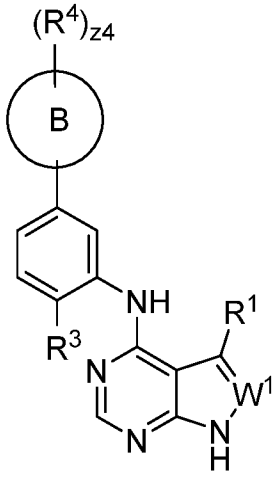
[0163] In embodiments, the compound has the formula:  (IB), wherein R^1, R^2, R^3, Ring A, W^1, and z3 are as described herein.



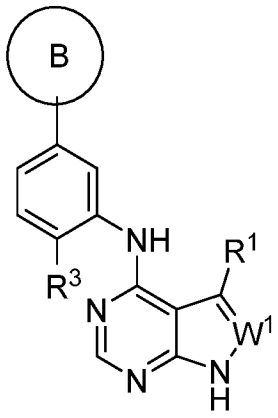
[0164] In embodiments, the compound has the formula: (IIB), wherein R^1, R^2, R^3, R^4, L^3, Ring A, Ring B, W^1, z3, and z4 are as described herein.

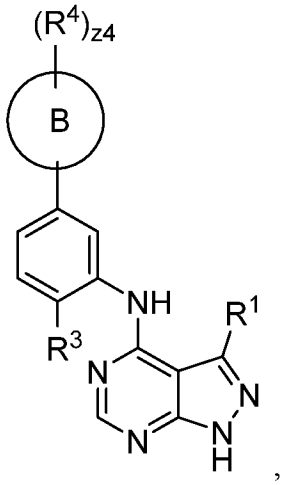


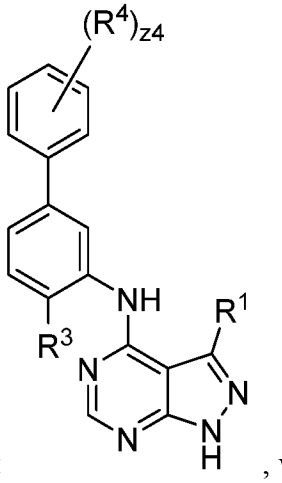
[0165] In embodiments, the compound has the formula: (IIIB), wherein R^1, R^3, R^4, Ring B, W^1, z3, and z4 are as described herein.

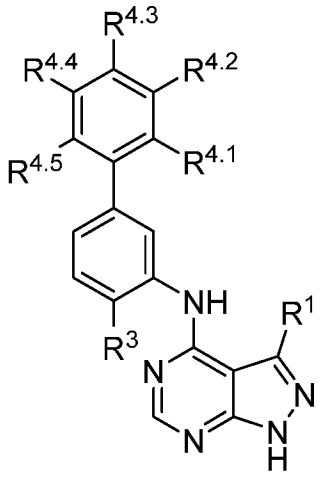


[0166] In embodiments, the compound has the formula: (IVB), wherein R^1, R^3, R^4, Ring B, W^1, and z4 are as described herein.

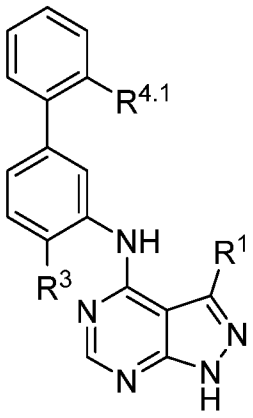
[0167] In embodiments, the compound has the formula:  (VB), wherein R^1, R^3, Ring B, and W^1 are as described herein.

[0168] In embodiments, the compound has the formula:  , wherein R^1, R^3, R^4, Ring B, and z4 are as described herein.

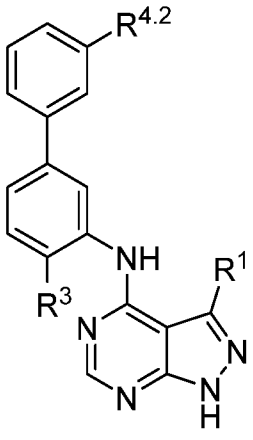
[0169] In embodiments, the compound has the formula:  , wherein R^1, R^3, R^4, and z4 are as described herein.



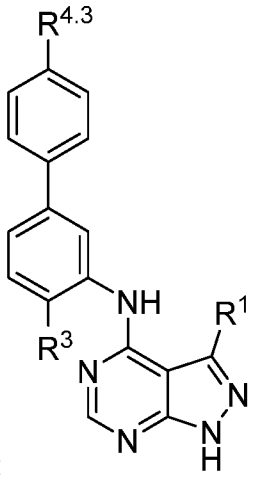
[0170] In embodiments, the compound has the formula: , wherein R^1 and R^3 are as described herein. $R^{4.1}$, $R^{4.2}$, $R^{4.3}$, $R^{4.4}$, and $R^{4.5}$ are each independently R^4 at a fixed position (e.g., non-floating as shown in the formula described herein) and may independently be any R^4 substituent.



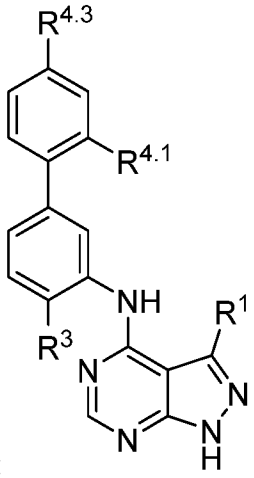
[0171] In embodiments, the compound has the formula: , wherein R^1 and R^3 are as described herein. $R^{4.1}$ is an R^4 substituent at a fixed position (e.g., non-floating as shown in the formula described herein) and may independently be any R^4 substituent.



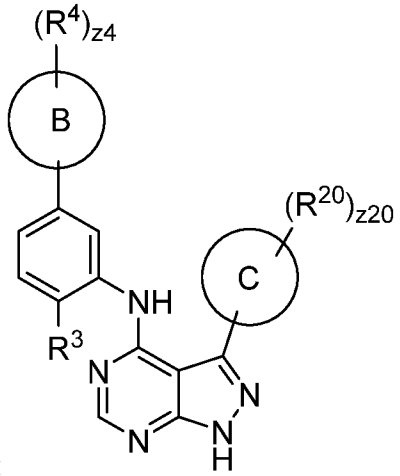
[0172] In embodiments, the compound has the formula: , wherein R^1 and R^3 are as described herein. $R^{4.2}$ is an R^4 substituent at a fixed position (e.g., non-floating as shown in the formula described herein) and may independently be any R^4 substituent.



[0173] In embodiments, the compound has the formula: , wherein R^1 and R^3 are as described herein. $R^{4.3}$ is an R^4 substituent at a fixed position (e.g., non-floating as shown in the formula described herein) and may independently be any R^4 substituent.

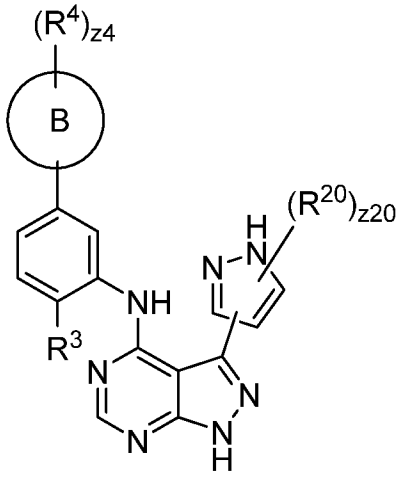


[0174] In embodiments, the compound has the formula: , wherein R^1 and R^3 are as described herein. $R^{4.1}$ and $R^{4.3}$ are each independently R^4 at a fixed position (e.g., non-floating as shown in the formula described herein) and may independently be any R^4 substituent.

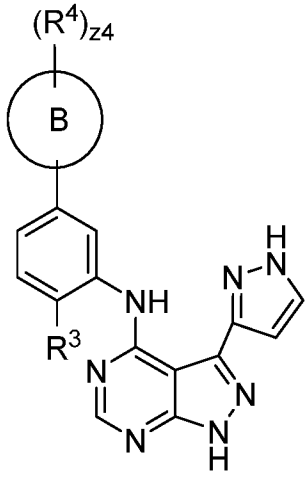


[0175] In embodiments, the compound has the formula: , wherein R^1, R^3, R^4, Ring B, R^{20}, and z4 are as described herein. Ring C is a substituted or

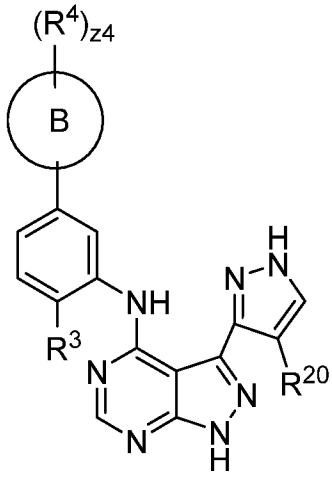
unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol z20 is an integer from 0 to 5.



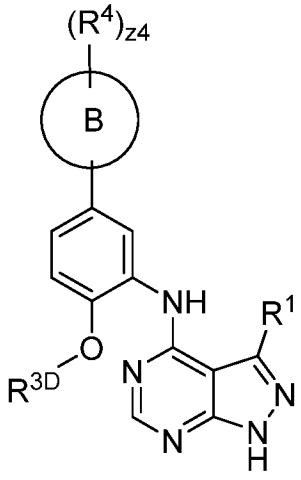
[0176] In embodiments, the compound has the formula: , wherein R^1, R^3, R^4, Ring B, R^{20}, z20, and z4 are as described herein. In embodiments, z20 is an integer from 0 to 4. In embodiments, z20 is an integer from 0 to 3. In embodiments, z20 is an integer from 0 to 2.



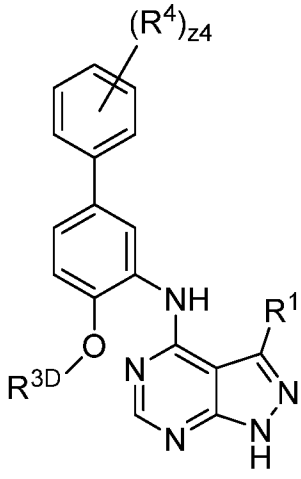
[0177] In embodiments, the compound has the formula: , wherein R^1, R^3, R^4, Ring B, and z4 are as described herein.



[0178] In embodiments, the compound has the formula: , wherein R^1, R^3, R^4, Ring B, and R^{20} are as described herein.



[0179] In embodiments, the compound has the formula: , wherein R^1, R^{3D}, R^4, Ring B, and z4 are as described herein.



[0180] In embodiments, the compound has the formula: , wherein R^1, R^3, R^4, and z4 are as described herein.

[0181] In embodiments, W^1 is C(H). In embodiments, W^1 is N.

[0182] In embodiments, Ring A is substituted or unsubstituted aryl. In embodiments, Ring A is substituted or unsubstituted heteroaryl. In embodiments, Ring A is substituted or unsubstituted C_6-C_{10} aryl. In embodiments, Ring A is substituted or unsubstituted C_{10} aryl. In embodiments, Ring A is substituted or unsubstituted phenyl. In embodiments, Ring A is substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, Ring A is substituted or unsubstituted 5 to 9 membered heteroaryl. In embodiments, Ring A is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring A is substituted or unsubstituted 10 membered heteroaryl. In embodiments, Ring A is substituted or unsubstituted 9 membered heteroaryl. In embodiments, Ring A is substituted or unsubstituted 5 membered heteroaryl. In embodiments, Ring A is substituted or unsubstituted 6 membered heteroaryl. In embodiments, Ring A is substituted or unsubstituted phenyl. In embodiments, Ring A is substituted or unsubstituted pyridyl. In embodiments, Ring A is substituted or unsubstituted pyrazolyl. In embodiments, Ring A is substituted or unsubstituted pyrimidyl. In embodiments, Ring A is substituted or unsubstituted imidazolyl. In embodiments, Ring A is substituted or unsubstituted oxazolyl. In embodiments, Ring A is substituted or unsubstituted isoxazolyl. In embodiments, Ring A is substituted or unsubstituted thiazolyl. In embodiments, Ring A is substituted or unsubstituted furanyl. In embodiments, Ring A is substituted or unsubstituted pyrrolyl. In embodiments, Ring A is substituted or unsubstituted thienyl. In embodiments, Ring A is a two fused ring aryl. In embodiments, Ring A is a two fused ring heteroaryl.

[0183] In embodiments, Ring A is substituted or unsubstituted aryl or heteroaryl. In embodiments, Ring A is substituted or unsubstituted phenyl or 5 to 6 membered heteroaryl. In embodiments, Ring A is substituted or unsubstituted phenyl. In embodiments, Ring A is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring A is substituted or unsubstituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0184] In embodiments, Ring A is substituted or unsubstituted phenyl. In embodiments, Ring A is substituted or unsubstituted pyridyl. In embodiments, Ring A is substituted or unsubstituted cyclohexyl. In embodiments, Ring A is substituted or unsubstituted morpholinyl. In embodiments, Ring A is substituted or unsubstituted piperazinyl. In embodiments, Ring A is substituted or unsubstituted furanyl. In embodiments, Ring A is substituted or unsubstituted thiazolyl. In embodiments, Ring A is substituted or unsubstituted pyrazolyl. In embodiments, Ring A is substituted or unsubstituted thienyl. In embodiments, Ring A is substituted or unsubstituted pyrazinyl. In embodiments, Ring A is substituted or unsubstituted pyrimidinyl. In

embodiments, Ring A is substituted or unsubstituted pyridazinyl. In embodiments, Ring A is substituted or unsubstituted triazinyl. In embodiments, Ring A is substituted or unsubstituted tetrazinyl. In embodiments, Ring A is substituted or unsubstituted tetrazolyl. In embodiments, Ring A is substituted or unsubstituted triazolyl. In embodiments, Ring A is substituted or unsubstituted quinolinyl. In embodiments, Ring A is substituted or unsubstituted isoquinolinyl. In embodiments, Ring A is substituted or unsubstituted quinazolinyl. In embodiments, Ring A is substituted or unsubstituted quinoxalinyl. In embodiments, Ring A is substituted or unsubstituted imidazolyl. In embodiments, Ring A is substituted or unsubstituted oxazolyl. In embodiments, Ring A is substituted or unsubstituted isoxazolyl. In embodiments, Ring A is substituted or unsubstituted thiazolyl. In embodiments, Ring A is substituted or unsubstituted piperidinyl. In embodiments, Ring A is substituted or unsubstituted thiomorpholinyl. In embodiments, Ring A is substituted or unsubstituted thianyl. In embodiments, Ring A is substituted or unsubstituted oxanyl. In embodiments, Ring A is substituted or unsubstituted tetrahydropuranyl. In embodiments, Ring A is substituted or unsubstituted dihydropuranyl. In embodiments, Ring A is substituted or unsubstituted dioxanyl. In embodiments, Ring A is substituted or unsubstituted pyrazolyl. In embodiments, Ring A is substituted or unsubstituted pyrrolyl. In embodiments, Ring A is substituted or unsubstituted thienyl. In embodiments, Ring A is substituted or unsubstituted benzofuranyl. In embodiments, Ring A is substituted or unsubstituted indolyl. In embodiments, Ring A is substituted or unsubstituted benzothienyl. In embodiments, Ring A is substituted or unsubstituted benzimidazolyl. In embodiments, Ring A is substituted or unsubstituted isobenzofuranyl. In embodiments, Ring A is substituted or unsubstituted isoindolyl. In embodiments, Ring A is substituted or unsubstituted benzo[c]thienyl. In embodiments, Ring A is substituted or unsubstituted purinyl. In embodiments, Ring A is substituted or unsubstituted indazolyl. In embodiments, Ring A is substituted or unsubstituted benzoxazolyl. In embodiments, Ring A is substituted or unsubstituted benzisoxazolyl. In embodiments, Ring A is substituted or unsubstituted benzothiazolyl. In embodiments, Ring A is substituted or unsubstituted cyclopentyl. In embodiments, Ring A is substituted or unsubstituted cyclobutyl. In embodiments, Ring A is substituted or unsubstituted 2-thienyl. In embodiments, Ring A is substituted or unsubstituted 3-thienyl. In embodiments, Ring A is substituted or unsubstituted 2-furanyl. In embodiments, Ring A is substituted or unsubstituted 3-furanyl. In embodiments, Ring A is substituted or unsubstituted 2-pyridyl. In embodiments, Ring A is substituted or unsubstituted 3-pyridyl. In embodiments, Ring A is substituted or unsubstituted 4-pyridyl. In embodiments, Ring A is substituted or unsubstituted 3-pyrazolyl. In embodiments, Ring A is substituted or unsubstituted

4-pyrazolyl. In embodiments, Ring A is substituted or unsubstituted 5- pyrazolyl. In embodiments, Ring A is substituted or unsubstituted 2-pyrrolyl. In embodiments, Ring A is substituted or unsubstituted 3- pyrrolyl. In embodiments, Ring A is substituted or unsubstituted 2-thiazolyl. In embodiments, Ring A is substituted or unsubstituted 4-thiazolyl. In embodiments, Ring A is substituted or unsubstituted 5-thiazolyl. In embodiments, Ring A is substituted or unsubstituted 2-pyridyl. In embodiments, Ring A is substituted or unsubstituted 3-pyridyl. In embodiments, Ring A is substituted or unsubstituted 4-pyridyl. In embodiments, Ring A is substituted or unsubstituted phenyl.

[0185] In embodiments, Ring A is a substituted aryl or substituted heteroaryl. In embodiments, Ring A is a substituted aryl. In embodiments, Ring A is a substituted heteroaryl. In embodiments, Ring A is a substituted C_6-C_{10} aryl. In embodiments, Ring A is a substituted C_{10} aryl. In embodiments, Ring A is a substituted phenyl. In embodiments, Ring A is a substituted 5 to 10 membered heteroaryl. In embodiments, Ring A is a substituted 5 to 9 membered heteroaryl. In embodiments, Ring A is a substituted 5 to 6 membered heteroaryl. In embodiments, Ring A is a substituted 10 membered heteroaryl. In embodiments, Ring A is a substituted 9 membered heteroaryl. In embodiments, Ring A is a substituted 5 membered heteroaryl. In embodiments, Ring A is a substituted 6 membered heteroaryl. In embodiments, Ring A is a substituted phenyl. In embodiments, Ring A is a substituted pyridyl. In embodiments, Ring A is a substituted pyrazolyl. In embodiments, Ring A is a substituted imidazolyl. In embodiments, Ring A is a substituted oxazolyl. In embodiments, Ring A is a substituted isoxazolyl. In embodiments, Ring A is a substituted thiazolyl. In embodiments, Ring A is a substituted furanyl. In embodiments, Ring A is a substituted pyrrolyl. In embodiments, Ring A is a substituted thienyl. In embodiments, Ring A is a two fused ring aryl. In embodiments, Ring A is a two fused ring heteroaryl.

[0186] In embodiments, Ring A is a substituted phenyl or 5 to 6 membered heteroaryl. In embodiments, Ring A is a substituted phenyl. In embodiments, Ring A is a substituted 5 to 6 membered heteroaryl. In embodiments, Ring A is a substituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0187] In embodiments, Ring A is a substituted phenyl. In embodiments, Ring A is a substituted pyridyl. In embodiments, Ring A is a substituted cyclohexyl. In embodiments, Ring A is a substituted morpholinyl. In embodiments, Ring A is a substituted piperazinyl. In embodiments, Ring A is a substituted furanyl. In embodiments, Ring A is a substituted thiazolyl.

In embodiments, Ring A is a substituted pyrazolyl. In embodiments, Ring A is a substituted thienyl. In embodiments, Ring A is a substituted pyrazinyl. In embodiments, Ring A is a substituted pyrimidinyl. In embodiments, Ring A is a substituted pyridazinyl. In embodiments, Ring A is a substituted triazinyl. In embodiments, Ring A is a substituted tetrazinyl. In embodiments, Ring A is a substituted tetrazolyl. In embodiments, Ring A is a substituted triazolyl. In embodiments, Ring A is a substituted quinolinyl. In embodiments, Ring A is a substituted isoquinolinyl. In embodiments, Ring A is a substituted quinazolinyl. In embodiments, Ring A is a substituted quinoxalinyl. In embodiments, Ring A is a substituted imidazolyl. In embodiments, Ring A is a substituted oxazolyl. In embodiments, Ring A is a substituted isoxazolyl. In embodiments, Ring A is a substituted thiazolyl. In embodiments, Ring A is a substituted piperidinyl. In embodiments, Ring A is a substituted thiomorpholinyl. In embodiments, Ring A is a substituted thianyl. In embodiments, Ring A is a substituted oxanyl. In embodiments, Ring A is a substituted tetrahydropuranyl. In embodiments, Ring A is a substituted dihydropuranyl. In embodiments, Ring A is a substituted dioxanyl. In embodiments, Ring A is a substituted pyrazolyl. In embodiments, Ring A is a substituted pyrrolyl. In embodiments, Ring A is a substituted thienyl. In embodiments, Ring A is a substituted benzofuranyl. In embodiments, Ring A is a substituted indolyl. In embodiments, Ring A is a substituted benzothienyl. In embodiments, Ring A is a substituted benzimidazolyl. In embodiments, Ring A is a substituted isobenzofuranyl. In embodiments, Ring A is a substituted isoindolyl. In embodiments, Ring A is a substituted benzo[c]thienyl. In embodiments, Ring A is a substituted purinyl. In embodiments, Ring A is a substituted indazolyl. In embodiments, Ring A is a substituted benzoxazolyl. In embodiments, Ring A is a substituted benzisoxazolyl. In embodiments, Ring A is a substituted benzothiazolyl. In embodiments, Ring A is a substituted cyclopentyl. In embodiments, Ring A is a substituted cyclobutyl. In embodiments, Ring A is a substituted 2-thienyl. In embodiments, Ring A is a substituted 3-thienyl. In embodiments, Ring A is a substituted 2-furanyl. In embodiments, Ring A is a substituted 3-furanyl. In embodiments, Ring A is a substituted 2-pyridyl. In embodiments, Ring A is a substituted 3-pyridyl. In embodiments, Ring A is a substituted 4-pyridyl. In embodiments, Ring A is a substituted 3-pyrazolyl. In embodiments, Ring A is a substituted 4-pyrazolyl. In embodiments, Ring A is a substituted 5- pyrazolyl. In embodiments, Ring A is a substituted 2-pyrrolyl. In embodiments, Ring A is a substituted 3- pyrrolyl. In embodiments, Ring A is a substituted 2-thiazolyl. In embodiments, Ring A is a substituted 4-thiazolyl. In embodiments, Ring A is a substituted 5-thiazolyl. In embodiments, Ring A is a substituted 2-pyridyl. In embodiments,

Ring A is a substituted 3-pyridyl. In embodiments, Ring A is a substituted 4-pyridyl. In embodiments, Ring A is a substituted phenyl.

[0188] In embodiments, Ring A is an unsubstituted aryl or heteroaryl. In embodiments, Ring A is an unsubstituted aryl. In embodiments, Ring A is an unsubstituted heteroaryl. In embodiments, Ring A is an unsubstituted C_6-C_{10} aryl. In embodiments, Ring A is an unsubstituted C_{10} aryl. In embodiments, Ring A is an unsubstituted phenyl. In embodiments, Ring A is an unsubstituted 5 to 10 membered heteroaryl. In embodiments, Ring A is an unsubstituted 5 to 9 membered heteroaryl. In embodiments, Ring A is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring A is an unsubstituted 10 membered heteroaryl. In embodiments, Ring A is an unsubstituted 9 membered heteroaryl. In embodiments, Ring A is an unsubstituted 5 membered heteroaryl. In embodiments, Ring A is an unsubstituted 6 membered heteroaryl. In embodiments, Ring A is an unsubstituted phenyl. In embodiments, Ring A is an unsubstituted pyridyl. In embodiments, Ring A is an unsubstituted pyrazolyl. In embodiments, Ring A is an unsubstituted imidazolyl. In embodiments, Ring A is an unsubstituted oxazolyl. In embodiments, Ring A is an unsubstituted isoxazolyl. In embodiments, Ring A is an unsubstituted thiazolyl. In embodiments, Ring A is an unsubstituted furanyl. In embodiments, Ring A is an unsubstituted pyrrolyl. In embodiments, Ring A is an unsubstituted thienyl. In embodiments, Ring A is a two fused ring aryl. In embodiments, Ring A is a two fused ring heteroaryl.

[0189] In embodiments, Ring A is an unsubstituted aryl or heteroaryl. In embodiments, Ring A is an unsubstituted phenyl or 5 to 6 membered heteroaryl. In embodiments, Ring A is an unsubstituted phenyl. In embodiments, Ring A is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring A is an unsubstituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0190] In embodiments, Ring A is an unsubstituted phenyl. In embodiments, Ring A is an unsubstituted pyridyl. In embodiments, Ring A is an unsubstituted cyclohexyl. In embodiments, Ring A is an unsubstituted morpholinyl. In embodiments, Ring A is an unsubstituted piperazinyl. In embodiments, Ring A is an unsubstituted furanyl. In embodiments, Ring A is an unsubstituted thiazolyl. In embodiments, Ring A is an unsubstituted pyrazolyl. In embodiments, Ring A is an unsubstituted thienyl. In embodiments, Ring A is an unsubstituted pyrazinyl. In embodiments, Ring A is an unsubstituted pyrimidinyl. In embodiments, Ring A is an unsubstituted pyridazinyl. In embodiments, Ring A is an unsubstituted triazinyl. In

embodiments, Ring A is an unsubstituted tetrazinyl. In embodiments, Ring A is an unsubstituted tetrazolyl. In embodiments, Ring A is an unsubstituted triazolyl. In embodiments, Ring A is an unsubstituted quinolinyl. In embodiments, Ring A is an unsubstituted isoquinolinyl. In embodiments, Ring A is an unsubstituted quinazolinyl. In embodiments, Ring A is an unsubstituted quinoxalinyl. In embodiments, Ring A is an unsubstituted imidazolyl. In embodiments, Ring A is an unsubstituted oxazolyl. In embodiments, Ring A is an unsubstituted isoxazolyl. In embodiments, Ring A is an unsubstituted thiazolyl. In embodiments, Ring A is an unsubstituted piperidinyl. In embodiments, Ring A is an unsubstituted thiomorpholinyl. In embodiments, Ring A is an unsubstituted thianyl. In embodiments, Ring A is an unsubstituted oxanyl. In embodiments, Ring A is an unsubstituted tetrahydropuranyl. In embodiments, Ring A is an unsubstituted dihydropuranyl. In embodiments, Ring A is an unsubstituted dioxanyl. In embodiments, Ring A is an unsubstituted pyrazolyl. In embodiments, Ring A is an unsubstituted pyrrolyl. In embodiments, Ring A is an unsubstituted thienyl. In embodiments, Ring A is an unsubstituted benzofuranyl. In embodiments, Ring A is an unsubstituted indolyl. In embodiments, Ring A is an unsubstituted benzothienyl. In embodiments, Ring A is an unsubstituted benzimidazolyl. In embodiments, Ring A is an unsubstituted isobenzofuranyl. In embodiments, Ring A is an unsubstituted isoindolyl. In embodiments, Ring A is an unsubstituted benzo[c]thienyl. In embodiments, Ring A is an unsubstituted purinyl. In embodiments, Ring A is an unsubstituted indazolyl. In embodiments, Ring A is an unsubstituted benzoxazolyl. In embodiments, Ring A is an unsubstituted benzisoxazolyl. In embodiments, Ring A is an unsubstituted benzothiazolyl. In embodiments, Ring A is an unsubstituted cyclopentyl. In embodiments, Ring A is an unsubstituted cyclobutyl. In embodiments, Ring A is an unsubstituted 2-thienyl. In embodiments, Ring A is an unsubstituted 3-thienyl. In embodiments, Ring A is an unsubstituted 2-furanyl. In embodiments, Ring A is an unsubstituted 3-furanyl. In embodiments, Ring A is an unsubstituted 2-pyridyl. In embodiments, Ring A is an unsubstituted 3-pyridyl. In embodiments, Ring A is an unsubstituted 4-pyridyl. In embodiments, Ring A is an unsubstituted 3-pyrazolyl. In embodiments, Ring A is an unsubstituted 4-pyrazolyl. In embodiments, Ring A is an unsubstituted 5- pyrazolyl. In embodiments, Ring A is an unsubstituted 2-pyrrolyl. In embodiments, Ring A is an unsubstituted 3- pyrrolyl. In embodiments, Ring A is an unsubstituted 2-thiazolyl. In embodiments, Ring A is an unsubstituted 4-thiazolyl. In embodiments, Ring A is an unsubstituted 5-thiazolyl. In embodiments, Ring A is an unsubstituted 2-pyridyl. In embodiments, Ring A is an unsubstituted 3-pyridyl. In embodiments, Ring A is an unsubstituted 4-pyridyl. In embodiments, Ring A is an unsubstituted phenyl.

[0191] In embodiments, Ring B is substituted or unsubstituted a cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_3-C_8 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_3-C_7 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_3-C_6 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_3-C_5 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_3-C_4 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_4-C_8 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_5-C_8 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_6-C_8 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_5-C_6 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_3 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_4 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_5 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_6 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_7 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted C_8 cycloalkyl. In embodiments, Ring B is substituted or unsubstituted cyclopropyl. In embodiments, Ring B is substituted or unsubstituted cyclobutyl. In embodiments, Ring B is substituted or unsubstituted cyclopentyl. In embodiments, Ring B is substituted or unsubstituted cyclohexyl. In embodiments, Ring B is substituted or unsubstituted cycloheptyl. In embodiments, Ring B is substituted or unsubstituted a heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 3 to 7 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 3 to 4 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 4 to 8 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 5 to 8 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 6 to 8 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 3 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 4 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 5 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 6 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 7 membered heterocycloalkyl. In embodiments, Ring B is substituted or unsubstituted 8 membered heterocycloalkyl.

[0192] In embodiments, Ring B is substituted or unsubstituted aryl or heteroaryl. In embodiments, Ring B is substituted or unsubstituted aryl. In embodiments, Ring B is substituted or unsubstituted heteroaryl. In embodiments, Ring B is substituted or unsubstituted C_6-C_{10} aryl. In embodiments, Ring B is substituted or unsubstituted C_{10} aryl. In embodiments, Ring B is substituted or unsubstituted phenyl. In embodiments, Ring B is substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, Ring B is substituted or unsubstituted 5 to 9 membered heteroaryl. In embodiments, Ring B is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring B is substituted or unsubstituted 10 membered heteroaryl. In embodiments, Ring B is substituted or unsubstituted 9 membered heteroaryl. In embodiments, Ring B is substituted or unsubstituted 5 membered heteroaryl. In embodiments, Ring B is substituted or unsubstituted 6 membered heteroaryl. In embodiments, Ring B is substituted or unsubstituted phenyl. In embodiments, Ring B is substituted or unsubstituted pyridyl. In embodiments, Ring B is substituted or unsubstituted pyrazolyl. In embodiments, Ring B is substituted or unsubstituted imidazolyl. In embodiments, Ring B is substituted or unsubstituted oxazolyl. In embodiments, Ring B is substituted or unsubstituted isoxazolyl. In embodiments, Ring B is substituted or unsubstituted thiazolyl. In embodiments, Ring B is substituted or unsubstituted furanyl. In embodiments, Ring B is substituted or unsubstituted pyrrolyl. In embodiments, Ring B is substituted or unsubstituted thienyl. In embodiments, Ring B is a two fused ring aryl. In embodiments, Ring B is a two fused ring heteroaryl.

[0193] In embodiments, Ring B is substituted or unsubstituted aryl or heteroaryl. In embodiments, Ring B is substituted or unsubstituted phenyl or 5 to 6 membered heteroaryl. In embodiments, Ring B is substituted or unsubstituted phenyl. In embodiments, Ring B is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring B is substituted or unsubstituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0194] In embodiments, Ring B is substituted or unsubstituted phenyl. In embodiments, Ring B is substituted or unsubstituted pyridyl. In embodiments, Ring B is substituted or unsubstituted cyclohexyl. In embodiments, Ring B is substituted or unsubstituted morpholinyl. In embodiments, Ring B is substituted or unsubstituted piperazinyl. In embodiments, Ring B is substituted or unsubstituted furanyl. In embodiments, Ring B is substituted or unsubstituted thiazolyl. In embodiments, Ring B is substituted or unsubstituted pyrazolyl. In embodiments, Ring B is substituted or unsubstituted thienyl. In embodiments, Ring B is substituted or unsubstituted pyrazinyl. In embodiments, Ring B is substituted or unsubstituted pyrimidinyl. In

embodiments, Ring B is substituted or unsubstituted pyridazinyl. In embodiments, Ring B is substituted or unsubstituted triazinyl. In embodiments, Ring B is substituted or unsubstituted tetrazinyl. In embodiments, Ring B is substituted or unsubstituted tetrazolyl. In embodiments, Ring B is substituted or unsubstituted triazolyl. In embodiments, Ring B is substituted or unsubstituted quinolinyl. In embodiments, Ring B is substituted or unsubstituted isoquinolinyl. In embodiments, Ring B is substituted or unsubstituted quinazolinyl. In embodiments, Ring B is substituted or unsubstituted quinoxalinyl. In embodiments, Ring B is substituted or unsubstituted imidazolyl. In embodiments, Ring B is substituted or unsubstituted oxazolyl. In embodiments, Ring B is substituted or unsubstituted isoxazolyl. In embodiments, Ring B is substituted or unsubstituted thiazolyl. In embodiments, Ring B is substituted or unsubstituted piperidinyl. In embodiments, Ring B is substituted or unsubstituted thiomorpholinyl. In embodiments, Ring B is substituted or unsubstituted thianyl. In embodiments, Ring B is substituted or unsubstituted oxanyl. In embodiments, Ring B is substituted or unsubstituted tetrahydropuranyl. In embodiments, Ring B is substituted or unsubstituted dihydropuranyl. In embodiments, Ring B is substituted or unsubstituted dioxanyl. In embodiments, Ring B is substituted or unsubstituted pyrazolyl. In embodiments, Ring B is substituted or unsubstituted pyrrolyl. In embodiments, Ring B is substituted or unsubstituted thienyl. In embodiments, Ring B is substituted or unsubstituted benzofuranyl. In embodiments, Ring B is substituted or unsubstituted indolyl. In embodiments, Ring B is substituted or unsubstituted benzothienyl. In embodiments, Ring B is substituted or unsubstituted benzimidazolyl. In embodiments, Ring B is substituted or unsubstituted isobenzofuranyl. In embodiments, Ring B is substituted or unsubstituted isoindolyl. In embodiments, Ring B is substituted or unsubstituted benzo[c]thienyl. In embodiments, Ring B is substituted or unsubstituted purinyl. In embodiments, Ring B is substituted or unsubstituted indazolyl. In embodiments, Ring B is substituted or unsubstituted benzoxazolyl. In embodiments, Ring B is substituted or unsubstituted benzisoxazolyl. In embodiments, Ring B is substituted or unsubstituted benzothiazolyl. In embodiments, Ring B is substituted or unsubstituted cyclopentyl. In embodiments, Ring B is substituted or unsubstituted cyclobutyl. In embodiments, Ring B is substituted or unsubstituted 2-thienyl. In embodiments, Ring B is substituted or unsubstituted 3-thienyl. In embodiments, Ring B is substituted or unsubstituted 2-furanyl. In embodiments, Ring B is substituted or unsubstituted 3-furanyl. In embodiments, Ring B is substituted or unsubstituted 2-pyridyl. In embodiments, Ring B is substituted or unsubstituted 3-pyridyl. In embodiments, Ring B is substituted or unsubstituted 4-pyridyl. In embodiments, Ring B is substituted or unsubstituted 3-pyrazolyl. In embodiments, Ring B is substituted or unsubstituted

4-pyrazolyl. In embodiments, Ring B is substituted or unsubstituted 5- pyrazolyl. In embodiments, Ring B is substituted or unsubstituted 2-pyrrolyl. In embodiments, Ring B is substituted or unsubstituted 3- pyrrolyl. In embodiments, Ring B is substituted or unsubstituted 2-thiazolyl. In embodiments, Ring B is substituted or unsubstituted 4-thiazolyl. In embodiments, Ring B is substituted or unsubstituted 5-thiazolyl. In embodiments, Ring B is substituted or unsubstituted 2-pyridyl. In embodiments, Ring B is substituted or unsubstituted 3-pyridyl. In embodiments, Ring B is substituted or unsubstituted 4-pyridyl. In embodiments, Ring B is substituted or unsubstituted phenyl.

[0195] In embodiments, Ring B is an unsubstituted cycloalkyl. In embodiments, Ring B is an unsubstituted C_3-C_8 cycloalkyl. In embodiments, Ring B is an unsubstituted C_3-C_7 cycloalkyl. In embodiments, Ring B is an unsubstituted C_3-C_6 cycloalkyl. In embodiments, Ring B is an unsubstituted C_3-C_5 cycloalkyl. In embodiments, Ring B is an unsubstituted C_3-C_4 cycloalkyl. In embodiments, Ring B is an unsubstituted C_4-C_8 cycloalkyl. In embodiments, Ring B is an unsubstituted C_5-C_8 cycloalkyl. In embodiments, Ring B is an unsubstituted C_6-C_8 cycloalkyl. In embodiments, Ring B is an unsubstituted C_5-C_6 cycloalkyl. In embodiments, Ring B is an unsubstituted C_3 cycloalkyl. In embodiments, Ring B is an unsubstituted C_4 cycloalkyl. In embodiments, Ring B is an unsubstituted C_5 cycloalkyl. In embodiments, Ring B is an unsubstituted C_6 cycloalkyl. In embodiments, Ring B is an unsubstituted C_7 cycloalkyl. In embodiments, Ring B is an unsubstituted C_8 cycloalkyl. In embodiments, Ring B is an unsubstituted cyclopropyl. In embodiments, Ring B is an unsubstituted cyclobutyl. In embodiments, Ring B is an unsubstituted cyclopentyl. In embodiments, Ring B is an unsubstituted cyclohexyl. In embodiments, Ring B is an unsubstituted cycloheptyl. In embodiments, Ring B is an unsubstituted a heterocycloalkyl. In embodiments, Ring B is an unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 3 to 7 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 3 to 4 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 4 to 8 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 5 to 8 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 6 to 8 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 3 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 4 membered heterocycloalkyl. In embodiments, Ring

B is an unsubstituted 5 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 6 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 7 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted 8 membered heterocycloalkyl. In embodiments, Ring B is an unsubstituted aryl or unsubstituted heteroaryl. In embodiments, Ring B is an unsubstituted aryl. In embodiments, Ring B is an unsubstituted heteroaryl. In embodiments, Ring B is an unsubstituted C_6-C_{10} aryl. In embodiments, Ring B is an unsubstituted C_{10} aryl. In embodiments, Ring B is an unsubstituted phenyl. In embodiments, Ring B is an unsubstituted 5 to 10 membered heteroaryl. In embodiments, Ring B is an unsubstituted 5 to 9 membered heteroaryl. In embodiments, Ring B is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring B is an unsubstituted 10 membered heteroaryl. In embodiments, Ring B is an unsubstituted 9 membered heteroaryl. In embodiments, Ring B is an unsubstituted 5 membered heteroaryl. In embodiments, Ring B is an unsubstituted 6 membered heteroaryl. In embodiments, Ring B is an unsubstituted phenyl. In embodiments, Ring B is an unsubstituted pyridyl. In embodiments, Ring B is an unsubstituted pyrazolyl. In embodiments, Ring B is an unsubstituted imidazolyl. In embodiments, Ring B is an unsubstituted oxazolyl. In embodiments, Ring B is an unsubstituted isoxazolyl. In embodiments, Ring B is an unsubstituted thiazolyl. In embodiments, Ring B is an unsubstituted furanyl. In embodiments, Ring B is an unsubstituted pyrrolyl. In embodiments, Ring B is an unsubstituted thienyl. In embodiments, Ring B is an unsubstituted two fused ring aryl. In embodiments, Ring B is an unsubstituted two fused ring heteroaryl.

[0196] In embodiments, Ring B is an unsubstituted aryl or unsubstituted heteroaryl. In embodiments, Ring B is an unsubstituted phenyl or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring B is an unsubstituted phenyl. In embodiments, Ring B is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring B is an unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl.

[0197] In embodiments, Ring B is an unsubstituted phenyl. In embodiments, Ring B is an unsubstituted pyridyl. In embodiments, Ring B is an unsubstituted cyclohexyl. In embodiments, Ring B is an unsubstituted morpholinyl. In embodiments, Ring B is an unsubstituted piperazinyl. In embodiments, Ring B is an unsubstituted furanyl. In embodiments, Ring B is an unsubstituted thiazolyl. In embodiments, Ring B is an unsubstituted pyrazolyl. In embodiments, Ring B is an unsubstituted thienyl. In embodiments, Ring B is an unsubstituted pyrazinyl. In embodiments, Ring B is an unsubstituted pyrimidinyl. In embodiments, Ring B is an

unsubstituted pyridazinyl. In embodiments, Ring B is an unsubstituted triazinyl. In embodiments, Ring B is an unsubstituted tetrazinyl. In embodiments, Ring B is an unsubstituted tetrazolyl. In embodiments, Ring B is an unsubstituted triazolyl. In embodiments, Ring B is an unsubstituted quinolinyl. In embodiments, Ring B is an unsubstituted isoquinolinyl. In embodiments, Ring B is an unsubstituted quinazolinyl. In embodiments, Ring B is an unsubstituted quinoxalinyl. In embodiments, Ring B is an unsubstituted imidazolyl. In embodiments, Ring B is an unsubstituted oxazolyl. In embodiments, Ring B is an unsubstituted isoxazolyl. In embodiments, Ring B is an unsubstituted thiazolyl. In embodiments, Ring B is an unsubstituted piperidinyl. In embodiments, Ring B is an unsubstituted thiomorpholinyl. In embodiments, Ring B is an unsubstituted thianyl. In embodiments, Ring B is an unsubstituted oxanyl. In embodiments, Ring B is an unsubstituted tetrahydropuranyl. In embodiments, Ring B is an unsubstituted dihydropuranyl. In embodiments, Ring B is an unsubstituted dioxanyl. In embodiments, Ring B is an unsubstituted pyrazolyl. In embodiments, Ring B is an unsubstituted pyrrolyl. In embodiments, Ring B is an unsubstituted thienyl. In embodiments, Ring B is an unsubstituted benzofuranyl. In embodiments, Ring B is an unsubstituted indolyl. In embodiments, Ring B is an unsubstituted benzothienyl. In embodiments, Ring B is an unsubstituted benzimidazolyl. In embodiments, Ring B is an unsubstituted isobenzofuranyl. In embodiments, Ring B is an unsubstituted isoindolyl. In embodiments, Ring B is an unsubstituted benzo[c]thienyl. In embodiments, Ring B is an unsubstituted purinyl. In embodiments, Ring B is an unsubstituted indazolyl. In embodiments, Ring B is an unsubstituted benzoxazolyl. In embodiments, Ring B is an unsubstituted benzisoxazolyl. In embodiments, Ring B is an unsubstituted benzothiazolyl. In embodiments, Ring B is an unsubstituted cyclopentyl. In embodiments, Ring B is an unsubstituted cyclobutyl. In embodiments, Ring B is an unsubstituted 2-thienyl. In embodiments, Ring B is an unsubstituted 3-thienyl. In embodiments, Ring B is an unsubstituted 2-furanyl. In embodiments, Ring B is an unsubstituted 3-furanyl. In embodiments, Ring B is an unsubstituted 2-pyridyl. In embodiments, Ring B is an unsubstituted 3-pyridyl. In embodiments, Ring B is an unsubstituted 4-pyridyl. In embodiments, Ring B is an unsubstituted 3-pyrazolyl. In embodiments, Ring B is an unsubstituted 4-pyrazolyl. In embodiments, Ring B is an unsubstituted 5- pyrazolyl. In embodiments, Ring B is an unsubstituted 2-pyrrolyl. In embodiments, Ring B is an unsubstituted 3- pyrrolyl. In embodiments, Ring B is an unsubstituted 2-thiazolyl. In embodiments, Ring B is an unsubstituted 4-thiazolyl. In embodiments, Ring B is an unsubstituted 5-thiazolyl. It will be understood that an unsubstituted Ring B does not have substituents in addition to the bond to L^3 and bonds to any R^4 substituents.

[0198] In embodiments, Ring C is substituted or unsubstituted a cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_3-C_8 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_3-C_7 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_3-C_6 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_3-C_5 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_3-C_4 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_4-C_8 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_5-C_8 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_6-C_8 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_5-C_6 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_3 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_4 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_5 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_6 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_7 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted C_8 cycloalkyl. In embodiments, Ring C is substituted or unsubstituted cyclopropyl. In embodiments, Ring C is substituted or unsubstituted cyclobutyl. In embodiments, Ring C is substituted or unsubstituted cyclopentyl. In embodiments, Ring C is substituted or unsubstituted cyclohexyl. In embodiments, Ring C is substituted or unsubstituted cycloheptyl. In embodiments, Ring C is substituted or unsubstituted a heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 3 to 7 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 3 to 4 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 4 to 8 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 5 to 8 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 6 to 8 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 3 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 4 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 5 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 6 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 7 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted 8 membered heterocycloalkyl. In embodiments, Ring C is substituted or unsubstituted aryl or heteroaryl. In embodiments, Ring C is substituted or unsubstituted aryl. In embodiments, Ring C is substituted

or unsubstituted heteroaryl. In embodiments, Ring C is substituted or unsubstituted C_6-C_{10} aryl. In embodiments, Ring C is substituted or unsubstituted C_{10} aryl. In embodiments, Ring C is substituted or unsubstituted phenyl. In embodiments, Ring C is substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, Ring C is substituted or unsubstituted 5 to 9 membered heteroaryl. In embodiments, Ring C is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring C is substituted or unsubstituted 10 membered heteroaryl. In embodiments, Ring C is substituted or unsubstituted 9 membered heteroaryl. In embodiments, Ring C is substituted or unsubstituted 5 membered heteroaryl. In embodiments, Ring C is substituted or unsubstituted 6 membered heteroaryl. In embodiments, Ring C is substituted or unsubstituted phenyl. In embodiments, Ring C is substituted or unsubstituted pyridyl. In embodiments, Ring C is substituted or unsubstituted pyrazolyl. In embodiments, Ring C is substituted or unsubstituted imidazolyl. In embodiments, Ring C is substituted or unsubstituted oxazolyl. In embodiments, Ring C is substituted or unsubstituted is substituted or unsubstitutedoxazolyl. In embodiments, Ring C is substituted or unsubstituted thiazolyl. In embodiments, Ring C is substituted or unsubstituted furanyl. In embodiments, Ring C is substituted or unsubstituted pyrrolyl. In embodiments, Ring C is substituted or unsubstituted thienyl. In embodiments, Ring C is a two fused ring aryl. In embodiments, Ring C is a two fused ring heteroaryl.

[0199] In embodiments, Ring C is substituted or unsubstituted aryl or heteroaryl. In embodiments, Ring C is substituted or unsubstituted phenyl or 5 to 6 membered heteroaryl. In embodiments, Ring C is substituted or unsubstituted phenyl. In embodiments, Ring C is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring C is substituted or unsubstituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0200] In embodiments, Ring C is substituted or unsubstituted phenyl. In embodiments, Ring C is substituted or unsubstituted pyridyl. In embodiments, Ring C is substituted or unsubstituted cyclohexyl. In embodiments, Ring C is substituted or unsubstituted morpholinyl. In embodiments, Ring C is substituted or unsubstituted piperazinyl. In embodiments, Ring C is substituted or unsubstituted furanyl. In embodiments, Ring C is substituted or unsubstituted thiazolyl. In embodiments, Ring C is substituted or unsubstituted pyrazolyl. In embodiments, Ring C is substituted or unsubstituted thienyl. In embodiments, Ring C is substituted or unsubstituted pyrazinyl. In embodiments, Ring C is substituted or unsubstituted pyrimidinyl. In embodiments, Ring C is substituted or unsubstituted pyridazinyl. In embodiments, Ring C is

substituted or unsubstituted triazinyl. In embodiments, Ring C is substituted or unsubstituted tetrazinyl. In embodiments, Ring C is substituted or unsubstituted tetrazolyl. In embodiments, Ring C is substituted or unsubstituted triazolyl. In embodiments, Ring C is substituted or unsubstituted quinolinyl. In embodiments, Ring C is substituted or unsubstituted isoquinolinyl. In embodiments, Ring C is substituted or unsubstituted quinazolinyl. In embodiments, Ring C is substituted or unsubstituted quinoxalinyl. In embodiments, Ring C is substituted or unsubstituted imidazolyl. In embodiments, Ring C is substituted or unsubstituted oxazolyl. In embodiments, Ring C is substituted or unsubstituted isoxazolyl. In embodiments, Ring C is substituted or unsubstituted thiazolyl. In embodiments, Ring C is substituted or unsubstituted piperidinyl. In embodiments, Ring C is substituted or unsubstituted thiomorpholinyl. In embodiments, Ring C is substituted or unsubstituted thianyl. In embodiments, Ring C is substituted or unsubstituted oxanyl. In embodiments, Ring C is substituted or unsubstituted tetrahydropuranyl. In embodiments, Ring C is substituted or unsubstituted dihydropuranyl. In embodiments, Ring C is substituted or unsubstituted dioxanyl. In embodiments, Ring C is substituted or unsubstituted pyrazolyl. In embodiments, Ring C is substituted or unsubstituted pyrrolyl. In embodiments, Ring C is substituted or unsubstituted thienyl. In embodiments, Ring C is substituted or unsubstituted benzofuranyl. In embodiments, Ring C is substituted or unsubstituted indolyl. In embodiments, Ring C is substituted or unsubstituted benzothienyl. In embodiments, Ring C is substituted or unsubstituted benzimidazolyl. In embodiments, Ring C is substituted or unsubstituted isobenzofuranyl. In embodiments, Ring C is substituted or unsubstituted isoindolyl. In embodiments, Ring C is substituted or unsubstituted benzo[c]thienyl. In embodiments, Ring C is substituted or unsubstituted purinyl. In embodiments, Ring C is substituted or unsubstituted indazolyl. In embodiments, Ring C is substituted or unsubstituted benzoxazolyl. In embodiments, Ring C is substituted or unsubstituted benzisoxazolyl. In embodiments, Ring C is substituted or unsubstituted benzothiazolyl. In embodiments, Ring C is substituted or unsubstituted cyclopentyl. In embodiments, Ring C is substituted or unsubstituted cyclobutyl. In embodiments, Ring C is substituted or unsubstituted 2-thienyl. In embodiments, Ring C is substituted or unsubstituted 3-thienyl. In embodiments, Ring C is substituted or unsubstituted 2-furanyl. In embodiments, Ring C is substituted or unsubstituted 3-furanyl. In embodiments, Ring C is substituted or unsubstituted 2-pyridyl. In embodiments, Ring C is substituted or unsubstituted 3-pyridyl. In embodiments, Ring C is substituted or unsubstituted 4-pyridyl. In embodiments, Ring C is substituted or unsubstituted 3-pyrazolyl. In embodiments, Ring C is substituted or unsubstituted 4-pyrazolyl. In embodiments, Ring C is substituted or unsubstituted 5- pyrazolyl. In

embodiments, Ring C is substituted or unsubstituted 2-pyrrolyl. In embodiments, Ring C is substituted or unsubstituted 3- pyrrolyl. In embodiments, Ring C is substituted or unsubstituted 2-thiazolyl. In embodiments, Ring C is substituted or unsubstituted 4-thiazolyl. In embodiments, Ring C is substituted or unsubstituted 5-thiazolyl. In embodiments, Ring C is substituted or unsubstituted 2-pyridyl. In embodiments, Ring C is substituted or unsubstituted 3-pyridyl. In embodiments, Ring C is substituted or unsubstituted 4-pyridyl. In embodiments, Ring C is substituted or unsubstituted phenyl.

[0201] In embodiments, Ring C is an unsubstituted cycloalkyl. In embodiments, Ring C is an unsubstituted C_3-C_8 cycloalkyl. In embodiments, Ring C is an unsubstituted C_3-C_7 cycloalkyl. In embodiments, Ring C is an unsubstituted C_3-C_6 cycloalkyl. In embodiments, Ring C is an unsubstituted C_3-C_5 cycloalkyl. In embodiments, Ring C is an unsubstituted C_3-C_4 cycloalkyl. In embodiments, Ring C is an unsubstituted C_4-C_8 cycloalkyl. In embodiments, Ring C is an unsubstituted C_5-C_8 cycloalkyl. In embodiments, Ring C is an unsubstituted C_6-C_8 cycloalkyl. In embodiments, Ring C is an unsubstituted C_5-C_6 cycloalkyl. In embodiments, Ring C is an unsubstituted C_3 cycloalkyl. In embodiments, Ring C is an unsubstituted C_4 cycloalkyl. In embodiments, Ring C is an unsubstituted C_5 cycloalkyl. In embodiments, Ring C is an unsubstituted C_6 cycloalkyl. In embodiments, Ring C is an unsubstituted C_7 cycloalkyl. In embodiments, Ring C is an unsubstituted C_8 cycloalkyl. In embodiments, Ring C is an unsubstituted cyclopropyl. In embodiments, Ring C is an unsubstituted cyclobutyl. In embodiments, Ring C is an unsubstituted cyclopentyl. In embodiments, Ring C is an unsubstituted cyclohexyl. In embodiments, Ring C is an unsubstituted cycloheptyl. In embodiments, Ring C is an unsubstituted a heterocycloalkyl. In embodiments, Ring C is an unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 3 to 7 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 3 to 4 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 4 to 8 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 5 to 8 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 6 to 8 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 3 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 4 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 5 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted

6 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 7 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted 8 membered heterocycloalkyl. In embodiments, Ring C is an unsubstituted aryl or unsubstituted heteroaryl. In embodiments, Ring C is an unsubstituted aryl. In embodiments, Ring C is an unsubstituted heteroaryl. In embodiments, Ring C is an unsubstituted C_6-C_{10} aryl. In embodiments, Ring C is an unsubstituted C_{10} aryl. In embodiments, Ring C is an unsubstituted phenyl. In embodiments, Ring C is an unsubstituted 5 to 10 membered heteroaryl. In embodiments, Ring C is an unsubstituted 5 to 9 membered heteroaryl. In embodiments, Ring C is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring C is an unsubstituted 10 membered heteroaryl. In embodiments, Ring C is an unsubstituted 9 membered heteroaryl. In embodiments, Ring C is an unsubstituted 5 membered heteroaryl. In embodiments, Ring C is an unsubstituted 6 membered heteroaryl. In embodiments, Ring C is an unsubstituted phenyl. In embodiments, Ring C is an unsubstituted pyridyl. In embodiments, Ring C is an unsubstituted pyrazolyl. In embodiments, Ring C is an unsubstituted imidazolyl. In embodiments, Ring C is an unsubstituted oxazolyl. In embodiments, Ring C is an unsubstituted isoxazolyl. In embodiments, Ring C is an unsubstituted thiazolyl. In embodiments, Ring C is an unsubstituted furanyl. In embodiments, Ring C is an unsubstituted pyrrolyl. In embodiments, Ring C is an unsubstituted thienyl. In embodiments, Ring C is an unsubstituted two fused ring aryl. In embodiments, Ring C is an unsubstituted two fused ring heteroaryl.

[0202] In embodiments, Ring C is an unsubstituted aryl or unsubstituted heteroaryl. In embodiments, Ring C is an unsubstituted phenyl or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring C is an unsubstituted phenyl. In embodiments, Ring C is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring C is an unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl.

[0203] In embodiments, Ring C is an unsubstituted phenyl. In embodiments, Ring C is an unsubstituted pyridyl. In embodiments, Ring C is an unsubstituted cyclohexyl. In embodiments, Ring C is an unsubstituted morpholinyl. In embodiments, Ring C is an unsubstituted piperazinyl. In embodiments, Ring C is an unsubstituted furanyl. In embodiments, Ring C is an unsubstituted thiazolyl. In embodiments, Ring C is an unsubstituted pyrazolyl. In embodiments, Ring C is an unsubstituted thienyl. In embodiments, Ring C is an unsubstituted pyrazinyl. In embodiments, Ring C is an unsubstituted pyrimidinyl. In embodiments, Ring C is an unsubstituted pyridazinyl. In embodiments, Ring C is an unsubstituted triazinyl. In

embodiments, Ring C is an unsubstituted tetrazinyl. In embodiments, Ring C is an unsubstituted tetrazolyl. In embodiments, Ring C is an unsubstituted triazolyl. In embodiments, Ring C is an unsubstituted quinolinyl. In embodiments, Ring C is an unsubstituted isoquinolinyl. In embodiments, Ring C is an unsubstituted quinazolinyl. In embodiments, Ring C is an unsubstituted quinoxalinyl. In embodiments, Ring C is an unsubstituted imidazolyl. In embodiments, Ring C is an unsubstituted oxazolyl. In embodiments, Ring C is an unsubstituted isoxazolyl. In embodiments, Ring C is an unsubstituted thiazolyl. In embodiments, Ring C is an unsubstituted piperidinyl. In embodiments, Ring C is an unsubstituted thiomorpholinyl. In embodiments, Ring C is an unsubstituted thianyl. In embodiments, Ring C is an unsubstituted oxanyl. In embodiments, Ring C is an unsubstituted tetrahydropuranyl. In embodiments, Ring C is an unsubstituted dihydropuranyl. In embodiments, Ring C is an unsubstituted dioxanyl. In embodiments, Ring C is an unsubstituted pyrazolyl. In embodiments, Ring C is an unsubstituted pyrrolyl. In embodiments, Ring C is an unsubstituted thienyl. In embodiments, Ring C is an unsubstituted benzofuranyl. In embodiments, Ring C is an unsubstituted indolyl. In embodiments, Ring C is an unsubstituted benzothienyl. In embodiments, Ring C is an unsubstituted benzimidazolyl. In embodiments, Ring C is an unsubstituted isobenzofuranyl. In embodiments, Ring C is an unsubstituted isoindolyl. In embodiments, Ring C is an unsubstituted benzo[c]thienyl. In embodiments, Ring C is an unsubstituted purinyl. In embodiments, Ring C is an unsubstituted indazolyl. In embodiments, Ring C is an unsubstituted benzoxazolyl. In embodiments, Ring C is an unsubstituted benzisoxazolyl. In embodiments, Ring C is an unsubstituted benzothiazolyl. In embodiments, Ring C is an unsubstituted cyclopentyl. In embodiments, Ring C is an unsubstituted cyclobutyl. In embodiments, Ring C is an unsubstituted 2-thienyl. In embodiments, Ring C is an unsubstituted 3-thienyl. In embodiments, Ring C is an unsubstituted 2-furanyl. In embodiments, Ring C is an unsubstituted 3-furanyl. In embodiments, Ring C is an unsubstituted 2-pyridyl. In embodiments, Ring C is an unsubstituted 3-pyridyl. In embodiments, Ring C is an unsubstituted 4-pyridyl. In embodiments, Ring C is an unsubstituted 3-pyrazolyl. In embodiments, Ring C is an unsubstituted 4-pyrazolyl. In embodiments, Ring C is an unsubstituted 5- pyrazolyl. In embodiments, Ring C is an unsubstituted 2-pyrrolyl. In embodiments, Ring C is an unsubstituted 3- pyrrolyl. In embodiments, Ring C is an unsubstituted 2-thiazolyl. In embodiments, Ring C is an unsubstituted 4-thiazolyl. In embodiments, Ring C is an unsubstituted 5-thiazolyl.

[0204] In embodiments, R^1 is $-L^1-L^2-E$, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R^1 is hydrogen. In embodiments, R^1 is substituted or

unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R^1 is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is substituted or unsubstituted phenyl. In embodiments, R^1 is an unsubstituted phenyl. In embodiments, R^1 is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, or substituted or unsubstituted thiazolyl. In embodiments, R^1 is an unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl. In embodiments, R^1 is $-L^1$-L^2-E.

[0205] In embodiments, R^1 is substituted phenyl. In embodiments, R^1 is substituted pyridyl. In embodiments, R^1 is substituted cyclohexyl. In embodiments, R^1 is substituted morpholinyl. In embodiments, R^1 is substituted piperazinyl. In embodiments, R^1 is substituted furanyl. In embodiments, R^1 is substituted thiazolyl. In embodiments, R^1 is substituted pyrazolyl. In embodiments, R^1 is substituted thienyl. In embodiments, R^1 is substituted pyrazinyl. In embodiments, R^1 is substituted pyrimidinyl. In embodiments, R^1 is substituted pyridazinyl. In embodiments, R^1 is substituted triazinyl. In embodiments, R^1 is substituted tetrazinyl. In embodiments, R^1 is substituted tetrazolyl. In embodiments, R^1 is substituted triazolyl. In embodiments, R^1 is substituted quinolinyl. In embodiments, R^1 is substituted isoquinolinyl. In embodiments, R^1 is substituted quinazolinyl. In embodiments, R^1 is substituted quinoxalinyl. In embodiments, R^1 is substituted imidazolyl. In embodiments, R^1 is substituted oxazolyl. In embodiments, R^1 is substituted isoxazolyl. In embodiments, R^1 is substituted thiazolyl. In embodiments, R^1 is substituted piperidinyl. In embodiments, R^1 is substituted thiomorpholinyl. In embodiments, R^1 is substituted thianyl. In embodiments, R^1 is substituted oxanyl. In embodiments, R^1 is substituted tetrahydropuranyl. In embodiments, R^1 is substituted dihydropuranyl. In embodiments, R^1 is substituted dioxanyl. In embodiments, R^1 is substituted pyrazolyl. In embodiments, R^1 is substituted pyrrolyl. In embodiments, R^1 is substituted thienyl. In embodiments, R^1 is substituted benzofuranyl. In embodiments, R^1 is substituted indolyl. In embodiments, R^1 is substituted benzothienyl. In embodiments, R^1 is substituted benzimidazolyl. In embodiments, R^1 is substituted isobenzofuranyl. In embodiments, R^1 is substituted isoindolyl. In embodiments, R^1 is substituted benzo[c]thienyl. In embodiments, R^1 is substituted purinyl. In

embodiments, R^1 is substituted indazolyl. In embodiments, R^1 is substituted benzoxazolyl. In embodiments, R^1 is substituted benzisoxazolyl. In embodiments, R^1 is substituted benzothiazolyl. In embodiments, R^1 is substituted cyclopentyl. In embodiments, R^1 is substituted cyclobutyl. In embodiments, R^1 is substituted naphthyl. In embodiments, R^1 is substituted 1-naphthyl. In embodiments, R^1 is substituted 2-naphthyl. In embodiments, R^1 is hydrogen. In embodiments, R^1 is substituted 2-thienyl. In embodiments, R^1 is substituted 3-thienyl. In embodiments, R^1 is substituted 2-furanyl. In embodiments, R^1 is substituted 3-furanyl. In embodiments, R^1 is substituted 2-pyridyl. In embodiments, R^1 is substituted 3-pyridyl. In embodiments, R^1 is substituted 4-pyridyl. In embodiments, R^1 is substituted 3-pyrazolyl. In embodiments, R^1 is substituted 4-pyrazolyl. In embodiments, R^1 is substituted 5-pyrazolyl. In embodiments, R^1 is substituted 2-pyrrolyl. In embodiments, R^1 is substituted 3-pyrrolyl.

[0206] In embodiments, R^1 is R^{20}-substituted phenyl. In embodiments, R^1 is R^{20}-substituted pyridyl. In embodiments, R^1 is R^{20}-substituted cyclohexyl. In embodiments, R^1 is R^{20}-substituted morpholinyl. In embodiments, R^1 is R^{20}-substituted piperazinyl. In embodiments, R^1 is R^{20}-substituted furanyl. In embodiments, R^1 is R^{20}-substituted thiazolyl. In embodiments, R^1 is R^{20}-substituted pyrazolyl. In embodiments, R^1 is R^{20}-substituted thienyl. In embodiments, R^1 is R^{20}-substituted pyrazinyl. In embodiments, R^1 is R^{20}-substituted pyrimidinyl. In embodiments, R^1 is R^{20}-substituted pyridazinyl. In embodiments, R^1 is R^{20}-substituted triazinyl. In embodiments, R^1 is R^{20}-substituted tetrazinyl. In embodiments, R^1 is R^{20}-substituted tetrazolyl. In embodiments, R^1 is R^{20}-substituted triazolyl. In embodiments, R^1 is R^{20}-substituted quinolinyl. In embodiments, R^1 is R^{20}-substituted isoquinolinyl. In embodiments, R^1 is R^{20}-substituted quinazolinyl. In embodiments, R^1 is R^{20}-substituted quinoxalinyl. In embodiments, R^1 is R^{20}-substituted imidazolyl. In embodiments, R^1 is R^{20}-substituted oxazolyl. In embodiments, R^1 is R^{20}-substituted isoxazolyl. In embodiments, R^1 is R^{20}-substituted thiazolyl. In embodiments, R^1 is R^{20}-substituted piperidinyl. In embodiments, R^1 is R^{20}-substituted thiomorpholinyl. In embodiments, R^1 is R^{20}-substituted thianyl. In embodiments, R^1 is R^{20}-substituted oxanyl. In embodiments, R^1 is R^{20}-substituted tetrahydropuranyl. In embodiments, R^1 is R^{20}-substituted dihydropuranyl. In embodiments, R^1 is R^{20}-substituted dioxanyl. In embodiments, R^1 is R^{20}-substituted pyrazolyl. In embodiments, R^1 is R^{20}-substituted pyrrolyl. In embodiments, R^1 is R^{20}-substituted thienyl. In embodiments, R^1 is R^{20}-substituted benzofuranyl. In embodiments, R^1 is R^{20}-substituted indolyl. In embodiments, R^1 is R^{20}-substituted benzothienyl. In embodiments, R^1 is R^{20}-substituted benzimidazolyl. In

embodiments, R^1 is R^{20}-substituted isobenzofuranyl. In embodiments, R^1 is R^{20}-substituted isoindolyl. In embodiments, R^1 is R^{20}-substituted benzo[c]thienyl. In embodiments, R^1 is R^{20}-substituted purinyl. In embodiments, R^1 is R^{20}-substituted indazolyl. In embodiments, R^1 is R^{20}-substituted benzoxazolyl. In embodiments, R^1 is R^{20}-substituted benzisoxazolyl. In embodiments, R^1 is R^{20}-substituted benzothiazolyl. In embodiments, R^1 is R^{20}-substituted cyclopentyl. In embodiments, R^1 is R^{20}-substituted cyclobutyl. In embodiments, R^1 is R^{20}-substituted naphthyl. In embodiments, R^1 is R^{20}-substituted 1-naphthyl. In embodiments, R^1 is R^{20}-substituted 2-naphthyl. In embodiments, R^1 is R^{20}-substituted 2-thienyl. In embodiments, R^1 is R^{20}-substituted 3-thienyl. In embodiments, R^1 is R^{20}-substituted 2-furanyl. In embodiments, R^1 is R^{20}-substituted 3-furanyl. In embodiments, R^1 is R^{20}-substituted 2-pyridyl. In embodiments, R^1 is R^{20}-substituted 3-pyridyl. In embodiments, R^1 is R^{20}-substituted 4-pyridyl. In embodiments, R^1 is R^{20}-substituted 3-pyrazolyl. In embodiments, R^1 is R^{20}-substituted 4-pyrazolyl. In embodiments, R^1 is R^{20}-substituted 5- pyrazolyl. In embodiments, R^1 is R^{20}-substituted 2-pyrrolyl. In embodiments, R^1 is R^{20}-substituted 3-pyrrolyl.

[0207] In embodiments, R^1 is an unsubstituted phenyl. In embodiments, R^1 is an unsubstituted pyridyl. In embodiments, R^1 is an unsubstituted cyclohexyl. In embodiments, R^1 is an unsubstituted morpholinyl. In embodiments, R^1 is an unsubstituted piperazinyl. In embodiments, R^1 is an unsubstituted furanyl. In embodiments, R^1 is an unsubstituted thiazolyl. In embodiments, R^1 is an unsubstituted pyrazolyl. In embodiments, R^1 is an unsubstituted thienyl. In embodiments, R^1 is an unsubstituted pyrazinyl. In embodiments, R^1 is an unsubstituted pyrimidinyl. In embodiments, R^1 is an unsubstituted pyridazinyl. In embodiments, R^1 is an unsubstituted triazinyl. In embodiments, R^1 is an unsubstituted tetrazinyl. In embodiments, R^1 is an unsubstituted tetrazolyl. In embodiments, R^1 is an unsubstituted triazolyl. In embodiments, R^1 is an unsubstituted quinolinyl. In embodiments, R^1 is an unsubstituted isoquinolinyl. In embodiments, R^1 is an unsubstituted quinazolinyl. In embodiments, R^1 is an unsubstituted quinoxalinyl. In embodiments, R^1 is an unsubstituted imidazolyl. In embodiments, R^1 is an unsubstituted oxazolyl. In embodiments, R^1 is an unsubstituted isoxazolyl. In embodiments, R^1 is an unsubstituted thiazolyl. In embodiments, R^1 is an unsubstituted piperidinyl. In embodiments, R^1 is an unsubstituted thiomorpholinyl. In embodiments, R^1 is an unsubstituted thianyl. In embodiments, R^1 is an unsubstituted oxanyl. In embodiments, R^1 is an unsubstituted tetrahydropuranyl. In embodiments, R^1 is an unsubstituted dihydropuranyl. In embodiments, R^1 is an unsubstituted dioxanyl. In embodiments, R^1 is an unsubstituted pyrazolyl. In embodiments, R^1 is an unsubstituted pyrrolyl. In embodiments, R^1 is

an unsubstituted thienyl. In embodiments, R^1 is an unsubstituted benzofuranyl. In embodiments, R^1 is an unsubstituted indolyl. In embodiments, R^1 is an unsubstituted benzothienyl. In embodiments, R^1 is an unsubstituted benzimidazolyl. In embodiments, R^1 is an unsubstituted isobenzofuranyl. In embodiments, R^1 is an unsubstituted isoindolyl. In embodiments, R^1 is an unsubstituted benzo[c]thienyl. In embodiments, R^1 is an unsubstituted purinyl. In embodiments, R^1 is an unsubstituted indazolyl. In embodiments, R^1 is an unsubstituted benzoxazolyl. In embodiments, R^1 is an unsubstituted benzisoxazolyl. In embodiments, R^1 is an unsubstituted benzothiazolyl. In embodiments, R^1 is an unsubstituted cyclopentyl. In embodiments, R^1 is an unsubstituted cyclobutyl. In embodiments, R^1 is an unsubstituted naphthyl. In embodiments, R^1 is an unsubstituted 1-naphthyl. In embodiments, R^1 is an unsubstituted 2-naphthyl. In embodiments, R^1 is an unsubstituted 2-thienyl. In embodiments, R^1 is an unsubstituted 3-thienyl. In embodiments, R^1 is an unsubstituted 2-furanyl. In embodiments, R^1 is an unsubstituted 3-furanyl. In embodiments, R^1 is an unsubstituted 2-pyridyl. In embodiments, R^1 is an unsubstituted 3-pyridyl. In embodiments, R^1 is an unsubstituted 4-pyridyl. In embodiments, R^1 is an unsubstituted 3-pyrazolyl. In embodiments, R^1 is an unsubstituted 4-pyrazolyl. In embodiments, R^1 is an unsubstituted 5- pyrazolyl. In embodiments, R^1 is an unsubstituted 2-pyrrolyl. In embodiments, R^1 is an unsubstituted 3-pyrrolyl.

[0208] In embodiments, R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R^1 is substituted aryl. In embodiments, R^1 is an unsubstituted aryl. In embodiments, R^1 is substituted C_6-C_{10} aryl. In embodiments, R^1 is an unsubstituted C_6-C_{10} aryl. In embodiments, R^1 is substituted phenyl. In embodiments, R^1 is an unsubstituted phenyl. In embodiments, R^1 is substituted heteroaryl. In embodiments, R^1 is an unsubstituted heteroaryl. In embodiments, R^1 is substituted 5 to 10 membered heteroaryl. In embodiments, R^1 is substituted 5 to 9 membered heteroaryl. In embodiments, R^1 is an unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^1 is an unsubstituted 5 to 9 membered heteroaryl. In embodiments, R^1 is substituted 5 to 6 membered heteroaryl. In embodiments, R^1 is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is substituted 9 membered heteroaryl. In embodiments, R^1 is substituted 10 membered heteroaryl. In embodiments, R^1 is an unsubstituted 9 membered heteroaryl. In embodiments, R^1 is an unsubstituted 10 membered heteroaryl. In embodiments, R^1 is substituted 5 membered heteroaryl. In embodiments, R^1 is substituted 6 membered heteroaryl. In embodiments, R^1 is an unsubstituted 5 membered heteroaryl. In embodiments, R^1 is an unsubstituted 6 membered heteroaryl.

[0209] In embodiments, R^1 is substituted or unsubstituted pyrazolyl. In embodiments, R^1 is substituted or unsubstituted pyridyl. In embodiments, R^1 is substituted or unsubstituted imidazolyl. In embodiments, R^1 is substituted or unsubstituted oxazolyl. In embodiments, R^1 is substituted or unsubstituted isoxazolyl. In embodiments, R^1 is substituted or unsubstituted thiazolyl. In embodiments, R^1 is substituted or unsubstituted furanyl. In embodiments, R^1 is substituted or unsubstituted pyrrolyl. In embodiments, R^1 is substituted or unsubstituted thienyl. In embodiments, R^1 is substituted pyrazolyl. In embodiments, R^1 is substituted pyridyl. In embodiments, R^1 is substituted imidazolyl. In embodiments, R^1 is substituted oxazolyl. In embodiments, R^1 is substituted isoxazolyl. In embodiments, R^1 is substituted thiazolyl. In embodiments, R^1 is substituted furanyl. In embodiments, R^1 is substituted pyrrolyl. In embodiments, R^1 is substituted thienyl.

[0210] In embodiments, R^1 is an unsubstituted pyrazolyl. In embodiments, R^1 is an unsubstituted pyridyl. In embodiments, R^1 is an unsubstituted imidazolyl. In embodiments, R^1 is an unsubstituted oxazolyl. In embodiments, R^1 is an unsubstituted isoxazolyl. In embodiments, R^1 is an unsubstituted thiazolyl. In embodiments, R^1 is an unsubstituted furanyl. In embodiments, R^1 is an unsubstituted pyrrolyl. In embodiments, R^1 is an unsubstituted thienyl.

[0211] In embodiments, R^1 is a methyl-substituted pyrazolyl. In embodiments, R^1 is a methyl-substituted pyridyl. In embodiments, R^1 is methyl-substituted imidazolyl. In embodiments, R^1 is a methyl-substituted oxazolyl. In embodiments, R^1 is a methyl-substituted isoxazolyl. In embodiments, R^1 is a methyl-substituted thiazolyl. In embodiments, R^1 is a methyl-substituted furanyl. In embodiments, R^1 is a methyl-substituted pyrrolyl. In embodiments, R^1 is a methyl-substituted thienyl.

[0212] In embodiments, R^1 is independently R^{20}-substituted or unsubstituted aryl or R^{20}-substituted or unsubstituted heteroaryl. In embodiments, R^1 is independently R^{20}-substituted or unsubstituted phenyl or R^{20}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^1 is –F, -Cl, -Br, or –I.

[0213] In embodiments, R^{20} is $-C(O)CH_3$. In embodiments, R^{20} is $-CH_3$. In embodiments, R^{20} is $-C(O)CH_2CH_3$. In embodiments, R^{20} is $-C(O)CH(CH_3)_2$. In embodiments, R^{20} is an unsubstituted methyl. In embodiments, R^{20} is $-C(O)N(CH_3)_2$. In embodiments, R^{20} is –CN. In embodiments, R^{20} is an unsubstituted methoxy. In embodiments, R^{20} is an unsubstituted tert-butyl. In embodiments, R^{20} is –OH. In embodiments, R^{20} is an unsubstituted ethoxy. In embodiments, R^{20} is $-N(CH_3)_2$. In embodiments, R^{20} is –SH. In embodiments, R^{20} is $-SCH_3$. In

embodiments, R^{20} is $-SCH_2CH_3$. In embodiments, R^{20} is an unsubstituted ethyl. In embodiments, R^{20} is an unsubstituted propyl. In embodiments, R^{20} is an unsubstituted isopropyl. In embodiments, R^{20} is an unsubstituted butyl. In embodiments, R^{20} is an unsubstituted isobutyl. In embodiments, R^{20} is $-NH_2$. In embodiments, R^{20} is $-NHCH_3$. In embodiments, R^{20} is $-NHCH_2CH_3$. In embodiments, R^{20} is $-N(CH_2CH_3)_2$. In embodiments, R^{20} is $-N(CH_3)(CH_2CH_3)$. In embodiments, R^{20} is halogen. In embodiments, R^{20} is $-F$. In embodiments, R^{20} is $-Cl$. In embodiments, R^{20} is $-I$. In embodiments, R^{20} is $-Br$. In embodiments, R^{20} is $-C(O)NH_2$. In embodiments, R^{20} is $-C(O)NHCH_3$. In embodiments, R^{20} is $-C(O)NHCH_2CH_3$. In embodiments, R^{20} is $-C(O)N(CH_2CH_3)_2$. In embodiments, R^{20} is $-C(O)N(CH_3)(CH_2CH_3)$. In embodiments, R^{20} is independently oxo. In embodiments, R^{20} is independently halogen. In embodiments, R^{20} is independently $-CX^{20}_3$. In embodiments, R^{20} is independently -CN. In embodiments, R^{20} is independently -OH. In embodiments, R^{20} is independently $-NH_2$. In embodiments, R^{20} is independently -COOH. In embodiments, R^{20} is independently $-CONH_2$. In embodiments, R^{20} is independently $-NO_2$. In embodiments, R^{20} is independently -SH. In embodiments, R^{20} is independently $-SO_3H$. In embodiments, R^{20} is independently $-SO_4H$. In embodiments, R^{20} is independently $-SO_2NH_2$. In embodiments, R^{20} is independently $-NHNH_2$. In embodiments, R^{20} is independently $-ONH_2$. In embodiments, R^{20} is independently $-NHC(O)NHNH_2$. In embodiments, R^{20} is independently $-NHC(O)NH_2$. In embodiments, R^{20} is independently $-NHSO_2H$. In embodiments, R^{20} is independently -NHC(O)H. In embodiments, R^{20} is independently -NHC(O)OH. In embodiments, R^{20} is independently -NHOH. In embodiments, R^{20} is independently $-OCX^{20}_3$. In embodiments, R^{20} is independently $-OCHX^{20}_2$. In embodiments, R^{20} is independently $-CF_3$.

[0214] R^{20} is independently oxo, halogen, $-CX^{20}_3$, $-CHX^{20}_2$, $-CH_2X^{20}$, $-OCX^{20}_3$, $-OCHX^{20}_2$, $-OCH_2X^{20}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{21}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{21}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{21}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{21}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{21}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{21}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{20} is $-F$, -Cl, -Br, or $-I$.

[0215] R^{21} is independently oxo, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCHX^{21}_2$, $-OCH_2X^{21}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{22}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{22}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{22}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{22}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{22}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{22}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{21} is –F, -Cl, -Br, or –I.

[0216] R^{22} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0217] In embodiments, R^1 is R^{20}-substituted or unsubstituted aryl or R^{20}-substituted or unsubstituted heteroaryl. In embodiments, R^1 is R^{20}-substituted aryl. In embodiments, R^1 is an unsubstituted aryl. In embodiments, R^1 is R^{20}-substituted C_6-C_{10} aryl. In embodiments, R^1 is an unsubstituted C_6-C_{10} aryl. In embodiments, R^1 is R^{20}-substituted phenyl. In embodiments, R^1 is an unsubstituted phenyl. In embodiments, R^1 is R^{20}-substituted heteroaryl. In embodiments, R^1 is an unsubstituted heteroaryl. In embodiments, R^1 is R^{20}-substituted 5 to 10 membered heteroaryl. In embodiments, R^1 is R^{20}-substituted 5 to 9 membered heteroaryl. In embodiments, R^1 is an unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^1 is an unsubstituted 5 to 9 membered heteroaryl. In embodiments, R^1 is R^{20}-substituted 5 to 6 membered heteroaryl. In embodiments, R^1 is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is R^{20}-substituted 9 membered heteroaryl. In embodiments, R^1 is R^{20}-substituted 10 membered heteroaryl. In embodiments, R^1 is an unsubstituted 9 membered heteroaryl. In embodiments, R^1 is an unsubstituted 10 membered heteroaryl. In embodiments, R^1 is R^{20}-substituted 5 membered

heteroaryl. In embodiments, R^1 is R^{20}-substituted 6 membered heteroaryl. In embodiments, R^1 is an unsubstituted 5 membered heteroaryl. In embodiments, R^1 is an unsubstituted 6 membered heteroaryl.

[0218] In embodiments, R^1 is R^{20}-substituted or unsubstituted pyrazolyl. In embodiments, R^1 is R^{20}-substituted or unsubstituted pyridyl. In embodiments, R^1 is R^{20}-substituted or unsubstituted imidazolyl. In embodiments, R^1 is R^{20}-substituted or unsubstituted oxazolyl. In embodiments, R^1 is R^{20}-substituted or unsubstituted isoxazolyl. In embodiments, R^1 is R^{20}-substituted or unsubstituted thiazolyl. In embodiments, R^1 is R^{20}-substituted or unsubstituted furanyl. In embodiments, R^1 is R^{20}-substituted or unsubstituted pyrrolyl. In embodiments, R^1 is R^{20}-substituted or unsubstituted thienyl.

[0219] In embodiments, R^1 is R^{20}-substituted pyrazolyl. In embodiments, R^1 is R^{20}-substituted pyridyl. In embodiments, R^1 is R^{20}-substituted imidazolyl. In embodiments, R^1 is R^{20}-substituted oxazolyl. In embodiments, R^1 is R^{20}-substituted isoxazolyl. In embodiments, R^1 is R^{20}-substituted thiazolyl. In embodiments, R^1 is R^{20}-substituted furanyl. In embodiments, R^1 is R^{20}-substituted pyrrolyl. In embodiments, R^1 is R^{20}-substituted thienyl. In embodiments, R^1 is an unsubstituted pyrazolyl. In embodiments, R^1 is an unsubstituted pyridyl. In embodiments, R^1 is an unsubstituted imidazolyl. In embodiments, R^1 is an unsubstituted oxazolyl. In embodiments, R^1 is an unsubstituted isoxazolyl. In embodiments, R^1 is an unsubstituted thiazolyl. In embodiments, R^1 is an unsubstituted furanyl. In embodiments, R^1 is an unsubstituted pyrrolyl. In embodiments, R^1 is an unsubstituted thienyl.

[0220] R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. In embodiments, R^2 is $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$.

[0221] In embodiments, R^2 is independently hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted C_1-C_8 alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, unsubstituted C_1-C_4 alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^2 is independently hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, unsubstituted methyl, unsubstituted ethyl, unsubstituted methoxy, or unsubstituted ethoxy. In embodiments, R^2 is independently hydrogen. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently unsubstituted propyl. In embodiments, R^2 is independently unsubstituted n-propyl. In embodiments, R^2 is independently

unsubstituted isopropyl. In embodiments, R^2 is independently unsubstituted butyl. In embodiments, R^2 is independently unsubstituted n-butyl. In embodiments, R^2 is independently unsubstituted isobutyl. In embodiments, R^2 is independently unsubstituted tert-butyl. In embodiments, R^2 is independently unsubstituted pentyl. In embodiments, R^2 is independently unsubstituted hexyl. In embodiments, R^2 is independently unsubstituted heptyl. In embodiments, R^2 is independently unsubstituted octyl. In embodiments, X^2 is independently -F. In embodiments, X^2 is independently -Cl. In embodiments, X^2 is independently -Br. In embodiments, X^2 is independently -I. In embodiments, R^2 is independently unsubstituted methoxy. In embodiments, R^2 is independently unsubstituted ethoxy. In embodiments, R^2 is independently $-CF_3$. In embodiments, R^2 is independently $-CCl_3$.

[0222] In embodiments, R^2 is independently $-CX^2_3$. In embodiments, R^2 is independently $-CHX^2_2$. In embodiments, R^2 is independently $-CH_2X^2$.

[0223] In embodiments, R^2 is independently substituted or unsubstituted alkyl. In embodiments, R^2 is independently substituted or unsubstituted heteroalkyl. In embodiments, R^2 is independently substituted alkyl. In embodiments, R^2 is independently substituted heteroalkyl. In embodiments, R^2 is independently unsubstituted alkyl. In embodiments, R^2 is independently unsubstituted heteroalkyl. In embodiments, R^2 is independently substituted or unsubstituted C_1-C_8 alkyl. In embodiments, R^2 is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^2 is independently substituted C_1-C_8 alkyl. In embodiments, R^2 is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R^2 is independently unsubstituted C_1-C_8 alkyl. In embodiments, R^2 is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^2 is independently substituted or unsubstituted C_1-C_4 alkyl. In embodiments, R^2 is independently substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^2 is independently substituted C_1-C_4 alkyl. In embodiments, R^2 is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R^2 is independently unsubstituted C_1-C_4 alkyl. In embodiments, R^2 is independently unsubstituted 2 to 4 membered heteroalkyl.

[0224] In embodiments, R^2 is independently hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, R^{23}-substituted or unsubstituted alkyl, or R^{23}-substituted or unsubstituted heteroalkyl. In embodiments, R^2 is independently hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, R^{23}-substituted or unsubstituted C_1-C_8 alkyl, or R^{23}-substituted or unsubstituted 2 to 8 membered heteroalkyl. X^2 is –F, -Cl, -Br, or –I. In embodiments, R^2 is independently hydrogen. In embodiments, R^2 is independently methyl. In embodiments, R^2 is independently ethyl.

[0225] R^{23} is independently oxo, halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-CH_2X^{23}$, $-OCX^{23}_3$, $-OCHX^{23}_2$, $-OCH_2X^{23}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{24}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{24}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{24}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{24}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{24}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{24}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{23} is –F, -Cl, -Br, or –I.

[0226] R^{24} is independently oxo, halogen, $-CX^{24}_3$, $-CHX^{24}_2$, $-CH_2X^{24}$, $-OCX^{24}_3$, $-OCHX^{24}_2$, $-OCH_2X^{24}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{25}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{25}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{25}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{25}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{25}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{25}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{24} is –F, -Cl, -Br, or –I.

[0227] R^{25} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH,unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0228] In embodiments, R^2 is independently hydrogen. In embodiments, R^2 is independently substituted or unsubstituted methyl. In embodiments, R^2 is independently substituted or

unsubstituted C_1-C_4 alkyl. In embodiments, R^2 is independently substituted methyl. In embodiments, R^2 is independently substituted C_1-C_4 alkyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted C_1-C_4 alkyl.

[0229] In embodiments, R^2 is independently substituted or unsubstituted C_1-C_4 alkyl. In embodiments, R^2 is independently substituted or unsubstituted C_1-C_3 alkyl. In embodiments, R^2 is independently substituted or unsubstituted C_1-C_2 alkyl. In embodiments, R^2 is independently substituted or unsubstituted methyl. In embodiments, R^2 is independently substituted or unsubstituted methyl or substituted or unsubstituted isopropyl.

[0230] In embodiments, R^3 is independently unsubstituted heteroalkyl. In embodiments, R^3 is independently unsubstituted 2 to 5 membered heteroalkyl. In embodiments, R^3 is independently $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, or -SH. In embodiments, R^3 is independently $-OCH_3$. In embodiments, R^3 is independently $-OCH_2CH_3$. In embodiments, R^3 is independently $-N(CH_3)_2$. In embodiments, R^3 is independently $-NH_2$. In embodiments, R^3 is independently $-NH(CH_3)$. In embodiments, R^3 is independently $-N(CH_2CH_3)_2$. In embodiments, R^3 is independently $-NH(CH_2CH_3)$. In embodiments, R^3 is independently -SH. In embodiments, R^3 is independently $-OCH_2CH_2CH_3$. In embodiments, R^3 is independently unsubstituted methoxy. In embodiments, R^3 is independently unsubstituted ethoxy. In embodiments, R^3 is independently unsubstituted propoxy. In embodiments, R^3 is independently unsubstituted isopropoxy. In embodiments, R^3 is independently unsubstituted butoxy. In embodiments, R^3 is independently unsubstituted tert-butoxy. In embodiments, R^3 is independently unsubstituted pentoxy. In embodiments, R^3 is independently unsubstituted hexoxy.

[0231] In embodiments, R^3 is an unsubstituted methoxy. In embodiments, R^3 is $-OCHF_2$. In embodiments, R^3 is an unsubstituted tert-butyl. In embodiments, R^3 is an unsubstituted phenoxy. In embodiments, R^3 is an unsubstituted methyl. In embodiments, R^3 is –OH. In embodiments, R^3 is an unsubstituted ethoxy. In embodiments, R^3 is $-N(CH_3)_2$. In embodiments, R^3 is –SH. In embodiments, R^3 is $-SCH_3$. In embodiments, R^3 is $-SCH_2CH_3$. In embodiments, R^3 is an unsubstituted ethyl. In embodiments, R^3 is an unsubstituted propyl. In embodiments, R^3 is an unsubstituted isopropyl. In embodiments, R^3 is an unsubstituted butyl. In embodiments, R^3 is an unsubstituted isobutyl. In embodiments, R^3 is $-NH_2$. In embodiments, R^3 is $-NHCH_3$. In embodiments, R^3 is $-NHCH_2CH_3$. In embodiments, R^3 is $-N(CH_2CH_3)_2$. In embodiments, R^3 is $-N(CH_3)(CH_2CH_3)$. In embodiments, R^3 is halogen. In embodiments, R^3 is –F. In

embodiments, R^3 is –Cl. In embodiments, R^3 is –I. In embodiments, R^3 is –Br. In embodiments, R^3 is independently -CF_3. In embodiments, R^3 is independently -OCH_3. In embodiments, R^3 is an unsubstituted phenyl. In embodiments, R^3 is independently –$C(O)N(CH_3)_2$. In embodiments, R^3 is independently –$C(O)NH(CH_3)$. In embodiments, R^3 is independently -$C(O)N(CH_2CH_3)_2$. In embodiments, R^3 is independently -$C(O)NH(CH_2CH_3)$.

[0232] In embodiments, R^3 is independently unsubstituted cyclohexyl. In embodiments, R^3 is independently unsubstituted morpholinyl. In embodiments, R^3 is independently unsubstituted piperazinyl. In embodiments, R^3 is independently N-methyl substituted piperazinyl. In embodiments, R^3 is independently unsubstituted pyridyl. In embodiments, R^3 is an unsubstituted cyclopentyl. In embodiments, R^3 is an unsubstituted cyclobutyl. In embodiments, R^3 is an unsubstituted naphthyl. In embodiments, R^3 is an unsubstituted 1-naphthyl. In embodiments, R^3 is an unsubstituted 2-naphthyl. In embodiments, R^3 is an unsubstituted 2-thienyl. In embodiments, R^3 is an unsubstituted 3-thienyl. In embodiments, R^3 is an unsubstituted 2-furanyl. In embodiments, R^3 is an unsubstituted 3-furanyl. In embodiments, R^3 is an unsubstituted 2-pyridyl. In embodiments, R^3 is an unsubstituted 3-pyridyl. In embodiments, R^3 is an unsubstituted 4-pyridyl. In embodiments, R^3 is an unsubstituted 3-pyrazolyl. In embodiments, R^3 is an unsubstituted 4-pyrazolyl. In embodiments, R^3 is an unsubstituted 5-pyrazolyl. In embodiments, R^3 is an unsubstituted 2-pyrrolyl. In embodiments, R^3 is an unsubstituted 3-pyrrolyl. In embodiments, R^3 is an unsubstituted 2-thiazolyl. In embodiments, R^3 is an unsubstituted 4-thiazolyl. In embodiments, R^3 is an unsubstituted 5-thiazolyl. In embodiments, R^3 is an unsubstituted thiazolyl. In embodiments, R^3 is substituted thiazolyl. In embodiments, R^3 is methyl substituted thiazolyl. In embodiments, R^3 is an unsubstituted thienyl. In embodiments, R^3 is substituted thienyl. In embodiments, R^3 is methyl substituted thienyl. In embodiments, R^3 is an unsubstituted pyrazolyl. In embodiments, R^3 is substituted pyrazolyl. In embodiments, R^3 is methyl substituted pyrazolyl. In embodiments, R^3 is an unsubstituted furanyl. In embodiments, R^3 is substituted furanyl. In embodiments, R^3 is methyl substituted furanyl.

[0233] In embodiments, R^3 is independently halogen. In embodiments, R^3 is independently -CX^3_3. In embodiments, R^3 is independently -CHX^3_2. In embodiments, R^3 is independently -CH_2X^3. In embodiments, R^3 is independently -OCX^3_3. In embodiments, R^3 is independently -OCH_2X^3. In embodiments, R^3 is independently -$OCHX^3_2$. In embodiments, R^3 is independently -CN. In embodiments, R^3 is independently -$SO_{n3}R^{3D}$. In embodiments, R^3 is independently -$SO_{v3}NR^{3A}R^{3B}$. In embodiments, R^3 is independently -$NHC(O)NR^{3A}R^{3B}$. In

embodiments, R^3 is independently $-N(O)_{m3}$. In embodiments, R^3 is independently $-NR^{3A}R^{3B}$. In embodiments, R^3 is independently $-C(O)R^{3C}$. In embodiments, R^3 is independently $-C(O)-OR^{3C}$. In embodiments, R^3 is independently $-C(O)NR^{3A}R^{3B}$. In embodiments, R^3 is independently $-OR^{3D}$. In embodiments, R^3 is independently $-NR^{3A}SO_2R^{3D}$. In embodiments, R^3 is independently $-NR^{3A}C(O)R^{3C}$. In embodiments, R^3 is independently $-NR^{3A}C(O)OR^{3C}$. In embodiments, R^3 is independently $-NR^{3A}OR^{3C}$. In embodiments, R^3 is independently -OH. In embodiments, R^3 is independently $-NH_2$. In embodiments, R^3 is independently -COOH. In embodiments, R^3 is independently $-CONH_2$. In embodiments, R^3 is independently $-NO_2$. In embodiments, R^3 is independently –SH.

[0234] In embodiments, R^3 is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^3 is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^3 is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^3 is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^3 is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^3 is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^3 is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^3 is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^3 is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6).

[0235] In embodiments, R^3 is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^3 is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^3 is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^3 is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^3 is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^3 is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^3 is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^3 is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^3 is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0236] In embodiments, R^3 is substituted or unsubstituted a cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_3-C_8 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_3-C_7 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_3-C_6 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_3-C_5 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_3-C_4 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_4-C_8 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_5-C_8 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_6-C_8 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_5-C_6 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_3 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_4 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_5 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_6 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_7 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted C_8 cycloalkyl. In embodiments, R^3 is substituted or unsubstituted cyclopropyl. In embodiments, R^3 is substituted or unsubstituted cyclobutyl. In embodiments, R^3 is substituted or unsubstituted cyclopentyl. In embodiments, R^3 is substituted or unsubstituted cyclohexyl. In embodiments, R^3 is substituted or unsubstituted cycloheptyl. In embodiments, R^3 is substituted or unsubstituted a heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 3 to 7 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 3 to 4 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 4 to 8 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 5 to 8 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 6 to 8 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 3 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 4 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 5 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 6 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 7 membered heterocycloalkyl. In embodiments, R^3 is substituted or unsubstituted 8 membered heterocycloalkyl.

[0237] In embodiments, R^3 is substituted or unsubstituted aryl or heteroaryl. In embodiments, R^3 is substituted or unsubstituted aryl. In embodiments, R^3 is substituted or unsubstituted

heteroaryl. In embodiments, R^3 is substituted or unsubstituted C_6-C_{10} aryl. In embodiments, R^3 is substituted or unsubstituted C_{10} aryl. In embodiments, R^3 is substituted or unsubstituted phenyl. In embodiments, R^3 is substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^3 is substituted or unsubstituted 5 to 9 membered heteroaryl. In embodiments, R^3 is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^3 is substituted or unsubstituted 10 membered heteroaryl. In embodiments, R^3 is substituted or unsubstituted 9 membered heteroaryl. In embodiments, R^3 is substituted or unsubstituted 5 membered heteroaryl. In embodiments, R^3 is substituted or unsubstituted 6 membered heteroaryl. In embodiments, R^3 is substituted or unsubstituted phenyl. In embodiments, R^3 is substituted or unsubstituted pyridyl. In embodiments, R^3 is substituted or unsubstituted pyrazolyl. In embodiments, R^3 is substituted or unsubstituted imidazolyl. In embodiments, R^3 is substituted or unsubstituted oxazolyl. In embodiments, R^3 is substituted or unsubstituted isoxazolyl. In embodiments, R^3 is substituted or unsubstituted thiazolyl. In embodiments, R^3 is substituted or unsubstituted furanyl. In embodiments, R^3 is substituted or unsubstituted pyrrolyl. In embodiments, R^3 is substituted or unsubstituted thienyl. In embodiments, R^3 is a two fused ring aryl. In embodiments, R^3 is a two fused ring heteroaryl.

[0238] In embodiments, R^3 is substituted or unsubstituted aryl or heteroaryl. In embodiments, R^3 is substituted or unsubstituted phenyl or 5 to 6 membered heteroaryl. In embodiments, R^3 is substituted or unsubstituted phenyl. In embodiments, R^3 is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^3 is substituted or unsubstituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0239] In embodiments, R^3 is substituted or unsubstituted phenyl. In embodiments, R^3 is substituted or unsubstituted pyridyl. In embodiments, R^3 is substituted or unsubstituted cyclohexyl. In embodiments, R^3 is substituted or unsubstituted morpholinyl. In embodiments, R^3 is substituted or unsubstituted piperazinyl. In embodiments, R^3 is substituted or unsubstituted furanyl. In embodiments, R^3 is substituted or unsubstituted thiazolyl. In embodiments, R^3 is substituted or unsubstituted pyrazolyl. In embodiments, R^3 is substituted or unsubstituted thienyl. In embodiments, R^3 is substituted or unsubstituted pyrazinyl. In embodiments, R^3 is substituted or unsubstituted pyrimidinyl. In embodiments, R^3 is substituted or unsubstituted pyridazinyl. In embodiments, R^3 is substituted or unsubstituted triazinyl. In embodiments, R^3 is substituted or unsubstituted tetrazinyl. In embodiments, R^3 is substituted or unsubstituted tetrazolyl. In embodiments, R^3 is substituted or unsubstituted triazolyl. In embodiments, R^3 is substituted or unsubstituted quinolinyl. In embodiments, R^3 is substituted or unsubstituted

isoquinolinyl. In embodiments, R^3 is substituted or unsubstituted quinazolinyl. In embodiments, R^3 is substituted or unsubstituted quinoxalinyl. In embodiments, R^3 is substituted or unsubstituted imidazolyl. In embodiments, R^3 is substituted or unsubstituted oxazolyl. In embodiments, R^3 is substituted or unsubstituted isoxazolyl. In embodiments, R^3 is substituted or unsubstituted thiazolyl. In embodiments, R^3 is substituted or unsubstituted piperidinyl. In embodiments, R^3 is substituted or unsubstituted thiomorpholinyl. In embodiments, R^3 is substituted or unsubstituted thianyl. In embodiments, R^3 is substituted or unsubstituted oxanyl. In embodiments, R^3 is substituted or unsubstituted tetrahydropuranyl. In embodiments, R^3 is substituted or unsubstituted dihydropuranyl. In embodiments, R^3 is substituted or unsubstituted dioxanyl. In embodiments, R^3 is substituted or unsubstituted pyrazolyl. In embodiments, R^3 is substituted or unsubstituted pyrrolyl. In embodiments, R^3 is substituted or unsubstituted thienyl. In embodiments, R^3 is substituted or unsubstituted benzofuranyl. In embodiments, R^3 is substituted or unsubstituted indolyl. In embodiments, R^3 is substituted or unsubstituted benzothienyl. In embodiments, R^3 is substituted or unsubstituted benzimidazolyl. In embodiments, R^3 is substituted or unsubstituted isobenzofuranyl. In embodiments, R^3 is substituted or unsubstituted isoindolyl. In embodiments, R^3 is substituted or unsubstituted benzo[c]thienyl. In embodiments, R^3 is substituted or unsubstituted purinyl. In embodiments, R^3 is substituted or unsubstituted indazolyl. In embodiments, R^3 is substituted or unsubstituted benzoxazolyl. In embodiments, R^3 is substituted or unsubstituted benzisoxazolyl. In embodiments, R^3 is substituted or unsubstituted benzothiazolyl. In embodiments, R^3 is substituted or unsubstituted cyclopentyl. In embodiments, R^3 is substituted or unsubstituted cyclobutyl. In embodiments, R^3 is substituted or unsubstituted 2-thienyl. In embodiments, R^3 is substituted or unsubstituted 3-thienyl. In embodiments, R^3 is substituted or unsubstituted 2-furanyl. In embodiments, R^3 is substituted or unsubstituted 3-furanyl. In embodiments, R^3 is substituted or unsubstituted 2-pyridyl. In embodiments, R^3 is substituted or unsubstituted 3-pyridyl. In embodiments, R^3 is substituted or unsubstituted 4-pyridyl. In embodiments, R^3 is substituted or unsubstituted 3-pyrazolyl. In embodiments, R^3 is substituted or unsubstituted 4-pyrazolyl. In embodiments, R^3 is substituted or unsubstituted 5- pyrazolyl. In embodiments, R^3 is substituted or unsubstituted 2-pyrrolyl. In embodiments, R^3 is substituted or unsubstituted 3-pyrrolyl. In embodiments, R^3 is substituted or unsubstituted 2-thiazolyl. In embodiments, R^3 is substituted or unsubstituted 4-thiazolyl. In embodiments, R^3 is substituted or unsubstituted 5-thiazolyl. In embodiments, R^3 is substituted or unsubstituted 2-pyridyl. In embodiments, R^3 is substituted or unsubstituted 3-pyridyl. In embodiments, R^3 is substituted or unsubstituted 4-pyridyl. In embodiments, R^3 is substituted or unsubstituted phenyl.

[0240] In embodiments, R^3 is an unsubstituted cycloalkyl. In embodiments, R^3 is an unsubstituted C_3-C_8 cycloalkyl. In embodiments, R^3 is an unsubstituted C_3-C_7 cycloalkyl. In embodiments, R^3 is an unsubstituted C_3-C_6 cycloalkyl. In embodiments, R^3 is an unsubstituted C_3-C_5 cycloalkyl. In embodiments, R^3 is an unsubstituted C_3-C_4 cycloalkyl. In embodiments, R^3 is an unsubstituted C_4-C_8 cycloalkyl. In embodiments, R^3 is an unsubstituted C_5-C_8 cycloalkyl. In embodiments, R^3 is an unsubstituted C_6-C_8 cycloalkyl. In embodiments, R^3 is an unsubstituted C_5-C_6 cycloalkyl. In embodiments, R^3 is an unsubstituted C_3 cycloalkyl. In embodiments, R^3 is an unsubstituted C_4 cycloalkyl. In embodiments, R^3 is an unsubstituted C_5 cycloalkyl. In embodiments, R^3 is an unsubstituted C_6 cycloalkyl. In embodiments, R^3 is an unsubstituted C_7 cycloalkyl. In embodiments, R^3 is an unsubstituted C_8 cycloalkyl. In embodiments, R^3 is an unsubstituted cyclopropyl. In embodiments, R^3 is an unsubstituted cyclobutyl. In embodiments, R^3 is an unsubstituted cyclopentyl. In embodiments, R^3 is an unsubstituted cyclohexyl. In embodiments, R^3 is an unsubstituted cycloheptyl. In embodiments, R^3 is an unsubstituted a heterocycloalkyl. In embodiments, R^3 is an unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 3 to 7 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 3 to 4 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 4 to 8 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 5 to 8 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 6 to 8 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 3 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 4 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 5 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 6 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 7 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted 8 membered heterocycloalkyl. In embodiments, R^3 is an unsubstituted aryl or unsubstituted heteroaryl. In embodiments, R^3 is an unsubstituted aryl. In embodiments, R^3 is an unsubstituted heteroaryl. In embodiments, R^3 is an unsubstituted C_6-C_{10} aryl. In embodiments, R^3 is an unsubstituted C_{10} aryl. In embodiments, R^3 is an unsubstituted phenyl. In embodiments, R^3 is an unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^3 is an unsubstituted 5 to 9 membered heteroaryl. In embodiments, R^3 is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^3 is an unsubstituted 10 membered heteroaryl. In embodiments, R^3 is an unsubstituted 9 membered heteroaryl. In embodiments, R^3 is an unsubstituted 5 membered heteroaryl. In embodiments, R^3 is an unsubstituted 6 membered heteroaryl. In embodiments, R^3

is an unsubstituted phenyl. In embodiments, R^3 is an unsubstituted pyridyl. In embodiments, R^3 is an unsubstituted pyrazolyl. In embodiments, R^3 is an unsubstituted imidazolyl. In embodiments, R^3 is an unsubstituted oxazolyl. In embodiments, R^3 is an unsubstituted isoxazolyl. In embodiments, R^3 is an unsubstituted thiazolyl. In embodiments, R^3 is an unsubstituted furanyl. In embodiments, R^3 is an unsubstituted pyrrolyl. In embodiments, R^3 is an unsubstituted thienyl. In embodiments, R^3 is an unsubstituted two fused ring aryl. In embodiments, R^3 is an unsubstituted two fused ring heteroaryl.

[0241] In embodiments, R^3 is an unsubstituted aryl or unsubstituted heteroaryl. In embodiments, R^3 is an unsubstituted phenyl or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^3 is an unsubstituted phenyl. In embodiments, R^3 is an unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^3 is an unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl.

[0242] In embodiments, R^3 is an unsubstituted phenyl. In embodiments, R^3 is an unsubstituted pyridyl. In embodiments, R^3 is an unsubstituted cyclohexyl. In embodiments, R^3 is an unsubstituted morpholinyl. In embodiments, R^3 is an unsubstituted piperazinyl. In embodiments, R^3 is an unsubstituted furanyl. In embodiments, R^3 is an unsubstituted thiazolyl. In embodiments, R^3 is an unsubstituted pyrazolyl. In embodiments, R^3 is an unsubstituted thienyl. In embodiments, R^3 is an unsubstituted pyrazinyl. In embodiments, R^3 is an unsubstituted pyrimidinyl. In embodiments, R^3 is an unsubstituted pyridazinyl. In embodiments, R^3 is an unsubstituted triazinyl. In embodiments, R^3 is an unsubstituted tetrazinyl. In embodiments, R^3 is an unsubstituted tetrazolyl. In embodiments, R^3 is an unsubstituted triazolyl. In embodiments, R^3 is an unsubstituted quinolinyl. In embodiments, R^3 is an unsubstituted isoquinolinyl. In embodiments, R^3 is an unsubstituted quinazolinyl. In embodiments, R^3 is an unsubstituted quinoxalinyl. In embodiments, R^3 is an unsubstituted imidazolyl. In embodiments, R^3 is an unsubstituted oxazolyl. In embodiments, R^3 is an unsubstituted isoxazolyl. In embodiments, R^3 is an unsubstituted thiazolyl. In embodiments, R^3 is an unsubstituted piperidinyl. In embodiments, R^3 is an unsubstituted thiomorpholinyl. In embodiments, R^3 is an unsubstituted thianyl. In embodiments, R^3 is an unsubstituted oxanyl. In embodiments, R^3 is an unsubstituted tetrahydropuranyl. In embodiments, R^3 is an unsubstituted dihydropuranyl. In embodiments, R^3 is an unsubstituted dioxanyl. In embodiments, R^3 is an unsubstituted pyrazolyl. In embodiments, R^3 is an unsubstituted pyrrolyl. In embodiments, R^3 is an unsubstituted thienyl. In embodiments, R^3 is an unsubstituted benzofuranyl. In embodiments,

R^3 is an unsubstituted indolyl. In embodiments, R^3 is an unsubstituted benzothienyl. In embodiments, R^3 is an unsubstituted benzimidazolyl. In embodiments, R^3 is an unsubstituted isobenzofuranyl. In embodiments, R^3 is an unsubstituted isoindolyl. In embodiments, R^3 is an unsubstituted benzo[c]thienyl. In embodiments, R^3 is an unsubstituted purinyl. In embodiments, R^3 is an unsubstituted indazolyl. In embodiments, R^3 is an unsubstituted benzoxazolyl. In embodiments, R^3 is an unsubstituted benzisoxazolyl. In embodiments, R^3 is an unsubstituted benzothiazolyl. In embodiments, R^3 is an unsubstituted cyclopentyl. In embodiments, R^3 is an unsubstituted cyclobutyl. In embodiments, R^3 is an unsubstituted 2-thienyl. In embodiments, R^3 is an unsubstituted 3-thienyl. In embodiments, R^3 is an unsubstituted 2-furanyl. In embodiments, R^3 is an unsubstituted 3-furanyl. In embodiments, R^3 is an unsubstituted 2-pyridyl. In embodiments, R^3 is an unsubstituted 3-pyridyl. In embodiments, R^3 is an unsubstituted 4-pyridyl. In embodiments, R^3 is an unsubstituted 3-pyrazolyl. In embodiments, R^3 is an unsubstituted 4-pyrazolyl. In embodiments, R^3 is an unsubstituted 5- pyrazolyl. In embodiments, R^3 is an unsubstituted 2-pyrrolyl. In embodiments, R^3 is an unsubstituted 3-pyrrolyl. In embodiments, R^3 is an unsubstituted 2-thiazolyl. In embodiments, R^3 is an unsubstituted 4-thiazolyl. In embodiments, R^3 is an unsubstituted 5-thiazolyl.

[0243] In embodiments, R^{3A} is independently hydrogen. In embodiments, R^{3A} is independently $-CX^{3A}_3$. In embodiments, R^{3A} is independently $-CHX^{3A}_2$. In embodiments, R^{3A} is independently $-CH_2X^{3A}$. In embodiments, R^{3A} is independently -CN. In embodiments, R^{3A} is independently -COOH. In embodiments, R^{3A} is independently $-CONH_2$.

[0244] In embodiments, R^{3A} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3A} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3A} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3A} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3A} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3A} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3A} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3A} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3A} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3A} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently substituted heterocycloalkyl (e.g., 3 to 8

membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3A} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3A} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3A} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently unsubstituted methyl. In embodiments, R^{3A} is independently unsubstituted ethyl. In embodiments, R^{3A} is independently unsubstituted propyl. In embodiments, R^{3A} is independently unsubstituted isopropyl. In embodiments, R^{3A} is independently unsubstituted tert-butyl.

[0245] In embodiments, R^{3B} is independently hydrogen. In embodiments, R^{3B} is independently $-CX^{3B}_3$. In embodiments, R^{3B} is independently $-CHX^{3B}_2$. In embodiments, R^{3B} is independently $-CH_2X^{3B}$. In embodiments, R^{3B} is independently -CN. In embodiments, R^{3B} is independently -COOH. In embodiments, R^{3B} is independently $-CONH_2$.

[0246] In embodiments, R^{3B} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3B} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3B} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3B} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3B} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3B} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3B} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3B} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3B} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3B} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or

phenyl). In embodiments, R^{3B} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3B} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3B} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently unsubstituted methyl. In embodiments, R^{3B} is independently unsubstituted ethyl. In embodiments, R^{3B} is independently unsubstituted propyl. In embodiments, R^{3B} is independently unsubstituted isopropyl. In embodiments, R^{3B} is independently unsubstituted tert-butyl.

[0247] In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heterocycloalkyl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 10 membered heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to

form a substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 6 membered heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 6 membered heteroaryl.

[0248] In embodiments, R^{3C} is independently hydrogen. In embodiments, R^{3C} is independently $-CX^{3C}_3$. In embodiments, R^{3C} is independently $-CHX^{3C}_2$. In embodiments, R^{3C} is independently $-CH_2X^{3C}$. In embodiments, R^{3C} is independently -CN. In embodiments, R^{3C} is independently -COOH. In embodiments, R^{3C} is independently $-CONH_2$.

[0249] In embodiments, R^{3C} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3C} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3C} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3C} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3C} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3C} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3C} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3C} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3C} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3C} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3C} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3C} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3C} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently unsubstituted methyl.

In embodiments, R^{3C} is independently unsubstituted ethyl. In embodiments, R^{3C} is independently unsubstituted propyl. In embodiments, R^{3C} is independently unsubstituted isopropyl. In embodiments, R^{3C} is independently unsubstituted tert-butyl.

[0250] In embodiments, R^{3D} is independently hydrogen. In embodiments, R^{3D} is independently $-CX^{3D}_3$. In embodiments, R^{3D} is independently $-CHX^{3D}_2$. In embodiments, R^{3D} is independently $-CH_2X^{3D}$. In embodiments, R^{3D} is independently -CN. In embodiments, R^{3D} is independently -COOH. In embodiments, R^{3D} is independently $-CONH_2$. In embodiments, R^{3D} is independently $-CF_3$. In embodiments, R^{3D} is independently $-CHF_2$. In embodiments, R^{3D} is independently $-CH_2F$. In embodiments, R^{3D} is independently $-CCl_3$. In embodiments, R^{3D} is independently $-CHCl_2$. In embodiments, R^{3D} is independently $-CH_2Cl$. In embodiments, R^{3D} is independently $-CBr_3$. In embodiments, R^{3D} is independently $-CHBr_2$. In embodiments, R^{3D} is independently $-CH_2Br$. In embodiments, R^{3D} is independently $-CI_3$. In embodiments, R^{3D} is independently $-CHI_2$. In embodiments, R^{3D} is independently $-CH_2I$.

[0251] In embodiments, R^{3D} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3D} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3D} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3D} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3D} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3D} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3D} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3D} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3D} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3D} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3D} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3D} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3D} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently

substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently unsubstituted methyl. In embodiments, R^{3D} is independently unsubstituted ethyl. In embodiments, R^{3D} is independently unsubstituted propyl. In embodiments, R^{3D} is independently unsubstituted isopropyl. In embodiments, R^{3D} is independently unsubstituted tert-butyl.

[0252] In embodiments, R^3 is independently hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, R^{26}-substituted or unsubstituted alkyl, R^{26}-substituted or unsubstituted heteroalkyl, R^{26}-substituted or unsubstituted cycloalkyl, R^{26}-substituted or unsubstituted heterocycloalkyl, R^{26}-substituted or unsubstituted aryl, or R^{26}-substituted or unsubstituted heteroaryl.

[0253] In embodiments, R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{26}-substituted or unsubstituted alkyl, R^{26}-substituted or unsubstituted heteroalkyl, R^{26}-substituted or unsubstituted cycloalkyl, R^{26}-substituted or unsubstituted heterocycloalkyl, R^{26}-substituted or unsubstituted aryl, or R^{26}-substituted or unsubstituted heteroaryl.

[0254] In embodiments, R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{26}-substituted or unsubstituted C_1-C_8 alkyl, R^{26}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26}-substituted or unsubstituted phenyl, or R^{26}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^3 is –F, -Cl, -Br, or –I. In embodiments, R^3 is independently hydrogen. In embodiments, R^3 is independently methyl. In embodiments, R^3 is independently ethyl. In embodiments, R^3 is independently $-OCH_3$. In embodiments, R^3 is independently $-OCH_2CH_3$. In embodiments, R^3 is independently $-OCF_3$. In embodiments, R^3 is independently $-OCHF_2$. In embodiments, R^3 is independently $-OCH_2F$. In embodiments, R^3 is independently –

$OCBr_3$. In embodiments, R^3 is independently $-OCHBr_2$. In embodiments, R^3 is independently $-OCH_2Br$. In embodiments, R^3 is independently $-OCCl_3$. In embodiments, R^3 is independently $-OCHCl_2$. In embodiments, R^3 is independently $-OCH_2Cl$. In embodiments, R^3 is independently $-OCI_3$. In embodiments, R^3 is independently $-OCHI_2$. In embodiments, R^3 is independently $-OCH_2I$. In embodiments, R^3 is independently $-OCH_2CF_3$. In embodiments, R^3 is independently $-OCH_2CX^3{}_3$.

[0255] R^{26} is independently oxo, halogen, $-CX^{26}{}_3$, $-CHX^{26}{}_2$, $-CH_2X^{26}$, $-OCX^{26}{}_3$, $-OCH_2X^{26}$, $-OCHX^{26}{}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{27}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{26} is –F, -Cl, -Br, or –I.

[0256] R^{27} is independently oxo, halogen, $-CX^{27}{}_3$, $-CHX^{27}{}_2$, $-CH_2X^{27}$, $-OCX^{27}{}_3$, $-OCH_2X^{27}$, $-OCHX^{27}{}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, - R^{28}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{28}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{27} is –F, -Cl, -Br, or –I.

[0257] In embodiments, R^{3A} is independently hydrogen, $-CX^{3A}{}_3$, $-CHX^{3A}{}_2$, $-CH_2X^{3A}$, $-OCX^{3A}{}_3$, $-OCH_2X^{3A}$, $-OCHX^{3A}{}_2$, -CN, -COOH, $-CONH_2$, R^{26A}-substituted or unsubstituted alkyl, R^{26A}-substituted or unsubstituted heteroalkyl, R^{26A}-substituted or unsubstituted cycloalkyl, R^{26A}-substituted or unsubstituted heterocycloalkyl, R^{26A}-substituted or unsubstituted aryl, or R^{26A}-substituted or unsubstituted heteroaryl.

[0258] In embodiments, R^{3A} is independently hydrogen, $-CX^{3A}_3$, $-CHX^{3A}_2$, $-CH_2X^{3A}$, -CN, -COOH, $-CONH_2$, R^{26A}-substituted or unsubstituted C_1-C_8 alkyl, R^{26A}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26A}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26A}-substituted or unsubstituted phenyl, or R^{26A}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{3A} is –F, -Cl, -Br, or –I. In embodiments, R^{3A} is independently hydrogen. In embodiments, R^{3A} is independently methyl. In embodiments, R^{3A} is independently ethyl.

[0259] In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{26A}-substituted or unsubstituted heterocycloalkyl or R^{26A}-substituted or unsubstituted heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{26A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{26A}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0260] R^{26A} is independently oxo, halogen, $-CX^{26A}_3$, $-CHX^{26A}_2$, $-CH_2X^{26A}$, $-OCX^{26A}_3$, $-OCH_2X^{26A}$, $-OCHX^{26A}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{27A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{26A} is –F, -Cl, -Br, or –I.

[0261] R^{27A} is independently oxo, halogen, $-CX^{27A}_3$, $-CHX^{27A}_2$, $-CH_2X^{27A}$, $-OCX^{27A}_3$, $-OCH_2X^{27A}$, $-OCHX^{27A}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{28A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28A}-substituted or unsubstituted aryl (e.g.,

C_6-C_{10}, C_{10}, or phenyl), or R^{28A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{27A} is –F, -Cl, -Br, or –I.

[0262] In embodiments, R^{3B} is independently hydrogen, $-CX^{3A}_3$, $-CHX^{3B}_2$, $-CH_2X^{3B}$, -CN, -COOH, $-CONH_2$, R^{26B}-substituted or unsubstituted alkyl, R^{26B}-substituted or unsubstituted heteroalkyl, R^{26B}-substituted or unsubstituted cycloalkyl, R^{26B}-substituted or unsubstituted heterocycloalkyl, R^{26B}-substituted or unsubstituted aryl, or R^{26B}-substituted or unsubstituted heteroaryl. In embodiments, R^{3B} is independently hydrogen, $-CX^{3B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{3B}_2$, $-CH_2X^{3B}$, R^{26B}-substituted or unsubstituted C_1-C_8 alkyl, R^{26B}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26B}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26B}-substituted or unsubstituted phenyl, or R^{26B}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{3B} is –F, -Cl, -Br, or –I. In embodiments, R^{3B} is independently hydrogen. In embodiments, R^{3B} is independently methyl. In embodiments, R^{3B} is independently ethyl.

[0263] In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{26B}-substituted or unsubstituted heterocycloalkyl or R^{26B}-substituted or unsubstituted heteroaryl. In embodiments, R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{26B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{26B}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0264] R^{26B} is independently oxo, halogen, $-CX^{26B}_3$, $-CHX^{26B}_2$, $-CH_2X^{26B}$, $-OCX^{26B}_3$, $-OCH_2X^{26B}$, $-OCHX^{26B}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{27B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{26B} is –F, -Cl, -Br, or –I.

[0265] R^{27B} is independently oxo, halogen, $-CX^{27B}_3$, $-CHX^{27B}_2$, $-CH_2X^{27B}$, $-OCX^{27B}_3$, $-OCH_2X^{27B}$, $-OCHX^{27B}_2$, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{28B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{28B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{27B} is –F, -Cl, -Br, or –I.

[0266] In embodiments, R^{3C} is independently hydrogen, -CX^{3C}_3, -CN, -COOH, -$CONH_2$, -CHX^{3C}_2, -CH_2X^{3C}, R^{26C}-substituted or unsubstituted alkyl, R^{26C}-substituted or unsubstituted heteroalkyl, R^{26C}-substituted or unsubstituted cycloalkyl, R^{26C}-substituted or unsubstituted heterocycloalkyl, R^{26C}-substituted or unsubstituted aryl, or R^{26C}-substituted or unsubstituted heteroaryl. In embodiments, R^{3C} is independently hydrogen, -CX^{3C}_3, -CN, -COOH, -$CONH_2$, -CHX^{3C}_2, -CH_2X^{3C}, R^{26C}-substituted or unsubstituted C_1-C_8 alkyl, R^{26C}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26C}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26C}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26C}-substituted or unsubstituted phenyl, or R^{26C}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{3C} is –F, -Cl, -Br, or –I. In embodiments, R^{3C} is independently hydrogen. In embodiments, R^{3C} is independently methyl. In embodiments, R^{3C} is independently ethyl.

[0267] R^{26C} is independently oxo, halogen, -CX^{26C}_3, -CHX^{26C}_2, -CH_2X^{26C}, -OCX^{26C}_3, -OCH_2X^{26C}, -$OCHX^{26C}_2$, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{27C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{26C} is –F, -Cl, -Br, or –I.

[0268] R^{27C} is independently oxo, halogen, -CX^{27C}_3, -CHX^{27C}_2, -CH_2X^{27C}, -OCX^{27C}_3, -OCH_2X^{27C}, -$OCHX^{27C}_2$, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{28C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{28C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{27C} is –F, -Cl, -Br, or –I.

[0269] In embodiments, R^{3D} is independently hydrogen, -CX^{3D}_3, -CN, -COOH, -$CONH_2$, -CHX^{3D}_2, -CH_2X^{3D}, R^{26D}-substituted or unsubstituted alkyl, R^{26D}-substituted or unsubstituted heteroalkyl, R^{26D}-substituted or unsubstituted cycloalkyl, R^{26D}-substituted or unsubstituted heterocycloalkyl, R^{26D}-substituted or unsubstituted aryl, or R^{26D}-substituted or unsubstituted heteroaryl. In embodiments, R^{3D} is independently hydrogen, -CX^{3D}_3, -CN, -COOH, -$CONH_2$, -CHX^{3D}_2, -CH_2X^{3D}, R^{26D}-substituted or unsubstituted C_1-C_8 alkyl, R^{26D}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26D}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26D}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26D}-substituted or unsubstituted phenyl, or R^{26D}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{3D} is –F, -Cl, -Br, or –I. In embodiments, R^{3D} is independently hydrogen. In embodiments, R^{3D} is independently methyl. In embodiments, R^{3D} is independently ethyl.

[0270] R^{26D} is independently oxo, halogen, -CX^{26D}_3, -CHX^{26D}_2, -CH_2X^{26D}, -OCX^{26D}_3, -OCH_2X^{26D}, -$OCHX^{26D}_2$, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{27D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{26D} is –F, -Cl, -Br, or –I.

[0271] R^{27D} is independently oxo, halogen, -CX^{27D}_3, -CHX^{27D}_2, -CH_2X^{27D}, -OCX^{27D}_3, -OCH_2X^{27D}, -$OCHX^{27D}_2$, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{28D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{28D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{27D} is –F, -Cl, -Br, or –I.

[0272] R^{28}, R^{28A}, R^{28B}, R^{28C}, and R^{28D} are independently oxo, halogen, -CF_3, -CCl_3, -CBr_3, -CI_3, -CHF_2, -$CHCl_2$, -$CHBr_2$, -CHI_2, -CH_2F, -CH_2Cl, -CH_2Br, -CH_2I, -OCF_3, -$OCCl_3$, -$OCBr_3$, -OCI_3, -$OCHF_2$, -$OCHCl_2$, -$OCHBr_2$, -$OCHI_2$, -OCH_2F, -OCH_2Cl, -OCH_2Br, -OCH_2I, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0273] In embodiments, R^4 is an unsubstituted methyl. In embodiments, R^4 is -C(O)$N(CH_3)_2$. In embodiments, R^4 is –CN. In embodiments, R^4 is an unsubstituted methoxy. In embodiments, R^4 is an unsubstituted tert-butyl. In embodiments, R^4 is –OH. In embodiments, R^4 is an unsubstituted ethoxy. In embodiments, R^4 is -$N(CH_3)_2$. In embodiments, R^4 is –SH. In embodiments, R^4 is -SCH_3. In embodiments, R^4 is –SCH_2CH_3. In embodiments, R^4 is an unsubstituted ethyl. In embodiments, R^4 is an unsubstituted propyl. In embodiments, R^4 is an unsubstituted isopropyl. In embodiments, R^4 is an unsubstituted butyl. In embodiments, R^4 is an unsubstituted isobutyl. In embodiments, R^4 is –NH_2. In embodiments, R^4 is –C(CN). In embodiments, R^4 is -$NHCH_3$. In embodiments, R^4 is –$NHCH_2CH_3$. In embodiments, R^4 is -$N(CH_2CH_3)_2$. In embodiments, R^4 is -$N(CH_3)(CH_2CH_3)$. In embodiments, R^4 is –C(O)NH_2. In embodiments, R^4 is -C(O)$NHCH_3$. In embodiments, R^4 is –C(O)$NHCH_2CH_3$. In embodiments, R^4 is -C(O)$N(CH_2CH_3)_2$. In embodiments, R^4 is -C(O)$N(CH_3)(CH_2CH_3)$. In embodiments, R^4 is independently -CF_3. In embodiments, R^4 is independently -CHF_2. In embodiments, R^4 is independently -CH_2F. In embodiments, R^4 is independently -CCl_3. In embodiments, R^4 is independently -$CHCl_2$. In embodiments, R^4 is independently -CH_2Cl. In

embodiments, R^4 is independently $-CBr_3$. In embodiments, R^4 is independently $-CHBr_2$. In embodiments, R^4 is independently $-CH_2Br$. In embodiments, R^4 is independently $-CI_3$. In embodiments, R^4 is independently $-CHI_2$. In embodiments, R^4 is independently $-CH_2I$.

[0274] In embodiments, R^4 is independently unsubstituted heteroalkyl. In embodiments, R^4 is independently unsubstituted 2 to 5 membered heteroalkyl. In embodiments, R^4 is independently $–OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, or -SH. In embodiments, R^4 is independently $–OCH_3$. In embodiments, R^4 is independently $-OCH_2CH_3$. In embodiments, R^4 is independently $-N(CH_3)_2$. In embodiments, R^4 is independently $-NH_2$. In embodiments, R^4 is independently $-NH(CH_3)$. In embodiments, R^4 is independently $-N(CH_2CH_3)_2$. In embodiments, R^4 is independently $-NH(CH_2CH_3)$. In embodiments, R^4 is independently -SH. In embodiments, R^4 is independently $-OCH_2CH_2CH_3$. In embodiments, R^4 is independently unsubstituted methoxy. In embodiments, R^4 is independently unsubstituted ethoxy. In embodiments, R^4 is independently unsubstituted propoxy. In embodiments, R^4 is independently unsubstituted isopropoxy. In embodiments, R^4 is independently unsubstituted butoxy. In embodiments, R^4 is independently unsubstituted tert-butoxy. In embodiments, R^4 is independently unsubstituted pentoxy. In embodiments, R^4 is independently unsubstituted hexoxy.

[0275] In embodiments, R^4 is an unsubstituted methoxy. In embodiments, R^4 is an unsubstituted tert-butyl. In embodiments, R^4 is an unsubstituted phenoxy. In embodiments, R^4 is an unsubstituted methyl. In embodiments, R^4 is –OH. In embodiments, R^4 is an unsubstituted ethoxy. In embodiments, R^4 is –SH. In embodiments, R^4 is $-SCH_3$. In embodiments, R^4 is $–SCH_2CH_3$. In embodiments, R^4 is an unsubstituted ethyl. In embodiments, R^4 is an unsubstituted propyl. In embodiments, R^4 is an unsubstituted isopropyl. In embodiments, R^4 is an unsubstituted butyl. In embodiments, R^4 is an unsubstituted isobutyl. In embodiments, R^4 is $–NH_2$. In embodiments, R^4 is $-NHCH_3$. In embodiments, R^4 is $–NHCH_2CH_3$. In embodiments, R^4 is $-N(CH_2CH_3)_2$. In embodiments, R^4 is $-N(CH_3)(CH_2CH_3)$. In embodiments, R^4 is halogen. In embodiments, R^4 is –F. In embodiments, R^4 is –Cl. In embodiments, R^4 is –I. In embodiments, R^4 is –Br. In embodiments, R^4 is independently $-CF_3$. In embodiments, R^4 is independently $-OCH_3$. In embodiments, R^4 is an unsubstituted phenyl. In embodiments, R^4 is independently $–C(O)N(CH_3)_2$. In embodiments, R^4 is independently $–C(O)NH(CH_3)$. In embodiments, R^4 is independently $-C(O)N(CH_2CH_3)_2$. In embodiments, R^4 is independently $-C(O)NH(CH_2CH_3)$. In embodiments, R^4 is independently unsubstituted cyclohexyl. In embodiments, R^4 is independently unsubstituted morpholinyl. In embodiments,

R^4 is independently unsubstituted piperazinyl. In embodiments, R^4 is independently N-methyl substituted piperazinyl. In embodiments, R^4 is independently unsubstituted pyridyl. In embodiments, R^4 is an unsubstituted cyclopentyl. In embodiments, R^4 is an unsubstituted cyclobutyl. In embodiments, R^4 is an unsubstituted naphthyl. In embodiments, R^4 is an unsubstituted 1-naphthyl. In embodiments, R^4 is an unsubstituted 2-naphthyl. In embodiments, R^4 is an unsubstituted 2-thienyl. In embodiments, R^4 is an unsubstituted 3-thienyl. In embodiments, R^4 is an unsubstituted 2-furanyl. In embodiments, R^4 is an unsubstituted 3-furanyl. In embodiments, R^4 is an unsubstituted 2-pyridyl. In embodiments, R^4 is an unsubstituted 3-pyridyl. In embodiments, R^4 is an unsubstituted 4-pyridyl. In embodiments, R^4 is an unsubstituted 3-pyrazolyl. In embodiments, R^4 is an unsubstituted 4-pyrazolyl. In embodiments, R^4 is an unsubstituted 5- pyrazolyl. In embodiments, R^4 is an unsubstituted 2-pyrrolyl. In embodiments, R^4 is an unsubstituted 3-pyrrolyl. In embodiments, R^4 is an unsubstituted 2-thiazolyl. In embodiments, R^4 is an unsubstituted 4-thiazolyl. In embodiments, R^4 is an unsubstituted 5-thiazolyl. In embodiments, R^4 is an unsubstituted thiazolyl. In embodiments, R^4 is substituted thiazolyl. In embodiments, R^4 is methyl substituted thiazolyl. In embodiments, R^4 is an unsubstituted thienyl. In embodiments, R^4 is substituted thienyl. In embodiments, R^4 is methyl substituted thienyl. In embodiments, R^4 is an unsubstituted pyrazolyl. In embodiments, R^4 is substituted pyrazolyl. In embodiments, R^4 is methyl substituted pyrazolyl. In embodiments, R^4 is an unsubstituted furanyl. In embodiments, R^4 is substituted furanyl. In embodiments, R^4 is methyl substituted furanyl.

[0276] In embodiments, R^4 is independently halogen. In embodiments, R^4 is independently –F. In embodiments, R^4 is independently –Cl. In embodiments, R^4 is independently –Br. In embodiments, R^4 is independently –I. In embodiments, R^4 is independently $-CX^4_3$. In embodiments, R^4 is independently $-CHX^4_2$. In embodiments, R^4 is independently $-CH_2X^4$. In embodiments, R^4 is independently $-OCX^4_3$. In embodiments, R^4 is independently $-OCH_2X^4$. In embodiments, R^4 is independently $-OCHX^4_2$. In embodiments, R^4 is independently -CN. In embodiments, R^4 is independently $-SO_{n4}R^{4D}$. In embodiments, R^4 is independently $-SO_{v4}NR^{4A}R^{4B}$. In embodiments, R^4 is independently $-NHC(O)NR^{4A}R^{4B}$. In embodiments, R^4 is independently $-N(O)_{m4}$. In embodiments, R^4 is independently $-NR^{4A}R^{4B}$. In embodiments, R^4 is independently $-C(O)R^{4C}$. In embodiments, R^4 is independently $-C(O)\text{-}OR^{4C}$. In embodiments, R^4 is independently $-C(O)NR^{4A}R^{4B}$. In embodiments, R^4 is independently $-OR^{4D}$. In embodiments, R^4 is independently $-NR^{4A}SO_2R^{4D}$. In embodiments, R^4 is independently $-NR^{4A}C(O)R^{4C}$. In embodiments, R^4 is independently $-NR^{4A}C(O)OR^{4C}$. In

embodiments, R^4 is independently $-NR^{4A}OR^{4C}$. In embodiments, R^4 is independently -OH. In embodiments, R^4 is independently $-NH_2$. In embodiments, R^4 is independently -COOH. In embodiments, R^4 is independently $-CONH_2$. In embodiments, R^4 is independently $-NO_2$. In embodiments, R^4 is independently –SH.

[0277] In embodiments, R^4 is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^4 is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^4 is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^4 is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^4 is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^4 is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^4 is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^4 is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^4 is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^4 is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^4 is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^4 is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^4 is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^4 is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^4 is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^4 is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^4 is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^4 is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0278] In embodiments, $R^{4.1}$ is an unsubstituted methyl. In embodiments, $R^{4.1}$ is $-C(O)N(CH_3)_2$. In embodiments, $R^{4.1}$ is –CN. In embodiments, $R^{4.1}$ is an unsubstituted methoxy. In embodiments, $R^{4.1}$ is an unsubstituted tert-butyl. In embodiments, $R^{4.1}$ is –OH. In embodiments, $R^{4.1}$ is an unsubstituted ethoxy. In embodiments, $R^{4.1}$ is $-N(CH_3)_2$. In embodiments, $R^{4.1}$ is –SH. In embodiments, $R^{4.1}$ is $-SCH_3$. In embodiments, $R^{4.1}$ is –C(CN). In embodiments, $R^{4.1}$ is $-SCH_2CH_3$. In embodiments, $R^{4.1}$ is an unsubstituted ethyl. In

embodiments, $R^{4.1}$ is an unsubstituted propyl. In embodiments, $R^{4.1}$ is an unsubstituted isopropyl. In embodiments, $R^{4.1}$ is an unsubstituted butyl. In embodiments, $R^{4.1}$ is an unsubstituted isobutyl. In embodiments, $R^{4.1}$ is $-NH_2$. In embodiments, $R^{4.1}$ is $-NHCH_3$. In embodiments, $R^{4.1}$ is $-NHCH_2CH_3$. In embodiments, $R^{4.1}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.1}$ is $-N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.1}$ is halogen. In embodiments, $R^{4.1}$ is –F. In embodiments, $R^{4.1}$ is –Cl. In embodiments, $R^{4.1}$ is –I. In embodiments, $R^{4.1}$ is –Br. In embodiments, $R^{4.1}$ is $-C(O)NH_2$. In embodiments, $R^{4.1}$ is $-C(O)NHCH_3$. In embodiments, $R^{4.1}$ is $-C(O)NHCH_2CH_3$. In embodiments, $R^{4.1}$ is $-C(O)N(CH_2CH_3)_2$. In embodiments, $R^{4.1}$ is $-C(O)N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.1}$ is $-CF_3$. In embodiments, $R^{4.1}$ is $-CHF_2$. In embodiments, $R^{4.1}$ is $-CH_2F$. In embodiments, $R^{4.1}$ is $-CCl_3$. In embodiments, $R^{4.1}$ is $-CHCl_2$. In embodiments, $R^{4.1}$ is $-CH_2Cl$. In embodiments, $R^{4.1}$ is $-CBr_3$. In embodiments, $R^{4.1}$ is $-CHBr_2$. In embodiments, $R^{4.1}$ is $-CH_2Br$. In embodiments, $R^{4.1}$ is $-CI_3$. In embodiments, $R^{4.1}$ is $-CHI_2$. In embodiments, $R^{4.1}$ is $-CH_2I$.

[0279] In embodiments, $R^{4.1}$ is an unsubstituted heteroalkyl. In embodiments, $R^{4.1}$ is an unsubstituted 2 to 5 membered heteroalkyl. In embodiments, $R^{4.1}$ is $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, or -SH. In embodiments, $R^{4.1}$ is $-OCH_3$. In embodiments, $R^{4.1}$ is $-OCH_2CH_3$. In embodiments, $R^{4.1}$ is $-N(CH_3)_2$. In embodiments, $R^{4.1}$ is $-NH_2$. In embodiments, $R^{4.1}$ is $-NH(CH_3)$. In embodiments, $R^{4.1}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.1}$ is $-NH(CH_2CH_3)$. In embodiments, $R^{4.1}$ is -SH. In embodiments, $R^{4.1}$ is $-OCH_2CH_2CH_3$. In embodiments, $R^{4.1}$ is an unsubstituted methoxy. In embodiments, $R^{4.1}$ is an unsubstituted ethoxy. In embodiments, $R^{4.1}$ is an unsubstituted propoxy. In embodiments, $R^{4.1}$ is an unsubstituted isopropoxy. In embodiments, $R^{4.1}$ is an unsubstituted butoxy. In embodiments, $R^{4.1}$ is an unsubstituted tert-butoxy. In embodiments, $R^{4.1}$ is an unsubstituted pentoxy. In embodiments, $R^{4.1}$ is an unsubstituted hexoxy.

[0280] In embodiments, $R^{4.1}$ is an unsubstituted methoxy. In embodiments, $R^{4.1}$ is an unsubstituted tert-butyl. In embodiments, $R^{4.1}$ is an unsubstituted phenoxy. In embodiments, $R^{4.1}$ is an unsubstituted methyl. In embodiments, $R^{4.1}$ is –OH. In embodiments, $R^{4.1}$ is an unsubstituted ethoxy. In embodiments, $R^{4.1}$ is $-N(CH_3)_2$. In embodiments, $R^{4.1}$ is –SH. In embodiments, $R^{4.1}$ is $-SCH_3$. In embodiments, $R^{4.1}$ is $-SCH_2CH_3$. In embodiments, $R^{4.1}$ is an unsubstituted ethyl. In embodiments, $R^{4.1}$ is an unsubstituted propyl. In embodiments, $R^{4.1}$ is an unsubstituted isopropyl. In embodiments, $R^{4.1}$ is an unsubstituted butyl. In embodiments, $R^{4.1}$ is an unsubstituted isobutyl. In embodiments, $R^{4.1}$ is $-NH_2$. In embodiments, $R^{4.1}$ is $-NHCH_3$. In embodiments, $R^{4.1}$ is $-NHCH_2CH_3$. In embodiments, $R^{4.1}$ is $-N(CH_2CH_3)_2$. In embodiments,

$R^{4.1}$ is -N(CH_3)(CH_2CH_3). In embodiments, $R^{4.1}$ is -OCH_3. In embodiments, $R^{4.1}$ is an unsubstituted phenyl. In embodiments, $R^{4.1}$ is –C(O)N(CH_3)$_2$. In embodiments, $R^{4.1}$ is –C(O)NH(CH_3) . In embodiments, $R^{4.1}$ is -C(O)N(CH_2CH_3)$_2$. In embodiments, $R^{4.1}$ is -C(O)NH(CH_2CH_3) . In embodiments, $R^{4.1}$ is an unsubstituted cyclohexyl. In embodiments, $R^{4.1}$ is an unsubstituted morpholinyl. In embodiments, $R^{4.1}$ is an unsubstituted piperazinyl. In embodiments, $R^{4.1}$ is N-methyl substituted piperazinyl. In embodiments, $R^{4.1}$ is an unsubstituted pyridyl. In embodiments, $R^{4.1}$ is an unsubstituted cyclopentyl. In embodiments, $R^{4.1}$ is an unsubstituted cyclobutyl. In embodiments, $R^{4.1}$ is an unsubstituted naphthyl. In embodiments, $R^{4.1}$ is an unsubstituted 1-naphthyl. In embodiments, $R^{4.1}$ is an unsubstituted 2-naphthyl. In embodiments, $R^{4.1}$ is an unsubstituted 2-thienyl. In embodiments, $R^{4.1}$ is an unsubstituted 3-thienyl. In embodiments, $R^{4.1}$ is an unsubstituted 2-furanyl. In embodiments, $R^{4.1}$ is an unsubstituted 3-furanyl. In embodiments, $R^{4.1}$ is an unsubstituted 2-pyridyl. In embodiments, $R^{4.1}$ is an unsubstituted 3-pyridyl. In embodiments, $R^{4.1}$ is an unsubstituted 4-pyridyl. In embodiments, $R^{4.1}$ is an unsubstituted 3-pyrazolyl. In embodiments, $R^{4.1}$ is an unsubstituted 4-pyrazolyl. In embodiments, $R^{4.1}$ is an unsubstituted 5- pyrazolyl. In embodiments, $R^{4.1}$ is an unsubstituted 2-pyrrolyl. In embodiments, $R^{4.1}$ is an unsubstituted 3-pyrrolyl. In embodiments, $R^{4.1}$ is an unsubstituted 2-thiazolyl. In embodiments, $R^{4.1}$ is an unsubstituted 4-thiazolyl. In embodiments, $R^{4.1}$ is an unsubstituted 5-thiazolyl. In embodiments, $R^{4.1}$ is an unsubstituted thiazolyl. In embodiments, $R^{4.1}$ is substituted thiazolyl. In embodiments, $R^{4.1}$ is methyl substituted thiazolyl. In embodiments, $R^{4.1}$ is an unsubstituted thienyl. In embodiments, $R^{4.1}$ is substituted thienyl. In embodiments, $R^{4.1}$ is methyl substituted thienyl. In embodiments, $R^{4.1}$ is an unsubstituted pyrazolyl. In embodiments, $R^{4.1}$ is substituted pyrazolyl. In embodiments, $R^{4.1}$ is methyl substituted pyrazolyl. In embodiments, $R^{4.1}$ is an unsubstituted furanyl. In embodiments, $R^{4.1}$ is substituted furanyl. In embodiments, $R^{4.1}$ is methyl substituted furanyl.

[0281] In embodiments, $R^{4.1}$ is halogen. In embodiments, $R^{4.1}$ is –F. In embodiments, $R^{4.1}$ is –Cl. In embodiments, $R^{4.1}$ is –Br. In embodiments, $R^{4.1}$ is –I. In embodiments, $R^{4.1}$ is -$CX^{4.1}_3$. In embodiments, $R^{4.1}$ is -$CHX^{4.1}_2$. In embodiments, $R^{4.1}$ is -$CH_2X^{4.1}$. In embodiments, $R^{4.1}$ is -$OCX^{4.1}_3$. In embodiments, $R^{4.1}$ is -$OCH_2X^{4.1}$. In embodiments, $R^{4.1}$ is -$OCHX^{4.1}_2$. In embodiments, $R^{4.1}$ is -CN. In embodiments, $R^{4.1}$ is -$SO_{n4}R^{4.1D}$. In embodiments, $R^{4.1}$ is -$SO_{v4}NR^{4.1A}R^{4.1B}$. In embodiments, $R^{4.1}$ is -$NHC(O)NR^{4.1A}R^{4.1B}$. In embodiments, $R^{4.1}$ is -$N(O)_{m4}$. In embodiments, $R^{4.1}$ is -$NR^{4.1A}R^{4.1B}$. In embodiments, $R^{4.1}$ is -$C(O)R^{4.1C}$. In embodiments, $R^{4.1}$ is -C(O)-$OR^{4.1C}$. In embodiments, $R^{4.1}$ is -$C(O)NR^{4.1A}R^{4.1B}$. In embodiments, $R^{4.1}$ is -$OR^{4.1D}$. In embodiments, $R^{4.1}$ is -$NR^{4.1A}SO_2R^{4.1D}$. In embodiments, $R^{4.1}$

is -$NR^{4.1A}C(O)R^{4.1C}$. In embodiments, $R^{4.1}$ is -$NR^{4.1A}C(O)OR^{4.1C}$. In embodiments, $R^{4.1}$ is -$NR^{4.1A}OR^{4.1C}$. In embodiments, $R^{4.1}$ is -OH. In embodiments, $R^{4.1}$ is -NH_2. In embodiments, $R^{4.1}$ is -COOH. In embodiments, $R^{4.1}$ is -$CONH_2$. In embodiments, $R^{4.1}$ is -NO_2. In embodiments, $R^{4.1}$ is –SH.

[0282] In embodiments, $R^{4.1}$ is substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.1}$ is substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.1}$ is an unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.1}$ is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.1}$ is substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.1}$ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.1}$ is substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.1}$ is substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.1}$ is an unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.1}$ is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.1}$ is substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.1}$ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.1}$ is substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.1}$ is substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.1}$ is an unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.1}$ is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.1}$ is substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.1}$ is an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0283] In embodiments, $R^{4.2}$ is an unsubstituted methyl. In embodiments, $R^{4.2}$ is -$C(O)N(CH_3)_2$. In embodiments, $R^{4.2}$ is –CN. In embodiments, $R^{4.2}$ is an unsubstituted methoxy. In embodiments, $R^{4.2}$ is an unsubstituted tert-butyl. In embodiments, $R^{4.2}$ is –OH. In embodiments, $R^{4.2}$ is an unsubstituted ethoxy. In embodiments, $R^{4.2}$ is -$N(CH_3)_2$. In embodiments, $R^{4.2}$ is –C(CN). In embodiments, $R^{4.2}$ is –SH. In embodiments, $R^{4.2}$ is -SCH_3. In embodiments, $R^{4.2}$ is –SCH_2CH_3. In embodiments, $R^{4.2}$ is an unsubstituted ethyl. In embodiments, $R^{4.2}$ is an unsubstituted propyl. In embodiments, $R^{4.2}$ is an unsubstituted isopropyl. In embodiments, $R^{4.2}$ is an unsubstituted butyl. In embodiments, $R^{4.2}$ is an unsubstituted isobutyl. In embodiments, $R^{4.2}$ is –NH_2. In embodiments, $R^{4.2}$ is -$NHCH_3$. In

embodiments, $R^{4.2}$ is $-NHCH_2CH_3$. In embodiments, $R^{4.2}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.2}$ is $-N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.2}$ is halogen. In embodiments, $R^{4.2}$ is –F. In embodiments, $R^{4.2}$ is –Cl. In embodiments, $R^{4.2}$ is –I. In embodiments, $R^{4.2}$ is –Br. In embodiments, $R^{4.2}$ is $-C(O)NH_2$. In embodiments, $R^{4.2}$ is $-C(O)NHCH_3$. In embodiments, $R^{4.2}$ is $-C(O)NHCH_2CH_3$. In embodiments, $R^{4.2}$ is $-C(O)N(CH_2CH_3)_2$. In embodiments, $R^{4.2}$ is $-C(O)N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.2}$ is $-CF_3$. In embodiments, $R^{4.2}$ is $-CHF_2$. In embodiments, $R^{4.2}$ is $-CH_2F$. In embodiments, $R^{4.2}$ is $-CCl_3$. In embodiments, $R^{4.2}$ is $-CHCl_2$. In embodiments, $R^{4.2}$ is $-CH_2Cl$. In embodiments, $R^{4.2}$ is $-CBr_3$. In embodiments, $R^{4.2}$ is $-CHBr_2$. In embodiments, $R^{4.2}$ is $-CH_2Br$. In embodiments, $R^{4.2}$ is $-CI_3$. In embodiments, $R^{4.2}$ is $-CHI_2$. In embodiments, $R^{4.2}$ is $-CH_2I$.

[0284] In embodiments, $R^{4.2}$ is an unsubstituted heteroalkyl. In embodiments, $R^{4.2}$ is an unsubstituted 2 to 5 membered heteroalkyl. In embodiments, $R^{4.2}$ is $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, or -SH. In embodiments, $R^{4.2}$ is $-OCH_3$. In embodiments, $R^{4.2}$ is $-OCH_2CH_3$. In embodiments, $R^{4.2}$ is $-N(CH_3)_2$. In embodiments, $R^{4.2}$ is $-NH_2$. In embodiments, $R^{4.2}$ is $-NH(CH_3)$. In embodiments, $R^{4.2}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.2}$ is $-NH(CH_2CH_3)$. In embodiments, $R^{4.2}$ is -SH. In embodiments, $R^{4.2}$ is $-OCH_2CH_2CH_3$. In embodiments, $R^{4.2}$ is an unsubstituted methoxy. In embodiments, $R^{4.2}$ is an unsubstituted ethoxy. In embodiments, $R^{4.2}$ is an unsubstituted propoxy. In embodiments, $R^{4.2}$ is an unsubstituted isopropoxy. In embodiments, $R^{4.2}$ is an unsubstituted butoxy. In embodiments, $R^{4.2}$ is an unsubstituted tert-butoxy. In embodiments, $R^{4.2}$ is an unsubstituted pentoxy. In embodiments, $R^{4.2}$ is an unsubstituted hexoxy.

[0285] In embodiments, $R^{4.2}$ is an unsubstituted methoxy. In embodiments, $R^{4.2}$ is an unsubstituted tert-butyl. In embodiments, $R^{4.2}$ is an unsubstituted phenoxy. In embodiments, $R^{4.2}$ is an unsubstituted methyl. In embodiments, $R^{4.2}$ is –OH. In embodiments, $R^{4.2}$ is an unsubstituted ethoxy. In embodiments, $R^{4.2}$ is $-N(CH_3)_2$. In embodiments, $R^{4.2}$ is –SH. In embodiments, $R^{4.2}$ is $-SCH_3$. In embodiments, $R^{4.2}$ is $-SCH_2CH_3$. In embodiments, $R^{4.2}$ is an unsubstituted ethyl. In embodiments, $R^{4.2}$ is an unsubstituted propyl. In embodiments, $R^{4.2}$ is an unsubstituted isopropyl. In embodiments, $R^{4.2}$ is an unsubstituted butyl. In embodiments, $R^{4.2}$ is an unsubstituted isobutyl. In embodiments, $R^{4.2}$ is $-NH_2$. In embodiments, $R^{4.2}$ is $-NHCH_3$. In embodiments, $R^{4.2}$ is $-NHCH_2CH_3$. In embodiments, $R^{4.2}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.2}$ is $-N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.2}$ is $-OCH_3$. In embodiments, $R^{4.2}$ is an unsubstituted phenyl. In embodiments, $R^{4.2}$ is $-C(O)N(CH_3)_2$. In embodiments, $R^{4.2}$ is $-C(O)NH(CH_3)$. In embodiments, $R^{4.2}$ is $-C(O)N(CH_2CH_3)_2$. In embodiments, $R^{4.2}$

is -C(O)NH(CH_2CH_3) . In embodiments, $R^{4.2}$ is an unsubstituted cyclohexyl. In embodiments, $R^{4.2}$ is an unsubstituted morpholinyl. In embodiments, $R^{4.2}$ is an unsubstituted piperazinyl. In embodiments, $R^{4.2}$ is N-methyl substituted piperazinyl. In embodiments, $R^{4.2}$ is an unsubstituted pyridyl. In embodiments, $R^{4.2}$ is an unsubstituted cyclopentyl. In embodiments, $R^{4.2}$ is an unsubstituted cyclobutyl. In embodiments, $R^{4.2}$ is an unsubstituted naphthyl. In embodiments, $R^{4.2}$ is an unsubstituted 1-naphthyl. In embodiments, $R^{4.2}$ is an unsubstituted 2-naphthyl. In embodiments, $R^{4.2}$ is an unsubstituted 2-thienyl. In embodiments, $R^{4.2}$ is an unsubstituted 3-thienyl. In embodiments, $R^{4.2}$ is an unsubstituted 2-furanyl. In embodiments, $R^{4.2}$ is an unsubstituted 3-furanyl. In embodiments, $R^{4.2}$ is an unsubstituted 2-pyridyl. In embodiments, $R^{4.2}$ is an unsubstituted 3-pyridyl. In embodiments, $R^{4.2}$ is an unsubstituted 4-pyridyl. In embodiments, $R^{4.2}$ is an unsubstituted 3-pyrazolyl. In embodiments, $R^{4.2}$ is an unsubstituted 4-pyrazolyl. In embodiments, $R^{4.2}$ is an unsubstituted 5- pyrazolyl. In embodiments, $R^{4.2}$ is an unsubstituted 2-pyrrolyl. In embodiments, $R^{4.2}$ is an unsubstituted 3-pyrrolyl. In embodiments, $R^{4.2}$ is an unsubstituted 2-thiazolyl. In embodiments, $R^{4.2}$ is an unsubstituted 4-thiazolyl. In embodiments, $R^{4.2}$ is an unsubstituted 5-thiazolyl. In embodiments, $R^{4.2}$ is an unsubstituted thiazolyl. In embodiments, $R^{4.2}$ is substituted thiazolyl. In embodiments, $R^{4.2}$ is methyl substituted thiazolyl. In embodiments, $R^{4.2}$ is an unsubstituted thienyl. In embodiments, $R^{4.2}$ is substituted thienyl. In embodiments, $R^{4.2}$ is methyl substituted thienyl. In embodiments, $R^{4.2}$ is an unsubstituted pyrazolyl. In embodiments, $R^{4.2}$ is substituted pyrazolyl. In embodiments, $R^{4.2}$ is methyl substituted pyrazolyl. In embodiments, $R^{4.2}$ is an unsubstituted furanyl. In embodiments, $R^{4.2}$ is substituted furanyl. In embodiments, $R^{4.2}$ is methyl substituted furanyl.

[0286] In embodiments, $R^{4.2}$ is halogen. In embodiments, $R^{4.2}$ is –F. In embodiments, $R^{4.2}$ is –Cl. In embodiments, $R^{4.2}$ is –Br. In embodiments, $R^{4.2}$ is –I. In embodiments, $R^{4.2}$ is $-CX^{4.2}_3$. In embodiments, $R^{4.2}$ is $-CHX^{4.2}_2$. In embodiments, $R^{4.2}$ is $-CH_2X^{4.2}$. In embodiments, $R^{4.2}$ is $-OCX^{4.2}_3$. In embodiments, $R^{4.2}$ is $-OCH_2X^{4.2}$. In embodiments, $R^{4.2}$ is $-OCHX^{4.2}_2$. In embodiments, $R^{4.2}$ is -CN. In embodiments, $R^{4.2}$ is $-SO_{n4}R^{4.2D}$. In embodiments, $R^{4.2}$ is $-SO_{v4}NR^{4.2A}R^{4.2B}$. In embodiments, $R^{4.2}$ is $-NHC(O)NR^{4.2A}R^{4.2B}$. In embodiments, $R^{4.2}$ is $-N(O)_{m4}$. In embodiments, $R^{4.2}$ is $-NR^{4.2A}R^{4.2B}$. In embodiments, $R^{4.2}$ is $-C(O)R^{4.2C}$. In embodiments, $R^{4.2}$ is $-C(O)-OR^{4.2C}$. In embodiments, $R^{4.2}$ is $-C(O)NR^{4.2A}R^{4.2B}$. In embodiments, $R^{4.2}$ is $-OR^{4.2D}$. In embodiments, $R^{4.2}$ is $-NR^{4.2A}SO_2R^{4.2D}$. In embodiments, $R^{4.2}$ is $-NR^{4.2A}C(O)R^{4.2C}$. In embodiments, $R^{4.2}$ is $-NR^{4.2A}C(O)OR^{4.2C}$. In embodiments, $R^{4.2}$ is $-NR^{4.2A}OR^{4.2C}$. In embodiments, $R^{4.2}$ is -OH. In embodiments, $R^{4.2}$ is $-NH_2$. In embodiments,

$R^{4.2}$ is -COOH. In embodiments, $R^{4.2}$ is $-CONH_2$. In embodiments, $R^{4.2}$ is $-NO_2$. In embodiments, $R^{4.2}$ is –SH.

[0287] In embodiments, $R^{4.2}$ is substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.2}$ is substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.2}$ is an unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.2}$ is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.2}$ is substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.2}$ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.2}$ is substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.2}$ is substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.2}$ is an unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.2}$ is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.2}$ is substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.2}$ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.2}$ is substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.2}$ is substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.2}$ is an unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.2}$ is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.2}$ is substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.2}$ is an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0288] In embodiments, $R^{4.3}$ is an unsubstituted methyl. In embodiments, $R^{4.3}$ is $-C(O)N(CH_3)_2$. In embodiments, $R^{4.3}$ is –CN. In embodiments, $R^{4.3}$ is an unsubstituted methoxy. In embodiments, $R^{4.3}$ is an unsubstituted tert-butyl. In embodiments, $R^{4.3}$ is –OH. In embodiments, $R^{4.3}$ is an unsubstituted ethoxy. In embodiments, $R^{4.3}$ is $-N(CH_3)_2$. In embodiments, $R^{4.3}$ is –C(CN). In embodiments, $R^{4.3}$ is –SH. In embodiments, $R^{4.3}$ is $-SCH_3$. In embodiments, $R^{4.3}$ is $-SCH_2CH_3$. In embodiments, $R^{4.3}$ is an unsubstituted ethyl. In embodiments, $R^{4.3}$ is an unsubstituted propyl. In embodiments, $R^{4.3}$ is an unsubstituted isopropyl. In embodiments, $R^{4.3}$ is an unsubstituted butyl. In embodiments, $R^{4.3}$ is an unsubstituted isobutyl. In embodiments, $R^{4.3}$ is $-NH_2$. In embodiments, $R^{4.3}$ is $-NHCH_3$. In embodiments, $R^{4.3}$ is $-NHCH_2CH_3$. In embodiments, $R^{4.3}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.3}$ is $-N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.3}$ is halogen. In embodiments, $R^{4.3}$ is –F. In

embodiments, $R^{4.3}$ is –Cl. In embodiments, $R^{4.3}$ is –I. In embodiments, $R^{4.3}$ is –Br. In embodiments, $R^{4.3}$ is $-C(O)NH_2$. In embodiments, $R^{4.3}$ is $-C(O)NHCH_3$. In embodiments, $R^{4.3}$ is $-C(O)NHCH_2CH_3$. In embodiments, $R^{4.3}$ is $-C(O)N(CH_2CH_3)_2$. In embodiments, $R^{4.3}$ is $-C(O)N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.3}$ is $-CF_3$. In embodiments, $R^{4.3}$ is $-CHF_2$. In embodiments, $R^{4.3}$ is $-CH_2F$. In embodiments, $R^{4.3}$ is $-CCl_3$. In embodiments, $R^{4.3}$ is $-CHCl_2$. In embodiments, $R^{4.3}$ is $-CH_2Cl$. In embodiments, $R^{4.3}$ is $-CBr_3$. In embodiments, $R^{4.3}$ is $-CHBr_2$. In embodiments, $R^{4.3}$ is $-CH_2Br$. In embodiments, $R^{4.3}$ is $-CI_3$. In embodiments, $R^{4.3}$ is $-CHI_2$. In embodiments, $R^{4.3}$ is $-CH_2I$.

[0289] In embodiments, $R^{4.3}$ is an unsubstituted heteroalkyl. In embodiments, $R^{4.3}$ is an unsubstituted 2 to 5 membered heteroalkyl. In embodiments, $R^{4.3}$ is $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, or -SH. In embodiments, $R^{4.3}$ is $-OCH_3$. In embodiments, $R^{4.3}$ is $-OCH_2CH_3$. In embodiments, $R^{4.3}$ is $-N(CH_3)_2$. In embodiments, $R^{4.3}$ is $-NH_2$. In embodiments, $R^{4.3}$ is $-NH(CH_3)$. In embodiments, $R^{4.3}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.3}$ is $-NH(CH_2CH_3)$. In embodiments, $R^{4.3}$ is -SH. In embodiments, $R^{4.3}$ is $-OCH_2CH_2CH_3$. In embodiments, $R^{4.3}$ is an unsubstituted methoxy. In embodiments, $R^{4.3}$ is an unsubstituted ethoxy. In embodiments, $R^{4.3}$ is an unsubstituted propoxy. In embodiments, $R^{4.3}$ is an unsubstituted isopropoxy. In embodiments, $R^{4.3}$ is an unsubstituted butoxy. In embodiments, $R^{4.3}$ is an unsubstituted tert-butoxy. In embodiments, $R^{4.3}$ is an unsubstituted pentoxy. In embodiments, $R^{4.3}$ is an unsubstituted hexoxy.

[0290] In embodiments, $R^{4.3}$ is an unsubstituted methoxy. In embodiments, $R^{4.3}$ is an unsubstituted tert-butyl. In embodiments, $R^{4.3}$ is an unsubstituted phenoxy. In embodiments, $R^{4.3}$ is an unsubstituted methyl. In embodiments, $R^{4.3}$ is –OH. In embodiments, $R^{4.3}$ is an unsubstituted ethoxy. In embodiments, $R^{4.3}$ is $-N(CH_3)_2$. In embodiments, $R^{4.3}$ is –SH. In embodiments, $R^{4.3}$ is $-SCH_3$. In embodiments, $R^{4.3}$ is $-SCH_2CH_3$. In embodiments, $R^{4.3}$ is an unsubstituted ethyl. In embodiments, $R^{4.3}$ is an unsubstituted propyl. In embodiments, $R^{4.3}$ is an unsubstituted isopropyl. In embodiments, $R^{4.3}$ is an unsubstituted butyl. In embodiments, $R^{4.3}$ is an unsubstituted isobutyl. In embodiments, $R^{4.3}$ is $-NH_2$. In embodiments, $R^{4.3}$ is $-NHCH_3$. In embodiments, $R^{4.3}$ is $-NHCH_2CH_3$. In embodiments, $R^{4.3}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.3}$ is $-N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.3}$ is $-OCH_3$. In embodiments, $R^{4.3}$ is an unsubstituted phenyl. In embodiments, $R^{4.3}$ is $-C(O)N(CH_3)_2$. In embodiments, $R^{4.3}$ is $-C(O)NH(CH_3)$. In embodiments, $R^{4.3}$ is $-C(O)N(CH_2CH_3)_2$. In embodiments, $R^{4.3}$ is $-C(O)NH(CH_2CH_3)$. In embodiments, $R^{4.3}$ is an unsubstituted cyclohexyl. In embodiments, $R^{4.3}$ is an unsubstituted morpholinyl. In embodiments, $R^{4.3}$ is an unsubstituted piperazinyl. In

embodiments, $R^{4.3}$ is N-methyl substituted piperazinyl. In embodiments, $R^{4.3}$ is an unsubstituted pyridyl. In embodiments, $R^{4.3}$ is an unsubstituted cyclopentyl. In embodiments, $R^{4.3}$ is an unsubstituted cyclobutyl. In embodiments, $R^{4.3}$ is an unsubstituted naphthyl. In embodiments, $R^{4.3}$ is an unsubstituted 1-naphthyl. In embodiments, $R^{4.3}$ is an unsubstituted 2-naphthyl. In embodiments, $R^{4.3}$ is an unsubstituted 2-thienyl. In embodiments, $R^{4.3}$ is an unsubstituted 3-thienyl. In embodiments, $R^{4.3}$ is an unsubstituted 2-furanyl. In embodiments, $R^{4.3}$ is an unsubstituted 3-furanyl. In embodiments, $R^{4.3}$ is an unsubstituted 2-pyridyl. In embodiments, $R^{4.3}$ is an unsubstituted 3-pyridyl. In embodiments, $R^{4.3}$ is an unsubstituted 4-pyridyl. In embodiments, $R^{4.3}$ is an unsubstituted 3-pyrazolyl. In embodiments, $R^{4.3}$ is an unsubstituted 4-pyrazolyl. In embodiments, $R^{4.3}$ is an unsubstituted 5- pyrazolyl. In embodiments, $R^{4.3}$ is an unsubstituted 2-pyrrolyl. In embodiments, $R^{4.3}$ is an unsubstituted 3-pyrrolyl. In embodiments, $R^{4.3}$ is an unsubstituted 2-thiazolyl. In embodiments, $R^{4.3}$ is an unsubstituted 4-thiazolyl. In embodiments, $R^{4.3}$ is an unsubstituted 5-thiazolyl. In embodiments, $R^{4.3}$ is an unsubstituted thiazolyl. In embodiments, $R^{4.3}$ is substituted thiazolyl. In embodiments, $R^{4.3}$ is methyl substituted thiazolyl. In embodiments, $R^{4.3}$ is an unsubstituted thienyl. In embodiments, $R^{4.3}$ is substituted thienyl. In embodiments, $R^{4.3}$ is methyl substituted thienyl. In embodiments, $R^{4.3}$ is an unsubstituted pyrazolyl. In embodiments, $R^{4.3}$ is substituted pyrazolyl. In embodiments, $R^{4.3}$ is methyl substituted pyrazolyl. In embodiments, $R^{4.3}$ is an unsubstituted furanyl. In embodiments, $R^{4.3}$ is substituted furanyl. In embodiments, $R^{4.3}$ is methyl substituted furanyl.

[0291] In embodiments, $R^{4.3}$ is halogen. In embodiments, $R^{4.3}$ is –F. In embodiments, $R^{4.3}$ is –Cl. In embodiments, $R^{4.3}$ is –Br. In embodiments, $R^{4.3}$ is –I. In embodiments, $R^{4.3}$ is $-CX^{4.3}_3$. In embodiments, $R^{4.3}$ is $-CHX^{4.3}_2$. In embodiments, $R^{4.3}$ is $-CH_2X^{4.3}$. In embodiments, $R^{4.3}$ is $-OCX^{4.3}_3$. In embodiments, $R^{4.3}$ is $-OCH_2X^{4.3}$. In embodiments, $R^{4.3}$ is $-OCHX^{4.3}_2$. In embodiments, $R^{4.3}$ is -CN. In embodiments, $R^{4.3}$ is $-SO_{n4}R^{4.3D}$. In embodiments, $R^{4.3}$ is $-SO_{v4}NR^{4.3A}R^{4.3B}$. In embodiments, $R^{4.3}$ is $-NHC(O)NR^{4.3A}R^{4.3B}$. In embodiments, $R^{4.3}$ is $-N(O)_{m4}$. In embodiments, $R^{4.3}$ is $-NR^{4.3A}R^{4.3B}$. In embodiments, $R^{4.3}$ is $-C(O)R^{4.3C}$. In embodiments, $R^{4.3}$ is $-C(O)-OR^{4.3C}$. In embodiments, $R^{4.3}$ is $-C(O)NR^{4.3A}R^{4.3B}$. In embodiments, $R^{4.3}$ is $-OR^{4.3D}$. In embodiments, $R^{4.3}$ is $-NR^{4.3A}SO_2R^{4.3D}$. In embodiments, $R^{4.3}$ is $-NR^{4.3A}C(O)R^{4.3C}$. In embodiments, $R^{4.3}$ is $-NR^{4.3A}C(O)OR^{4.3C}$. In embodiments, $R^{4.3}$ is $-NR^{4.3A}OR^{4.3C}$. In embodiments, $R^{4.3}$ is -OH. In embodiments, $R^{4.3}$ is $-NH_2$. In embodiments, $R^{4.3}$ is -COOH. In embodiments, $R^{4.3}$ is $-CONH_2$. In embodiments, $R^{4.3}$ is $-NO_2$. In embodiments, $R^{4.3}$ is –SH.

[0292] In embodiments, $R^{4.3}$ is substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.3}$ is substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.3}$ is an unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.3}$ is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.3}$ is substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.3}$ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.3}$ is substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.3}$ is substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.3}$ is an unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.3}$ is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.3}$ is substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.3}$ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.3}$ is substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.3}$ is substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.3}$ is an unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.3}$ is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.3}$ is substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.3}$ is an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0293] In embodiments, $R^{4.4}$ is an unsubstituted methyl. In embodiments, $R^{4.4}$ is $-C(O)N(CH_3)_2$. In embodiments, $R^{4.4}$ is –CN. In embodiments, $R^{4.4}$ is an unsubstituted methoxy. In embodiments, $R^{4.4}$ is an unsubstituted tert-butyl. In embodiments, $R^{4.4}$ is –OH. In embodiments, $R^{4.4}$ is an unsubstituted ethoxy. In embodiments, $R^{4.4}$ is $-N(CH_3)_2$. In embodiments, $R^{4.4}$ is –C(CN). In embodiments, $R^{4.4}$ is –SH. In embodiments, $R^{4.4}$ is $-SCH_3$. In embodiments, $R^{4.4}$ is $–SCH_2CH_3$. In embodiments, $R^{4.4}$ is an unsubstituted ethyl. In embodiments, $R^{4.4}$ is an unsubstituted propyl. In embodiments, $R^{4.4}$ is an unsubstituted isopropyl. In embodiments, $R^{4.4}$ is an unsubstituted butyl. In embodiments, $R^{4.4}$ is an unsubstituted isobutyl. In embodiments, $R^{4.4}$ is $–NH_2$. In embodiments, $R^{4.4}$ is $-NHCH_3$. In embodiments, $R^{4.4}$ is $–NHCH_2CH_3$. In embodiments, $R^{4.4}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.4}$ is $-N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.4}$ is halogen. In embodiments, $R^{4.4}$ is –F. In embodiments, $R^{4.4}$ is –Cl. In embodiments, $R^{4.4}$ is –I. In embodiments, $R^{4.4}$ is –Br. In embodiments, $R^{4.4}$ is $–C(O)NH_2$. In embodiments, $R^{4.4}$ is $-C(O)NHCH_3$. In embodiments, $R^{4.4}$ is

–C(O)NHCH$_2$CH$_3$. In embodiments, R$^{4.4}$ is -C(O)N(CH$_2$CH$_3$)$_2$. In embodiments, R$^{4.4}$ is -C(O)N(CH$_3$)(CH$_2$CH$_3$). In embodiments, R$^{4.4}$ is -CF$_3$. In embodiments, R$^{4.4}$ is -CHF$_2$. In embodiments, R$^{4.4}$ is -CH$_2$F. In embodiments, R$^{4.4}$ is -CCl$_3$. In embodiments, R$^{4.4}$ is -CHCl$_2$. In embodiments, R$^{4.4}$ is -CH$_2$Cl. In embodiments, R$^{4.4}$ is -CBr$_3$. In embodiments, R$^{4.4}$ is -CHBr$_2$. In embodiments, R$^{4.4}$ is -CH$_2$Br. In embodiments, R$^{4.4}$ is -CI$_3$. In embodiments, R$^{4.4}$ is -CHI$_2$. In embodiments, R$^{4.4}$ is -CH$_2$I.

[0294] In embodiments, R$^{4.4}$ is an unsubstituted heteroalkyl. In embodiments, R$^{4.4}$ is an unsubstituted 2 to 5 membered heteroalkyl. In embodiments, R$^{4.4}$ is –OCH$_3$, -OCH$_2$CH$_3$, -N(CH$_3$)$_2$, -NH$_2$, -NH(CH$_3$), -N(CH$_2$CH$_3$)$_2$, -NH(CH$_2$CH$_3$), or -SH. In embodiments, R$^{4.4}$ is –OCH$_3$. In embodiments, R$^{4.4}$ is -OCH$_2$CH$_3$. In embodiments, R$^{4.4}$ is -N(CH$_3$)$_2$. In embodiments, R$^{4.4}$ is -NH$_2$. In embodiments, R$^{4.4}$ is -NH(CH$_3$) . In embodiments, R$^{4.4}$ is -N(CH$_2$CH$_3$)$_2$. In embodiments, R$^{4.4}$ is -NH(CH$_2$CH$_3$) . In embodiments, R$^{4.4}$ is -SH. In embodiments, R$^{4.4}$ is -OCH$_2$CH$_2$CH$_3$. In embodiments, R$^{4.4}$ is an unsubstituted methoxy. In embodiments, R$^{4.4}$ is an unsubstituted ethoxy. In embodiments, R$^{4.4}$ is an unsubstituted propoxy. In embodiments, R$^{4.4}$ is an unsubstituted isopropoxy. In embodiments, R$^{4.4}$ is an unsubstituted butoxy. In embodiments, R$^{4.4}$ is an unsubstituted tert-butoxy. In embodiments, R$^{4.4}$ is an unsubstituted pentoxy. In embodiments, R$^{4.4}$ is an unsubstituted hexoxy.

[0295] In embodiments, R$^{4.4}$ is an unsubstituted methoxy. In embodiments, R$^{4.4}$ is an unsubstituted tert-butyl. In embodiments, R$^{4.4}$ is an unsubstituted phenoxy. In embodiments, R$^{4.4}$ is an unsubstituted methyl. In embodiments, R$^{4.4}$ is –OH. In embodiments, R$^{4.4}$ is an unsubstituted ethoxy. In embodiments, R$^{4.4}$ is -N(CH$_3$)$_2$. In embodiments, R$^{4.4}$ is –SH. In embodiments, R$^{4.4}$ is -SCH$_3$. In embodiments, R$^{4.4}$ is –SCH$_2$CH$_3$. In embodiments, R$^{4.4}$ is an unsubstituted ethyl. In embodiments, R$^{4.4}$ is an unsubstituted propyl. In embodiments, R$^{4.4}$ is an unsubstituted isopropyl. In embodiments, R$^{4.4}$ is an unsubstituted butyl. In embodiments, R$^{4.4}$ is an unsubstituted isobutyl. In embodiments, R$^{4.4}$ is –NH$_2$. In embodiments, R$^{4.4}$ is -NHCH$_3$. In embodiments, R$^{4.4}$ is –NHCH$_2$CH$_3$. In embodiments, R$^{4.4}$ is -N(CH$_2$CH$_3$)$_2$. In embodiments, R$^{4.4}$ is -N(CH$_3$)(CH$_2$CH$_3$). In embodiments, R$^{4.4}$ is -OCH$_3$. In embodiments, R$^{4.4}$ is an unsubstituted phenyl. In embodiments, R$^{4.4}$ is –C(O)N(CH$_3$)$_2$. In embodiments, R$^{4.4}$ is –C(O)NH(CH$_3$) . In embodiments, R$^{4.4}$ is -C(O)N(CH$_2$CH$_3$)$_2$. In embodiments, R$^{4.4}$ is -C(O)NH(CH$_2$CH$_3$) . In embodiments, R$^{4.4}$ is an unsubstituted cyclohexyl. In embodiments, R$^{4.4}$ is an unsubstituted morpholinyl. In embodiments, R$^{4.4}$ is an unsubstituted piperazinyl. In embodiments, R$^{4.4}$ is N-methyl substituted piperazinyl. In embodiments, R$^{4.4}$ is an unsubstituted pyridyl. In embodiments, R$^{4.4}$ is an unsubstituted cyclopentyl. In embodiments, R$^{4.4}$ is an

unsubstituted cyclobutyl. In embodiments, $R^{4.4}$ is an unsubstituted naphthyl. In embodiments, $R^{4.4}$ is an unsubstituted 1-naphthyl. In embodiments, $R^{4.4}$ is an unsubstituted 2-naphthyl. In embodiments, $R^{4.4}$ is an unsubstituted 2-thienyl. In embodiments, $R^{4.4}$ is an unsubstituted 3-thienyl. In embodiments, $R^{4.4}$ is an unsubstituted 2-furanyl. In embodiments, $R^{4.4}$ is an unsubstituted 3-furanyl. In embodiments, $R^{4.4}$ is an unsubstituted 2-pyridyl. In embodiments, $R^{4.4}$ is an unsubstituted 3-pyridyl. In embodiments, $R^{4.4}$ is an unsubstituted 4-pyridyl. In embodiments, $R^{4.4}$ is an unsubstituted 3-pyrazolyl. In embodiments, $R^{4.4}$ is an unsubstituted 4-pyrazolyl. In embodiments, $R^{4.4}$ is an unsubstituted 5- pyrazolyl. In embodiments, $R^{4.4}$ is an unsubstituted 2-pyrrolyl. In embodiments, $R^{4.4}$ is an unsubstituted 3-pyrrolyl. In embodiments, $R^{4.4}$ is an unsubstituted 2-thiazolyl. In embodiments, $R^{4.4}$ is an unsubstituted 4-thiazolyl. In embodiments, $R^{4.4}$ is an unsubstituted 5-thiazolyl. In embodiments, $R^{4.4}$ is an unsubstituted thiazolyl. In embodiments, $R^{4.4}$ is substituted thiazolyl. In embodiments, $R^{4.4}$ is methyl substituted thiazolyl. In embodiments, $R^{4.4}$ is an unsubstituted thienyl. In embodiments, $R^{4.4}$ is substituted thienyl. In embodiments, $R^{4.4}$ is methyl substituted thienyl. In embodiments, $R^{4.4}$ is an unsubstituted pyrazolyl. In embodiments, $R^{4.4}$ is substituted pyrazolyl. In embodiments, $R^{4.4}$ is methyl substituted pyrazolyl. In embodiments, $R^{4.4}$ is an unsubstituted furanyl. In embodiments, $R^{4.4}$ is substituted furanyl. In embodiments, $R^{4.4}$ is methyl substituted furanyl.

[0296] In embodiments, $R^{4.4}$ is halogen. In embodiments, $R^{4.4}$ is –F. In embodiments, $R^{4.4}$ is –Cl. In embodiments, $R^{4.4}$ is –Br. In embodiments, $R^{4.4}$ is –I. In embodiments, $R^{4.4}$ is $-CX^{4.4}_3$. In embodiments, $R^{4.4}$ is $-CHX^{4.4}_2$. In embodiments, $R^{4.4}$ is $-CH_2X^{4.4}$. In embodiments, $R^{4.4}$ is $-OCX^{4.4}_3$. In embodiments, $R^{4.4}$ is $-OCH_2X^{4.4}$. In embodiments, $R^{4.4}$ is $-OCHX^{4.4}_2$. In embodiments, $R^{4.4}$ is -CN. In embodiments, $R^{4.4}$ is $-SO_{n4}R^{4.4D}$. In embodiments, $R^{4.4}$ is $-SO_{v4}NR^{4.4A}R^{4.4B}$. In embodiments, $R^{4.4}$ is $-NHC(O)NR^{4.4A}R^{4.4B}$. In embodiments, $R^{4.4}$ is $-N(O)_{m4}$. In embodiments, $R^{4.4}$ is $-NR^{4.4A}R^{4.4B}$. In embodiments, $R^{4.4}$ is $-C(O)R^{4.4C}$. In embodiments, $R^{4.4}$ is $-C(O)-OR^{4.4C}$. In embodiments, $R^{4.4}$ is $-C(O)NR^{4.4A}R^{4.4B}$. In embodiments, $R^{4.4}$ is $-OR^{4.4D}$. In embodiments, $R^{4.4}$ is $-NR^{4.4A}SO_2R^{4.4D}$. In embodiments, $R^{4.4}$ is $-NR^{4.4A}C(O)R^{4.4C}$. In embodiments, $R^{4.4}$ is $-NR^{4.4A}C(O)OR^{4.4C}$. In embodiments, $R^{4.4}$ is $-NR^{4.4A}OR^{4.4C}$. In embodiments, $R^{4.4}$ is -OH. In embodiments, $R^{4.4}$ is $-NH_2$. In embodiments, $R^{4.4}$ is -COOH. In embodiments, $R^{4.4}$ is $-CONH_2$. In embodiments, $R^{4.4}$ is $-NO_2$. In embodiments, $R^{4.4}$ is –SH.

[0297] In embodiments, $R^{4.4}$ is substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.4}$ is substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.4}$ is an unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.4}$ is substituted or

unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.4}$ is substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.4}$ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.4}$ is substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.4}$ is substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.4}$ is an unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.4}$ is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.4}$ is substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.4}$ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.4}$ is substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.4}$ is substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.4}$ is an unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.4}$ is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.4}$ is substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.4}$ is an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0298] In embodiments, $R^{4.5}$ is an unsubstituted methyl. In embodiments, $R^{4.5}$ is $-C(O)N(CH_3)_2$. In embodiments, $R^{4.5}$ is –CN. In embodiments, $R^{4.5}$ is an unsubstituted methoxy. In embodiments, $R^{4.5}$ is an unsubstituted tert-butyl. In embodiments, $R^{4.5}$ is –OH. In embodiments, $R^{4.5}$ is an unsubstituted ethoxy. In embodiments, $R^{4.5}$ is $-N(CH_3)_2$. In embodiments, $R^{4.5}$ is –SH. In embodiments, $R^{4.5}$ is $-SCH_3$. In embodiments, $R^{4.5}$ is $–SCH_2CH_3$. In embodiments, $R^{4.5}$ is an unsubstituted ethyl. In embodiments, $R^{4.5}$ is an unsubstituted propyl. In embodiments, $R^{4.5}$ is an unsubstituted isopropyl. In embodiments, $R^{4.5}$ is an unsubstituted butyl. In embodiments, $R^{4.5}$ is an unsubstituted isobutyl. In embodiments, $R^{4.5}$ is $–NH_2$. In embodiments, $R^{4.5}$ is $-NHCH_3$. In embodiments, $R^{4.5}$ is –C(CN). In embodiments, $R^{4.5}$ is $–NHCH_2CH_3$. In embodiments, $R^{4.5}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.5}$ is $-N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.5}$ is halogen. In embodiments, $R^{4.5}$ is –F. In embodiments, $R^{4.5}$ is –Cl. In embodiments, $R^{4.5}$ is –I. In embodiments, $R^{4.5}$ is –Br. In embodiments, $R^{4.5}$ is $–C(O)NH_2$. In embodiments, $R^{4.5}$ is $-C(O)NHCH_3$. In embodiments, $R^{4.5}$ is $–C(O)NHCH_2CH_3$. In embodiments, $R^{4.5}$ is $-C(O)N(CH_2CH_3)_2$. In embodiments, $R^{4.5}$ is $-C(O)N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.5}$ is $-CF_3$. In embodiments, $R^{4.5}$ is $-CHF_2$. In embodiments, $R^{4.5}$ is $-CH_2F$. In embodiments, $R^{4.5}$ is $-CCl_3$. In embodiments, $R^{4.5}$ is $-CHCl_2$. In embodiments, $R^{4.5}$ is $-CH_2Cl$.

In embodiments, $R^{4.5}$ is $-CBr_3$. In embodiments, $R^{4.5}$ is $-CHBr_2$. In embodiments, $R^{4.5}$ is $-CH_2Br$. In embodiments, $R^{4.5}$ is $-CI_3$. In embodiments, $R^{4.5}$ is $-CHI_2$. In embodiments, $R^{4.5}$ is $-CH_2I$.

[0299] In embodiments, $R^{4.5}$ is an unsubstituted heteroalkyl. In embodiments, $R^{4.5}$ is an unsubstituted 2 to 5 membered heteroalkyl. In embodiments, $R^{4.5}$ is $-OCH_3$, $-OCH_2CH_3$, $-N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, or $-SH$. In embodiments, $R^{4.5}$ is $-OCH_3$. In embodiments, $R^{4.5}$ is $-OCH_2CH_3$. In embodiments, $R^{4.5}$ is $-N(CH_3)_2$. In embodiments, $R^{4.5}$ is $-NH_2$. In embodiments, $R^{4.5}$ is $-NH(CH_3)$. In embodiments, $R^{4.5}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.5}$ is $-NH(CH_2CH_3)$. In embodiments, $R^{4.5}$ is $-SH$. In embodiments, $R^{4.5}$ is $-OCH_2CH_2CH_3$. In embodiments, $R^{4.5}$ is an unsubstituted methoxy. In embodiments, $R^{4.5}$ is an unsubstituted ethoxy. In embodiments, $R^{4.5}$ is an unsubstituted propoxy. In embodiments, $R^{4.5}$ is an unsubstituted isopropoxy. In embodiments, $R^{4.5}$ is an unsubstituted butoxy. In embodiments, $R^{4.5}$ is an unsubstituted tert-butoxy. In embodiments, $R^{4.5}$ is an unsubstituted pentoxy. In embodiments, $R^{4.5}$ is an unsubstituted hexoxy.

[0300] In embodiments, $R^{4.5}$ is an unsubstituted methoxy. In embodiments, $R^{4.5}$ is an unsubstituted tert-butyl. In embodiments, $R^{4.5}$ is an unsubstituted phenoxy. In embodiments, $R^{4.5}$ is an unsubstituted methyl. In embodiments, $R^{4.5}$ is $-OH$. In embodiments, $R^{4.5}$ is an unsubstituted ethoxy. In embodiments, $R^{4.5}$ is $-N(CH_3)_2$. In embodiments, $R^{4.5}$ is $-SH$. In embodiments, $R^{4.5}$ is $-SCH_3$. In embodiments, $R^{4.5}$ is $-SCH_2CH_3$. In embodiments, $R^{4.5}$ is an unsubstituted ethyl. In embodiments, $R^{4.5}$ is an unsubstituted propyl. In embodiments, $R^{4.5}$ is an unsubstituted isopropyl. In embodiments, $R^{4.5}$ is an unsubstituted butyl. In embodiments, $R^{4.5}$ is an unsubstituted isobutyl. In embodiments, $R^{4.5}$ is $-NH_2$. In embodiments, $R^{4.5}$ is $-NHCH_3$. In embodiments, $R^{4.5}$ is $-NHCH_2CH_3$. In embodiments, $R^{4.5}$ is $-N(CH_2CH_3)_2$. In embodiments, $R^{4.5}$ is $-N(CH_3)(CH_2CH_3)$. In embodiments, $R^{4.5}$ is $-OCH_3$. In embodiments, $R^{4.5}$ is an unsubstituted phenyl. In embodiments, $R^{4.5}$ is $-C(O)N(CH_3)_2$. In embodiments, $R^{4.5}$ is $-C(O)NH(CH_3)$. In embodiments, $R^{4.5}$ is $-C(O)N(CH_2CH_3)_2$. In embodiments, $R^{4.5}$ is $-C(O)NH(CH_2CH_3)$. In embodiments, $R^{4.5}$ is an unsubstituted cyclohexyl. In embodiments, $R^{4.5}$ is an unsubstituted morpholinyl. In embodiments, $R^{4.5}$ is an unsubstituted piperazinyl. In embodiments, $R^{4.5}$ is N-methyl substituted piperazinyl. In embodiments, $R^{4.5}$ is an unsubstituted pyridyl. In embodiments, $R^{4.5}$ is an unsubstituted cyclopentyl. In embodiments, $R^{4.5}$ is an unsubstituted cyclobutyl. In embodiments, $R^{4.5}$ is an unsubstituted naphthyl. In embodiments, $R^{4.5}$ is an unsubstituted 1-naphthyl. In embodiments, $R^{4.5}$ is an unsubstituted 2-naphthyl. In embodiments, $R^{4.5}$ is an unsubstituted 2-thienyl. In embodiments, $R^{4.5}$ is an unsubstituted 3-

thienyl. In embodiments, $R^{4.5}$ is an unsubstituted 2-furanyl. In embodiments, $R^{4.5}$ is an unsubstituted 3-furanyl. In embodiments, $R^{4.5}$ is an unsubstituted 2-pyridyl. In embodiments, $R^{4.5}$ is an unsubstituted 3-pyridyl. In embodiments, $R^{4.5}$ is an unsubstituted 4-pyridyl. In embodiments, $R^{4.5}$ is an unsubstituted 3-pyrazolyl. In embodiments, $R^{4.5}$ is an unsubstituted 4-pyrazolyl. In embodiments, $R^{4.5}$ is an unsubstituted 5- pyrazolyl. In embodiments, $R^{4.5}$ is an unsubstituted 2-pyrrolyl. In embodiments, $R^{4.5}$ is an unsubstituted 3-pyrrolyl. In embodiments, $R^{4.5}$ is an unsubstituted 2-thiazolyl. In embodiments, $R^{4.5}$ is an unsubstituted 4-thiazolyl. In embodiments, $R^{4.5}$ is an unsubstituted 5-thiazolyl. In embodiments, $R^{4.5}$ is an unsubstituted thiazolyl. In embodiments, $R^{4.5}$ is substituted thiazolyl. In embodiments, $R^{4.5}$ is methyl substituted thiazolyl. In embodiments, $R^{4.5}$ is an unsubstituted thienyl. In embodiments, $R^{4.5}$ is substituted thienyl. In embodiments, $R^{4.5}$ is methyl substituted thienyl. In embodiments, $R^{4.5}$ is an unsubstituted pyrazolyl. In embodiments, $R^{4.5}$ is substituted pyrazolyl. In embodiments, $R^{4.5}$ is methyl substituted pyrazolyl. In embodiments, $R^{4.5}$ is an unsubstituted furanyl. In embodiments, $R^{4.5}$ is substituted furanyl. In embodiments, $R^{4.5}$ is methyl substituted furanyl.

[0301] In embodiments, $R^{4.5}$ is halogen. In embodiments, $R^{4.5}$ is –F. In embodiments, $R^{4.5}$ is –Cl. In embodiments, $R^{4.5}$ is –Br. In embodiments, $R^{4.5}$ is –I. In embodiments, $R^{4.5}$ is $-CX^{4.5}_3$. In embodiments, $R^{4.5}$ is $-CHX^{4.5}_2$. In embodiments, $R^{4.5}$ is $-CH_2X^{4.5}$. In embodiments, $R^{4.5}$ is $-OCX^{4.5}_3$. In embodiments, $R^{4.5}$ is $-OCH_2X^{4.5}$. In embodiments, $R^{4.5}$ is $-OCHX^{4.5}_2$. In embodiments, $R^{4.5}$ is -CN. In embodiments, $R^{4.5}$ is $-SO_{n4}R^{4.5D}$. In embodiments, $R^{4.5}$ is $-SO_{v4}NR^{4.5A}R^{4.5B}$. In embodiments, $R^{4.5}$ is $-NHC(O)NR^{4.5A}R^{4.5B}$. In embodiments, $R^{4.5}$ is $-N(O)_{m4}$. In embodiments, $R^{4.5}$ is $-NR^{4.5A}R^{4.5B}$. In embodiments, $R^{4.5}$ is $-C(O)R^{4.5C}$. In embodiments, $R^{4.5}$ is $-C(O)-OR^{4.5C}$. In embodiments, $R^{4.5}$ is $-C(O)NR^{4.5A}R^{4.5B}$. In embodiments, $R^{4.5}$ is $-OR^{4.5D}$. In embodiments, $R^{4.5}$ is $-NR^{4.5A}SO_2R^{4.5D}$. In embodiments, $R^{4.5}$ is $-NR^{4.5A}C(O)R^{4.5C}$. In embodiments, $R^{4.5}$ is $-NR^{4.5A}C(O)OR^{4.5C}$. In embodiments, $R^{4.5}$ is $-NR^{4.5A}OR^{4.5C}$. In embodiments, $R^{4.5}$ is -OH. In embodiments, $R^{4.5}$ is $-NH_2$. In embodiments, $R^{4.5}$ is -COOH. In embodiments, $R^{4.5}$ is $-CONH_2$. In embodiments, $R^{4.5}$ is $-NO_2$. In embodiments, $R^{4.5}$ is –SH.

[0302] In embodiments, $R^{4.5}$ is substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.5}$ is substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.5}$ is an unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, $R^{4.5}$ is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.5}$ is substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^{4.5}$ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6

membered, or 2 to 4 membered). In embodiments, $R^{4.5}$ is substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.5}$ is substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.5}$ is an unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, $R^{4.5}$ is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.5}$ is substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.5}$ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, $R^{4.5}$ is substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.5}$ is substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.5}$ is an unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, $R^{4.5}$ is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.5}$ is substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{4.5}$ is an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0303] In embodiments, R^{4A} is independently hydrogen. In embodiments, R^{4A} is independently $-CX^{4A}_3$. In embodiments, R^{4A} is independently $-CHX^{4A}_2$. In embodiments, R^{4A} is independently $-CH_2X^{4A}$. In embodiments, R^{4A} is independently -CN. In embodiments, R^{4A} is independently -COOH. In embodiments, R^{4A} is independently $-CONH_2$.

[0304] In embodiments, R^{4A} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4A} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4A} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4A} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4A} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4A} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4A} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4A} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4A} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4A} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4A} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4A} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered).

In embodiments, R^{4A} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4A} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4A} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4A} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4A} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4A} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4A} is independently unsubstituted methyl. In embodiments, R^{4A} is independently unsubstituted ethyl. In embodiments, R^{4A} is independently unsubstituted propyl. In embodiments, R^{4A} is independently unsubstituted isopropyl. In embodiments, R^{4A} is independently unsubstituted tert-butyl.

[0305] In embodiments, R^{4B} is independently hydrogen. In embodiments, R^{4B} is independently $-CX^{4B}_3$. In embodiments, R^{4B} is independently $-CHX^{4B}_2$. In embodiments, R^{4B} is independently $-CH_2X^{4B}$. In embodiments, R^{4B} is independently -CN. In embodiments, R^{4B} is independently -COOH. In embodiments, R^{4B} is independently $-CONH_2$.

[0306] In embodiments, R^{4B} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4B} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4B} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4B} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4B} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4B} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4B} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4B} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4B} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4B} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4B} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4B} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4B} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4B} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4B} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In

embodiments, R^{4B} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4B} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4B} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4B} is independently unsubstituted methyl. In embodiments, R^{4B} is independently unsubstituted ethyl. In embodiments, R^{4B} is independently unsubstituted propyl. In embodiments, R^{4B} is independently unsubstituted isopropyl. In embodiments, R^{4B} is independently unsubstituted tert-butyl.

[0307] In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heterocycloalkyl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 10 membered heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 6 membered

heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 6 membered heteroaryl.

[0308] In embodiments, R^{4C} is independently hydrogen. In embodiments, R^{4C} is independently $-CX^{4C}_3$. In embodiments, R^{4C} is independently $-CHX^{4C}_2$. In embodiments, R^{4C} is independently $-CH_2X^{4C}$. In embodiments, R^{4C} is independently -CN. In embodiments, R^{4C} is independently -COOH. In embodiments, R^{4C} is independently $-CONH_2$.

[0309] In embodiments, R^{4C} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4C} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4C} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4C} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4C} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4C} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4C} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4C} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4C} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4C} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4C} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4C} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4C} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4C} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4C} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4C} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4C} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4C} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4C} is independently unsubstituted methyl. In embodiments, R^{4C} is independently unsubstituted ethyl. In embodiments, R^{4C} is

independently unsubstituted propyl. In embodiments, R^{4C} is independently unsubstituted isopropyl. In embodiments, R^{4C} is independently unsubstituted tert-butyl.

[0310] In embodiments, R^{4D} is independently hydrogen. In embodiments, R^{4D} is independently $-CX^{4D}_3$. In embodiments, R^{4D} is independently $-CHX^{4D}_2$. In embodiments, R^{4D} is independently $-CH_2X^{4D}$. In embodiments, R^{4D} is independently -CN. In embodiments, R^{4D} is independently -COOH. In embodiments, R^{4D} is independently $-CONH_2$.

[0311] In embodiments, R^{4D} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4D} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4D} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{4D} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4D} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4D} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{4D} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4D} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4D} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{4D} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4D} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4D} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{4D} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4D} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4D} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{4D} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4D} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4D} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{4D} is independently unsubstituted methyl. In embodiments, R^{4D} is independently unsubstituted ethyl. In embodiments, R^{4D} is independently unsubstituted propyl. In embodiments, R^{4D} is independently unsubstituted isopropyl. In embodiments, R^{4D} is independently unsubstituted tert-butyl.

[0312] In embodiments, R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, R^{29}-substituted or unsubstituted alkyl, R^{29}-substituted or unsubstituted heteroalkyl, R^{29}-substituted or unsubstituted cycloalkyl, R^{29}-substituted or unsubstituted heterocycloalkyl, R^{29}-substituted or unsubstituted aryl, or R^{29}-substituted or unsubstituted heteroaryl. In embodiments, R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$,-CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{29}-substituted or unsubstituted C_1-C_8 alkyl, R^{29}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{29}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{29}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{29}-substituted or unsubstituted phenyl, or R^{29}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^4 is –F, -Cl, -Br, or –I. In embodiments, R^4 is independently hydrogen. In embodiments, R^4 is independently methyl. In embodiments, R^4 is independently ethyl.

[0313] R^{29} is independently oxo, halogen, $-CX^{29}_3$, $-CHX^{29}_2$, $-CH_2X^{29}$, $-OCX^{29}_3$, $-OCHX^{29}_2$, $-OCH_2X^{29}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{30}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{30}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{30}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{30}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{30}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{30}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{29} is –F, -Cl, -Br, or –I.

[0314] R^{30} is independently oxo, halogen, $-CX^{30}_3$, $-CHX^{30}_2$, $-CH_2X^{30}$, $-OCX^{30}_3$, $-OCHX^{30}_2$, $-OCH_2X^{30}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{31}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{31}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{31}-substituted or unsubstituted cycloalkyl

(e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{31}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{31}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{31}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{30} is –F, -Cl, -Br, or –I.

[0315] In embodiments, R^{4A} is independently hydrogen, $-CX^{4A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{4A}_2$, $-CH_2X^{4A}$, R^{29A}-substituted or unsubstituted alkyl, R^{29A}-substituted or unsubstituted heteroalkyl, R^{29A}-substituted or unsubstituted cycloalkyl, R^{29A}-substituted or unsubstituted heterocycloalkyl, R^{29A}-substituted or unsubstituted aryl, or R^{29A}-substituted or unsubstituted heteroaryl. In embodiments, R^{4A} is independently hydrogen, $-CX^{4A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{4A}_2$, $-CH_2X^{4A}$, R^{29A}-substituted or unsubstituted C_1-C_8 alkyl, R^{29A}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{29A}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{29A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{29A}-substituted or unsubstituted phenyl, or R^{29A}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{4A} is –F, -Cl, -Br, or –I. In embodiments, R^{4A} is independently hydrogen. In embodiments, R^{4A} is independently methyl. In embodiments, R^{4A} is independently ethyl.

[0316] In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{29A}-substituted or unsubstituted heterocycloalkyl or R^{29A}-substituted or unsubstituted heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{29A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{29A}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0317] R^{29A} is independently oxo, halogen, $-CX^{29A}_3$, $-CHX^{29A}_2$, $-CH_2X^{29A}$, $-OCX^{29A}_3$, $-OCHX^{29A}_2$, $-OCH_2X^{29A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{30A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{30A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{30A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{30A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{30A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{30A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{29A} is –F, -Cl, -Br, or –I.

[0318] R^{30A} is independently oxo, halogen, $-CX^{30A}_3$, $-CHX^{30A}_2$, $-CH_2X^{30A}$, $-OCX^{30A}_3$, $-OCHX^{30A}_2$, $-OCH_2X^{30A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{31A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{31A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{31A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{31A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{31A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{31A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{30A} is –F, -Cl, -Br, or –I.

[0319] In embodiments, R^{4B} is independently hydrogen, $-CX^{4B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{4B}_2$, $-CH_2X^{4B}$, R^{29B}-substituted or unsubstituted alkyl, R^{29B}-substituted or unsubstituted heteroalkyl, R^{29B}-substituted or unsubstituted cycloalkyl, R^{29B}-substituted or unsubstituted heterocycloalkyl, R^{29B}-substituted or unsubstituted aryl, or R^{29B}-substituted or unsubstituted heteroaryl. In embodiments, R^{4B} is independently hydrogen, $-CX^{4B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{4B}_2$, $-CH_2X^{4B}$, R^{29B}-substituted or unsubstituted C_1-C_8 alkyl, R^{29B}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{29B}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{29B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{29B}-substituted or unsubstituted phenyl, or R^{29B}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{4B} is –F, -Cl, -Br, or –I. In embodiments, R^{4B} is independently hydrogen. In embodiments, R^{4B} is independently methyl. In embodiments, R^{4B} is independently ethyl.

[0320] In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{29B}-substituted or unsubstituted heterocycloalkyl or R^{29B}-substituted or unsubstituted heteroaryl. In embodiments, R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{29B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{29B}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0321] R^{29B} is independently oxo, halogen, $-CX^{29B}_3$, $-CHX^{29B}_2$, $-CH_2X^{29B}$, $-OCX^{29B}_3$, $-OCHX^{29B}_2$, $-OCH_2X^{29B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{30B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{30B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, or 2 to 4 membered), R^{30B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{30B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{30B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{30B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{29B} is –F, -Cl, -Br, or –I.

[0322] R^{30B} is independently oxo, halogen, $-CX^{30B}_3$, $-CHX^{30B}_2$, $-CH_2X^{30B}$, $-OCX^{30B}_3$, $-OCHX^{30B}_2$, $-OCH_2X^{30B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{31A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{31A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{31A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{31A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{31A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{31A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{30B} is –F, -Cl, -Br, or –I.

[0323] In embodiments, R^{4C} is independently hydrogen, $-CX^{4C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{4C}_2$, $-CH_2X^{4C}$, R^{29C}-substituted or unsubstituted alkyl, R^{29C}-substituted or unsubstituted heteroalkyl, R^{29C}-substituted or unsubstituted cycloalkyl, R^{29C}-substituted or unsubstituted heterocycloalkyl, R^{29C}-substituted or unsubstituted aryl, or R^{29C}-substituted or unsubstituted heteroaryl. In embodiments, R^{4C} is independently hydrogen, $-CX^{4C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{4C}_2$, $-CH_2X^{4C}$, R^{29C}-substituted or unsubstituted C_1-C_8 alkyl, R^{29C}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{29C}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{29C}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{29C}-substituted or unsubstituted phenyl, or R^{29C}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{4C} is –F, -Cl, -Br, or –I. In embodiments, R^{4C} is independently hydrogen. In embodiments, R^{4C} is independently methyl. In embodiments, R^{4C} is independently ethyl.

[0324] R^{29C} is independently oxo, halogen, $-CX^{29C}_3$, $-CHX^{29C}_2$, $-CH_2X^{29C}$, $-OCX^{29C}_3$, $-OCHX^{29C}_2$, $-OCH_2X^{29C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{30C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{30C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, or 2 to 4 membered), R^{30C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{30C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{30C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{30C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{29C} is –F, -Cl, -Br, or –I.

[0325] R^{30C} is independently oxo, halogen, $-CX^{30C}_3$, $-CHX^{30C}_2$, $-CH_2X^{30C}$, $-OCX^{30C}_3$, $-OCHX^{30C}_2$, $-OCH_2X^{30C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{31A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{31A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{31A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{31A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{31A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{31A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{30C} is –F, -Cl, -Br, or –I.

[0326] In embodiments, R^{4D} is independently hydrogen, $-CX^{4D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{4D}_2$, $-CH_2X^{4D}$, R^{29D}-substituted or unsubstituted alkyl, R^{29D}-substituted or unsubstituted heteroalkyl, R^{29D}-substituted or unsubstituted cycloalkyl, R^{29D}-substituted or unsubstituted heterocycloalkyl, R^{29D}-substituted or unsubstituted aryl, or R^{29D}-substituted or unsubstituted heteroaryl. In embodiments, R^{4D} is independently hydrogen, $-CX^{4D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{4D}_2$, $-CH_2X^{4D}$, R^{29D}-substituted or unsubstituted C_1-C_8 alkyl, R^{29D}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{29D}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{29D}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{29D}-substituted or unsubstituted phenyl, or R^{29D}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{4D} is –F, -Cl, -Br, or –I. In embodiments, R^{4D} is independently hydrogen. In embodiments, R^{4D} is independently methyl. In embodiments, R^{4D} is independently ethyl.

[0327] R^{29D} is independently oxo, halogen, $-CX^{29D}_3$, $-CHX^{29D}_2$, $-CH_2X^{29D}$, $-OCX^{29D}_3$, $-OCHX^{29D}_2$, $-OCH_2X^{29D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{30D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{30D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, or 2 to 4 membered), R^{30D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{30D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{30D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{30D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{29D} is –F, -Cl, -Br, or –I.

[0328] R^{30D} is independently oxo, halogen, $-CX^{30D}_3$, $-CHX^{30D}_2$, $-CH_2X^{30D}$, $-OCX^{30D}_3$, $-OCHX^{30D}_2$, $-OCH_2X^{30D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{31A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{31A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{31A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{31A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{31A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{31A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{30D} is –F, -Cl, -Br, or –I.

[0329] R^{31}, R^{31A}, R^{31B}, R^{31C}, and R^{31D} are independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH,unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0330] In embodiments, L^1 is a bond, -C(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^1 is a substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^1 is $–C(O)CH_2CH_2CH_2$-, $–C(O)CH_2CH_2$-, or $–C(O)CH_2$-.

[0331] In embodiments, L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, substituted or unsubstituted C_1-C_8 alkylene, substituted or unsubstituted 2 to 8 membered heteroalkylene, substituted or unsubstituted C_3-C_8 cycloalkylene, substituted or unsubstituted 3 to 8 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to

6 membered heteroarylene. In embodiments, L^1 is a bond. In embodiments, L^1 is a substituted or unsubstituted C_1-C_6 alkylene, substituted or unsubstituted 2 to 6 membered heteroalkylene, substituted or unsubstituted C_3-C_6 cycloalkylene, substituted or unsubstituted 3 to 6 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene. In embodiments, L^1 is an unsubstituted C_1-C_6 alkylene, unsubstituted 2 to 6 membered heteroalkylene, or unsubstituted C_3-C_6 cycloalkylene. In embodiments, L^1 is an unsubstituted methylene.

[0332] In embodiments, L^1 is a bond. In embodiments, L^1 is -$S(O)_2$-. In embodiments, L^1 is -$S(O)_2$-Ph-. In embodiments, L^1 is -NR^6-. In embodiments, L^1 is -O-. In embodiments, L^1 is -S-. In embodiments, L^1 is -C(O)- . In embodiments, L^1 is -$C(O)NR^6$-. In embodiments, L^1 is -$NR^6C(O)$- . In embodiments, L^1 is -$NR^6C(O)NH$-. In embodiments, L^1 is -$NHC(O)NR^6$-. In embodiments, L^1 is -C(O)O-. In embodiments, L^1 is -OC(O)-. In embodiments, L^1 is -NH-. In embodiments, L^1 is -C(O)NH-. In embodiments, L^1 is -NHC(O)- . In embodiments, L^1 is -NHC(O)NH-. In embodiments, L^1 is $–CH_2$-. In embodiments, L^1 is $–OCH_2$-. In embodiments, L^1 is $–CH_2O$-. In embodiments, L^1 is $–CH_2CH_2$-. In embodiments, L^1 is $–SCH_2$-. In embodiments, L^1 is $–CH_2S$-. In embodiments, L^1 is –CHCH-. In embodiments, L^1 is –CC-. In embodiments, L^1 is $–NHCH_2$-. In embodiments, L^1 is $–CH_2NH$-.

[0333] In embodiments, L^1 is a substituted or unsubstituted alkylene. In embodiments, L^1 is a substituted or unsubstituted heteroalkylene. In embodiments, L^1 is a substituted or unsubstituted cycloalkylene. In embodiments, L^1 is a substituted or unsubstituted heterocycloalkylene. In embodiments, L^1 is a substituted or unsubstituted arylene. In embodiments, L^1 is a substituted or unsubstituted heteroarylene. In embodiments, L^1 is a substituted alkylene. In embodiments, L^1 is a substituted heteroalkylene. In embodiments, L^1 is a substituted cycloalkylene. In embodiments, L^1 is a substituted heterocycloalkylene. In embodiments, L^1 is a substituted arylene. In embodiments, L^1 is a substituted heteroarylene. In embodiments, L^1 is an unsubstituted alkylene. In embodiments, L^1 is an unsubstituted heteroalkylene. In embodiments, L^1 is an unsubstituted cycloalkylene. In embodiments, L^1 is an unsubstituted heterocycloalkylene. In embodiments, L^1 is an unsubstituted arylene. In embodiments, L^1 is an unsubstituted heteroarylene. In embodiments, L^1 is a substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^1 is a substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^1 is a substituted or unsubstituted C_3-C_8 cycloalkylene. In embodiments, L^1 is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene. In embodiments, L^1 is a substituted or unsubstituted C_6-C_{10} arylene. In embodiments, L^1 is a substituted or unsubstituted

5 to 10 membered heteroarylene. In embodiments, L^1 is a substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^1 is a substituted or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^1 is a substituted or unsubstituted C_3-C_6 cycloalkylene. In embodiments, L^1 is a substituted or unsubstituted 3 to 6 membered heterocycloalkylene. In embodiments, L^1 is a substituted or unsubstituted phenylene. In embodiments, L^1 is a substituted or unsubstituted 5 to 6 membered heteroarylene.

[0334] In embodiments, L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, R^{41}-substituted or unsubstituted alkylene, R^{41}-substituted or unsubstituted heteroalkylene, R^{41}-substituted or unsubstituted cycloalkylene, R^{41}-substituted or unsubstituted heterocycloalkylene, R^{41}-substituted or unsubstituted arylene, or R^{41}-substituted or unsubstituted heteroarylene.

[0335] In embodiments, L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, -NH-, -O-, -S-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, R^{41}-substituted or unsubstituted alkylene, R^{41}-substituted or unsubstituted heteroalkylene, R^{41}-substituted or unsubstituted cycloalkylene, R^{41}-substituted or unsubstituted heterocycloalkylene, R^{41}-substituted or unsubstituted arylene, or R^{41}-substituted or unsubstituted heteroarylene.

[0336] In embodiments, L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, -NH-, -O-, -S-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, R^{41}-substituted or unsubstituted C_1-C_8 alkylene, R^{41}-substituted or unsubstituted 2 to 8 membered heteroalkylene, R^{41}-substituted or unsubstituted C_3-C_8 cycloalkylene, R^{41}-substituted or unsubstituted 3 to 6 membered heterocycloalkylene, R^{41}-substituted or unsubstituted phenylene, or R^{41}-substituted or unsubstituted 5 to 6 membered heteroarylene.

[0337] R^{41} is independently oxo, halogen, $-CX^{41}_3$, $-CHX^{41}_2$, $-CH_2X^{41}$, $-OCX^{41}_3$, $-OCHX^{41}_2$, $-OCH_2X^{41}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{42}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{42}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{42}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{42}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{42}-substituted or unsubstituted aryl (e.g., C_6-

C_{10}, C_{10}, or phenyl), or R^{42}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{41} is –F, -Cl, -Br, or –I.

[0338] R^{42} is independently oxo, halogen, $-CX^{42}_3$, $-CHX^{42}_2$, $-CH_2X^{42}$, $-OCX^{42}_3$, $-OCHX^{42}_2$, $-OCH_2X^{42}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{43}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{43}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{43}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{43}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{43}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{43}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{42} is –F, -Cl, -Br, or –I.

[0339] R^{43} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0340] In embodiments, L^1 is a bond. In embodiments, L^1 is R^{41}-substituted or unsubstituted C_1-C_2 alkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, C_1-C_4 alkylene, C_1-C_2 alkylene). In embodiments, L^1 is R^{41}-substituted C_1-C_2 alkylene. In embodiments, L^1 is R^{41}-substituted C_1-C_4 alkylene. In embodiments, L^1 is R^{41}-substituted C_1-C_6 alkylene. In embodiments, L^1 is R^{41}-substituted C_1-C_8 alkylene. In embodiments, L^1 is R^{41}-substituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, C_1-C_4 alkylene, C_1-C_2 alkylene). In embodiments, L^1 is R^{41}-substituted methylene. In embodiments, L^1 is an unsubstituted C_1-C_2 alkylene. In embodiments, L^1 is an

unsubstituted C_1-C_4 alkylene. In embodiments, L^1 is an unsubstituted C_1-C_6 alkylene. In embodiments, L^1 is an unsubstituted C_1-C_8 alkylene. In embodiments, L^1 is an unsubstituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, C_1-C_4 alkylene, C_1-C_2 alkylene). In embodiments, L^1 is R^{41}-substituted or unsubstituted methylene. In embodiments, L^1 is R^{41}-substituted methylene. In embodiments, L^1 is an unsubstituted methylene.

[0341] In embodiments, L^1 is R^{41}-substituted or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, 2 to 4 membered heteroalkylene). In embodiments, L^1 is R^{41}-substituted 2 to 4 membered heteroalkylene. In embodiments, L^1 is R^{41}-substituted 2 to 6 membered heteroalkylene. In embodiments, L^1 is R^{41}-substituted 2 to 8 membered heteroalkylene. In embodiments, L^1 is R^{41}-substituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, 2 to 4 membered heteroalkylene). In embodiments, L^1 is an unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^1 is an unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^1 is an unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^1 is an unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, 2 to 4 membered heteroalkylene).

[0342] In embodiments, L^1 is R^{41}-substituted or unsubstituted ethylaminylene. In embodiments, L^1 is R^{41}-substituted ethylaminylene. In embodiments, L^1 is an unsubstituted ethylaminylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted propylaminylene. In embodiments, L^1 is R^{41}-substituted propyl aminylene. In embodiments, L^1 is an unsubstituted propylaminylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted butylaminylene. In embodiments, L^1 is R^{41}-substituted butylaminylene. In embodiments, L^1 is an unsubstituted butylaminylene.

[0343] In embodiments, L^1 is R^{41}-substituted or unsubstituted C_3-C_8 cycloalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted C_4-C_6 cycloalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted C_5-C_6 cycloalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted cyclocalkylene (e.g., C_3-C_8 cycloalkylene, C_4-C_6 cycloalkylene, or C_5-C_6 cycloalkylene). In embodiments, L^1 is R^{41}-substituted C_3-C_8 cycloalkylene. In embodiments, L^1 is R^{41}-substituted C_4-C_6 cycloalkylene. In embodiments, L^1 is R^{41}-substituted C_5-C_6 cycloalkylene. In embodiments, L^1 is R^{41}-substituted cyclocalkylene (e.g., C_3-C_8 cycloalkylene,

C_4-C_6 cycloalkylene, or C_5-C_6 cycloalkylene). In embodiments, L^1 is an unsubstituted C_3-C_8 cycloalkylene. In embodiments, L^1 is an unsubstituted C_4-C_6 cycloalkylene. In embodiments, L^1 is an unsubstituted C_5-C_6 cycloalkylene. In embodiments, L^1 is an unsubstituted cycloalkylene (e.g., C_3-C_8 cycloalkylene, C_4-C_6 cycloalkylene, or C_5-C_6 cycloalkylene).

[0344] In embodiments, L^1 is R^{41}-substituted or unsubstituted C_3-C_8 cycloalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted C_4-C_6 cycloalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted C_5-C_6 cycloalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted cyclocalkylene (e.g., C_3-C_8 cycloalkylene, C_4-C_6 cycloalkylene, or C_5-C_6 cycloalkylene). In embodiments, L^1 is R^{41}-substituted C_3-C_8 cycloalkylene. In embodiments, L^1 is R^{41}-substituted C_4-C_6 cycloalkylene. In embodiments, L^1 is R^{41}-substituted C_5-C_6 cycloalkylene. In embodiments, L^1 is R^{41}-substituted cycloalkylene (e.g., C_3-C_8 cycloalkylene, C_4-C_6 cycloalkylene, or C_5-C_6 cycloalkylene). In embodiments, L^1 is an unsubstituted C_3-C_8 cycloalkylene. In embodiments, L^1 is an unsubstituted C_4-C_6 cycloalkylene. In embodiments, L^1 is an unsubstituted C_5-C_6 cycloalkylene. In embodiments, L^1 is an unsubstituted cycloalkylene (e.g., C_3-C_8 cycloalkylene, C_4-C_6 cycloalkylene, or C_5-C_6 cycloalkylene).

[0345] In embodiments, L^1 is R^{41}-substituted or unsubstituted 4 membered heterocycloalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted 5 membered heterocycloalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted 6 membered heterocycloalkylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted heterocycloalkylene (e.g., 3 to 6 membered heterocycloalkylene, 4 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^1 is R^{41}-substituted 4 membered heterocycloalkylene. In embodiments, L^1 is R^{41}-substituted 5 membered heterocycloalkylene. In embodiments, L^1 is R^{41}-substituted 6 membered heterocycloalkylene. In embodiments, L^1 is R^{41}-substituted heterocycloalkylene (e.g., 3 to 6 membered heterocycloalkylene, 4 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^1 is an unsubstituted 4 membered heterocycloalkylene. In embodiments, L^1 is an unsubstituted 5 membered heterocycloalkylene. In embodiments, L^1 unsubstituted 6 membered heterocycloalkylene. In embodiments, L^1 is an unsubstituted heterocycloalkylene (e.g., 3 to 6 membered heterocycloalkylene, 4 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene).

[0346] In embodiments, L^1 is R^{41}-substituted or unsubstituted arylene (e.g. C_6-C_{10} arylene or C_6 arylene). In embodiments, L^1 is R^{41}-substituted or unsubstituted C_6-C_{10} arylene. In

embodiments, L^1 is R^{41}-substituted or unsubstituted C_6 arylene. In embodiments, L^1 is R^{41}-substituted arylene (e.g. C_6-C_{10} arylene or C_6 arylene). In embodiments, L^1 is R^{41}-substituted C_6-C_{10} arylene. In embodiments, L^1 is R^{41}-substituted C_6 arylene. In embodiments, L^1 is an unsubstituted C_6-C_{10} arylene. In embodiments, L^1 is an unsubstituted C_6 arylene.

[0347] In embodiments, L^1 is R^{41}-substituted or unsubstituted heteroarylene (e.g. 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^1 is R^{41}-substituted or unsubstituted 5 to 10 membered heteroarylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted 5 to 9 membered heteroarylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted 5 to 6 membered heteroarylene. In embodiments, L^1 is R^{41}-substituted heteroarylene (e.g. 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^1 is R^{41}-substituted 5 to 10 membered heteroarylene. In embodiments, L^1 is R^{41}-substituted 5 to 9 membered heteroarylene. In embodiments, L^1 is R^{41}-substituted 5 to 6 membered heteroarylene. In embodiments, L^1 is an unsubstituted heteroarylene (e.g. 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^1 is an unsubstituted 5 to 10 membered heteroarylene. In embodiments, L^1 is an unsubstituted 5 to 9 membered heteroarylene. In embodiments, L^1 is an unsubstituted 5 to 6 membered heteroarylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted indolinylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted indazolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted benzimidazolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted benzoxazolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted azaindolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted purinylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted indolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted pyrazinylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted pyrrolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted imidazolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted pyrazolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted triazolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted tetrazolylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted furanylene. In embodiments, L^1 is R^{41}-substituted or unsubstituted thienylene.

[0348] In embodiments, R^6 is independently hydrogen. In embodiments, R^6 is independently halogen. In embodiments, R^6 is independently $-CX^6_3$. In embodiments, R^6 is independently $-CHX^6_2$. In embodiments, R^6 is independently $-CH_2X^6$. In embodiments, R^6 is independently $-OCX^6_3$. In embodiments, R^6 is independently $-OCH_2X^6$. In embodiments, R^6 is

independently -$OCHX^6_2$. In embodiments, R^6 is independently -CN. In embodiments, R^6 is independently -$SO_{n6}R^{6D}$. In embodiments, R^6 is independently -$SO_{v6}NR^{6A}R^{6B}$. In embodiments, R^6 is independently -$NHC(O)NR^{6A}R^{6B}$. In embodiments, R^6 is independently -$N(O)_{m6}$. In embodiments, R^6 is independently -$NR^{6A}R^{6B}$. In embodiments, R^6 is independently -$C(O)R^{6C}$. In embodiments, R^6 is independently -$C(O)$-OR^{6C}. In embodiments, R^6 is independently -$C(O)NR^{6A}R^{6B}$. In embodiments, R^6 is independently -OR^{6D}. In embodiments, R^6 is independently -$NR^{6A}SO_2R^{6D}$. In embodiments, R^6 is independently -$NR^{6A}C(O)R^{6C}$. In embodiments, R^6 is independently -$NR^{6A}C(O)OR^{6C}$. In embodiments, R^6 is independently -$NR^{6A}OR^{6C}$. In embodiments, R^6 is independently -OH. In embodiments, R^6 is independently -NH_2. In embodiments, R^6 is independently -COOH. In embodiments, R^6 is independently -$CONH_2$. In embodiments, R^6 is independently -NO_2. In embodiments, R^6 is independently –SH.

[0349] In embodiments, R^6 is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^6 is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^6 is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^6 is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^6 is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^6 is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^6 is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^6 is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^6 is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^6 is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^6 is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^6 is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^6 is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^6 is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^6 is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^6 is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^6 is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In

embodiments, R^6 is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0350] In embodiments, R^{6A} is independently hydrogen. In embodiments, R^{6A} is independently $-CX^{6A}_3$. In embodiments, R^{6A} is independently $-CHX^{6A}_2$. In embodiments, R^{6A} is independently $-CH_2X^{6A}$. In embodiments, R^{6A} is independently -CN. In embodiments, R^{6A} is independently -COOH. In embodiments, R^{6A} is independently $-CONH_2$.

[0351] In embodiments, R^{6A} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6A} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6A} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6A} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6A} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6A} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6A} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6A} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6A} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6A} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6A} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6A} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6A} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6A} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6A} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6A} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6A} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6A} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6A} is independently unsubstituted methyl. In embodiments, R^{6A} is independently unsubstituted ethyl. In embodiments, R^{6A} is independently unsubstituted propyl. In embodiments, R^{6A} is independently unsubstituted isopropyl. In embodiments, R^{6A} is independently unsubstituted tert-butyl.

[0352] In embodiments, R^{6B} is independently hydrogen. In embodiments, R^{6B} is independently $-CX^{6B}_3$. In embodiments, R^{6B} is independently $-CHX^{6B}_2$. In embodiments, R^{6B} is independently $-CH_2X^{6B}$. In embodiments, R^{6B} is independently -CN. In embodiments, R^{6B} is independently -COOH. In embodiments, R^{6B} is independently $-CONH_2$.

[0353] In embodiments, R^{6B} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6B} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6B} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6B} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6B} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6B} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6B} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6B} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6B} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6B} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6B} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6B} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6B} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6B} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6B} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6B} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6B} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6B} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6B} is independently unsubstituted methyl. In embodiments, R^{6B} is independently unsubstituted ethyl. In embodiments, R^{6B} is independently unsubstituted propyl. In embodiments, R^{6B} is independently unsubstituted isopropyl. In embodiments, R^{6B} is independently unsubstituted tert-butyl.

[0354] In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted or

unsubstituted heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heterocycloalkyl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 10 membered heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 6 membered heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 6 membered heteroaryl.

[0355] In embodiments, R^{6C} is independently hydrogen. In embodiments, R^{6C} is independently $-CX^{6C}_3$. In embodiments, R^{6C} is independently $-CHX^{6C}_2$. In embodiments, R^{6C} is independently $-CH_2X^{6C}$. In embodiments, R^{6C} is independently -CN. In embodiments, R^{6C} is independently -COOH. In embodiments, R^{6C} is independently $-CONH_2$.

[0356] In embodiments, R^{6C} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6C} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6C} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4).

In embodiments, R^{6C} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6C} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6C} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6C} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6C} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6C} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6C} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6C} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6C} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6C} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6C} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6C} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6C} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6C} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6C} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6C} is independently unsubstituted methyl. In embodiments, R^{6C} is independently unsubstituted ethyl. In embodiments, R^{6C} is independently unsubstituted propyl. In embodiments, R^{6C} is independently unsubstituted isopropyl. In embodiments, R^{6C} is independently unsubstituted tert-butyl.

[0357] In embodiments, R^{6D} is independently hydrogen. In embodiments, R^{6D} is independently $-CX^{6D}_3$. In embodiments, R^{6D} is independently $-CHX^{6D}_2$. In embodiments, R^{6D} is independently $-CH_2X^{6D}$. In embodiments, R^{6D} is independently -CN. In embodiments, R^{6D} is independently -COOH. In embodiments, R^{6D} is independently $-CONH_2$.

[0358] In embodiments, R^{6D} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6D} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6D} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{6D} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6D} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In

embodiments, R^{6D} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{6D} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6D} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6D} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{6D} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6D} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6D} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{6D} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6D} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6D} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{6D} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6D} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6D} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{6D} is independently unsubstituted methyl. In embodiments, R^{6D} is independently unsubstituted ethyl. In embodiments, R^{6D} is independently unsubstituted propyl. In embodiments, R^{6D} is independently unsubstituted isopropyl. In embodiments, R^{6D} is independently unsubstituted tert-butyl.

[0359] In embodiments, R^6 is independently hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, R^{35}-substituted or unsubstituted alkyl, R^{35}-substituted or unsubstituted heteroalkyl, R^{35}-substituted or unsubstituted cycloalkyl, R^{35}-substituted or unsubstituted heterocycloalkyl, R^{35}-substituted or unsubstituted aryl, or R^{35}-substituted or unsubstituted heteroaryl. In embodiments, R^6 is independently halogen, $-CX^6_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^6_3$, $-OCHX^6_2$, R^{35}-substituted or unsubstituted alkyl, R^{35}-substituted or unsubstituted heteroalkyl, R^{35}-substituted or unsubstituted cycloalkyl, R^{35}-substituted or unsubstituted heterocycloalkyl, R^{35}-substituted or unsubstituted aryl, or R^{35}-substituted or unsubstituted heteroaryl. In embodiments, R^6 is independently

halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCHX^{26}_2$, $-OCH_2X^6$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{35}-substituted or unsubstituted C_1-C_8 alkyl, R^{35}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{35}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{35}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{35}-substituted or unsubstituted phenyl, or R^{35}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^6 is –F,-Cl, -Br, or –I. In embodiments, R^6 is independently hydrogen. In embodiments, R^6 is independently methyl. In embodiments, R^6 is independently ethyl.

[0360] R^{35} is independently oxo, halogen, $-CX^{35}_3$, $-CHX^{35}_2$, $-CH_2X^{35}$, $-OCX^{35}_3$, $-OCHX^{35}_2$, $-OCH_2X^{35}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{36}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{36}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{36}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{36}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{36}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{36}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{35} is –F, -Cl, -Br, or –I.

[0361] R^{36} is independently oxo, halogen, $-CX^{36}_3$, $-CHX^{36}_2$, $-CH_2X^{36}$, $-OCX^{36}_3$, $-OCHX^{36}_2$, $-OCH_2X^{36}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{37}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{37}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{37}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{37}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{37}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{37}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{36} is –F, -Cl, -Br, or –I.

[0362] In embodiments, R^{6A} is independently hydrogen, $-CX^{6A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{6A}_2$, $-CH_2X^{6A}$, R^{35A}-substituted or unsubstituted alkyl, R^{35A}-substituted or unsubstituted heteroalkyl, R^{35A}-substituted or unsubstituted cycloalkyl, R^{35A}-substituted or unsubstituted heterocycloalkyl, R^{35A}-substituted or unsubstituted aryl, or

R^{35A}-substituted or unsubstituted heteroaryl. In embodiments, R^{6A} is independently hydrogen, $-CX^{6A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{6A}_2$, $-CH_2X^{6A}$, R^{35A}-substituted or unsubstituted C_1-C_8 alkyl, R^{35A}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{35A}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{35A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{35A}-substituted or unsubstituted phenyl, or R^{35A}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{6A} is –F, -Cl, -Br, or –I. In embodiments, R^{6A} is independently hydrogen. In embodiments, R^{6A} is independently methyl. In embodiments, R^{6A} is independently ethyl.

[0363] In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{35A}-substituted or unsubstituted heterocycloalkyl or R^{35A}-substituted or unsubstituted heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{35A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{35A}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0364] R^{35A} is independently oxo, halogen, $-CX^{35A}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{35A}_3$, $-OCHX^{35A}_2$, R^{36A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{36A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{36A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{36A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{36A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{36A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{35A} is –F, -Cl, -Br, or –I.

[0365] R^{36A} is independently oxo, halogen, $-CX^{36A}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{36A}_3$, $-OCHX^{36A}_2$, R^{37A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{37A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{37A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{37A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{37A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{37A}-

substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{36A} is –F, -Cl, -Br, or –I.

[0366] In embodiments, R^{6B} is independently hydrogen, $-CX^{6B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{6B}_2$, $-CH_2X^{6B}$, R^{35B}-substituted or unsubstituted alkyl, R^{35B}-substituted or unsubstituted heteroalkyl, R^{35B}-substituted or unsubstituted cycloalkyl, R^{35B}-substituted or unsubstituted heterocycloalkyl, R^{35B}-substituted or unsubstituted aryl, or R^{35B}-substituted or unsubstituted heteroaryl. In embodiments, R^{6B} is independently hydrogen, $-CX^{6B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{6B}_2$, $-CH_2X^{6B}$, R^{35B}-substituted or unsubstituted C_1-C_8 alkyl, R^{35B}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{35B}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{35B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{35B}-substituted or unsubstituted phenyl, or R^{35B}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{6B} is –F, -Cl, -Br, or –I. In embodiments, R^{6B} is independently hydrogen. In embodiments, R^{6B} is independently methyl. In embodiments, R^{6B} is independently ethyl.

[0367] In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{35B}-substituted or unsubstituted heterocycloalkyl or R^{35B}-substituted or unsubstituted heteroaryl. In embodiments, R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{35B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{35B}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0368] R^{35B} is independently oxo, halogen, $-CX^{35B}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{35B}_3$, $-OCHX^{35B}_2$, R^{36B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{36B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{36B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{36B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{36B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{36B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{35B} is –F, -Cl, -Br, or –I.

[0369] R^{36B} is independently oxo, halogen, $-CX^{36B}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH,

-NHOH, -OCX^{36B}_3, -$OCHX^{36B}_2$, R^{37B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{37B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{37B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{37B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{37B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{37B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{36B} is –F, -Cl, -Br, or –I.

[0370] In embodiments, R^{6C} is independently hydrogen, -CX^{6C}_3, -CN, -COOH, -$CONH_2$, -CHX^{6C}_2, -CH_2X^{6C}, R^{35C}-substituted or unsubstituted alkyl, R^{35C}-substituted or unsubstituted heteroalkyl, R^{35C}-substituted or unsubstituted cycloalkyl, R^{35C}-substituted or unsubstituted heterocycloalkyl, R^{35C}-substituted or unsubstituted aryl, or R^{35C}-substituted or unsubstituted heteroaryl. In embodiments, R^{6C} is independently hydrogen, -CX^{6C}_3, -CN, -COOH, -$CONH_2$, -CHX^{6C}_2, -CH_2X^{6C}, R^{35C}-substituted or unsubstituted C_1-C_8 alkyl, R^{35C}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{35C}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{35C}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{35C}-substituted or unsubstituted phenyl, or R^{35C}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{6C} is –F, -Cl, -Br, or –I. In embodiments, R^{6C} is independently hydrogen. In embodiments, R^{6C} is independently methyl. In embodiments, R^{6C} is independently ethyl.

[0371] R^{35C} is independently oxo, halogen, -CX^{35C}_3, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX^{35C}_3, -$OCHX^{35C}_2$, R^{36C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{36C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{36C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{36C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{36C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{36C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{35C} is –F, -Cl, -Br, or –I.

[0372] R^{36C} is independently oxo, halogen, -CX^{36C}_3, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH,

-NHOH, -OCX^{36C}_3, -$OCHX^{36C}_2$, R^{37C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{37C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{37C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{37C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{37C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{37C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{36C} is –F, -Cl, -Br, or –I.

[0373] In embodiments, R^{6D} is independently hydrogen, -CX^{6D}_3, -CN, -COOH, -$CONH_2$, -CHX^{6D}_2, -CH_2X^{6D}, R^{35D}-substituted or unsubstituted alkyl, R^{35D}-substituted or unsubstituted heteroalkyl, R^{35D}-substituted or unsubstituted cycloalkyl, R^{35D}-substituted or unsubstituted heterocycloalkyl, R^{35D}-substituted or unsubstituted aryl, or R^{35D}-substituted or unsubstituted heteroaryl. In embodiments, R^{6D} is independently hydrogen, -CX^{6D}_3, -CN, -COOH, -$CONH_2$, -CHX^{6D}_2, -CH_2X^{6D}, R^{35D}-substituted or unsubstituted C_1-C_8 alkyl, R^{35D}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{35D}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{35D}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{35D}-substituted or unsubstituted phenyl, or R^{35D}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{6D} is –F, -Cl, -Br, or –I. In embodiments, R^{6D} is independently hydrogen. In embodiments, R^{6D} is independently methyl. In embodiments, R^{6D} is independently ethyl.

[0374] R^{35D} is independently oxo, halogen, -CX^{35D}_3, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX^{35D}_3, -$OCHX^{35D}_2$, R^{36D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{36D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{36D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{36D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{36D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{36D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{35D} is –F, -Cl, -Br, or –I.

[0375] R^{36D} is independently oxo, halogen, -CX^{36D}_3, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH,

-NHOH, -OCX^{36D}_3, -$OCHX^{36D}_2$, R^{37D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{37D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{37D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{37D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{37D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{37D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{36D} is –F, -Cl, -Br, or –I.

[0376] R^{37}, R^{37A}, R^{37B}, R^{37C}, and R^{37D} are independently oxo, halogen, -CF_3, -CCl_3, -CBr_3, -CI_3, -CHF_2, -$CHCl_2$, -$CHBr_2$, -CHI_2, -CH_2F, -CH_2Cl, -CH_2Br, -CH_2I, -OCF_3, -$OCCl_3$, -$OCBr_3$, -OCI_3, -$OCHF_2$, -$OCHCl_2$, -$OCHBr_2$, -$OCHI_2$, -OCH_2F, -OCH_2Cl, -OCH_2Br, -OCH_2I, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0377] In embodiments, L^2 is -NR^7-, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heterocycloalkylene. In embodiments, L^2 is -NH-.

[0378] In embodiments, L^2 is -NR^7- or substituted or unsubstituted heterocycloalkylene including a ring nitrogen bonded directly to E. In embodiments, L^2 is -NR^7-. In embodiments, L^2 is substituted or unsubstituted heterocycloalkylene. In embodiments, L^2 is substituted or unsubstituted piperidinylene or substituted or unsubstituted pyrrolindinylene. In embodiments, L^2 is an unsubstituted piperidinylene or unsubstituted pyrrolindinylene.

[0379] In embodiments, L^2 is a bond. In embodiments, L^2 is -$S(O)_2$-. In embodiments, L^2 is -$S(O)_2$-Ph-. In embodiments, L^2 is -NR^7-. In embodiments, L^2 is -O-. In embodiments, L^2 is -S-. In embodiments, L^2 is -C(O)- . In embodiments, L^2 is -C(O)NR^7-. In embodiments, L^2 is -NR^7C(O)- . In embodiments, L^2 is -NR^7C(O)NH-. In embodiments, L^2 is -NHC(O)NR^7-. In embodiments, L^2 is -C(O)O-. In embodiments, L^2 is -OC(O)-. In embodiments, L^2 is -NH-. In embodiments, L^2 is -C(O)NH-. In embodiments, L^2 is -NHC(O)- . In embodiments, L^2 is -NHC(O)NH-. In embodiments, L^2 is –CH_2-. In embodiments, L^2 is –OCH_2-. In embodiments, L^2 is –CH_2O-. In embodiments, L^2 is –CH_2CH_2-. In embodiments, L^2 is –SCH_2-.

In embodiments, L^2 is $-CH_2S-$. In embodiments, L^2 is –CHCH-. In embodiments, L^2 is –CC-. In embodiments, L^2 is $-NHCH_2-$. In embodiments, L^2 is $-CH_2NH-$.

[0380] In embodiments, L^2 is a substituted or unsubstituted alkylene. In embodiments, L^2 is a substituted or unsubstituted heteroalkylene. In embodiments, L^2 is a substituted or unsubstituted cycloalkylene. In embodiments, L^2 is a substituted or unsubstituted heterocycloalkylene. In embodiments, L^2 is a substituted or unsubstituted arylene. In embodiments, L^2 is a substituted or unsubstituted heteroarylene. In embodiments, L^2 is a substituted alkylene. In embodiments, L^2 is a substituted heteroalkylene. In embodiments, L^2 is a substituted cycloalkylene. In embodiments, L^2 is a substituted heterocycloalkylene. In embodiments, L^2 is a substituted arylene. In embodiments, L^2 is a substituted heteroarylene. In embodiments, L^2 is an unsubstituted alkylene. In embodiments, L^2 is an unsubstituted heteroalkylene. In embodiments, L^2 is an unsubstituted cycloalkylene. In embodiments, L^2 is an unsubstituted heterocycloalkylene. In embodiments, L^2 is an unsubstituted arylene. In embodiments, L^2 is an unsubstituted heteroarylene. In embodiments, L^2 is a substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^2 is a substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^2 is a substituted or unsubstituted C_3-C_8 cycloalkylene. In embodiments, L^2 is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene. In embodiments, L^2 is a substituted or unsubstituted C_6-C_{10} arylene. In embodiments, L^2 is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0381] In embodiments, L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, R^{44}-substituted or unsubstituted alkylene, R^{44}-substituted or unsubstituted heteroalkylene, R^{44}-substituted or unsubstituted cycloalkylene, R^{44}-substituted or unsubstituted heterocycloalkylene, R^{44}-substituted or unsubstituted arylene, or R^{44}-substituted or unsubstituted heteroarylene. In embodiments, L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, -NH-, -O-, -S-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, R^{44}-substituted or unsubstituted alkylene, R^{44}-substituted or unsubstituted heteroalkylene, R^{44}-substituted or unsubstituted cycloalkylene, R^{44}-substituted or unsubstituted heterocycloalkylene, R^{44}-substituted or unsubstituted arylene, or R^{44}-substituted or unsubstituted heteroarylene. In embodiments, L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, -NH-, -O-, -S-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, R^{44}-substituted or unsubstituted C_1-C_8 alkylene, R^{44}-substituted or unsubstituted 2 to 8 membered heteroalkylene, R^{44}-substituted or unsubstituted C_3-C_8 cycloalkylene, R^{44}-substituted or unsubstituted 3 to 6 membered heterocycloalkylene, R^{44}-

substituted or unsubstituted phenylene, or R^{44}-substituted or unsubstituted 5 to 6 membered heteroarylene.

[0382] R^{44} is independently oxo, halogen, $-CX^{44}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{44}_3$, $-OCHX^{44}_2$, R^{45}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{45}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{45}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{45}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{45}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{45}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{44} is –F, -Cl, -Br, or –I.

[0383] R^{45} is independently oxo, halogen, $-CX^{45}_3$, $-CHX^{45}_2$, $-CH_2X^{45}$, $-OCX^{45}_3$, $-OCHX^{45}_2$, $-OCH_2X^{45}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{46}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{46}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{46}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{46}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{46}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{46}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{45} is –F, -Cl, -Br, or –I.

[0384] R^{46} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0385] In embodiments, L^2 is R^{44}-substituted or unsubstituted 4 membered heterocycloalkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted 5 membered heterocycloalkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted 6 membered heterocycloalkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted 7 membered heterocycloalkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted heterocycloalkylene (e.g., 3 to 6 membered heterocycloalkylene, 4 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^2 is R^{44}-substituted 4 membered heterocycloalkylene. In embodiments, L^2 is R^{44}-substituted 5 membered heterocycloalkylene. In embodiments, L^2 is R^{44}-substituted 6 membered heterocycloalkylene. In embodiments, L^2 is R^{44}-substituted 7 membered heterocycloalkylene. In embodiments, L^2 is R^{44}-substituted heterocycloalkylene (e.g., 3 to 6 membered heterocycloalkylene, 4 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^2 is an unsubstituted 4 membered heterocycloalkylene. In embodiments, L^2 is an unsubstituted 5 membered heterocycloalkylene. In embodiments, L^2 is an unsubstituted 6 membered heterocycloalkylene. In embodiments, L^2 is an unsubstituted 7 membered heterocycloalkylene. In embodiments, L^2 is an unsubstituted heterocycloalkylene (e.g., 3 to 6 membered heterocycloalkylene, 4 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene).

[0386] In embodiments, L^2 is R^{44}-substituted or unsubstituted piperidinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted pyrrolidinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted imidazolidinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted pyrazolidinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted piperazinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted piperazinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted azetidinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted aziridinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted morpholinylene.

[0387] In embodiments, L^2 is a R^{44}-substituted or unsubstituted 5 to 10 membered heteroarylene. In embodiments, L^2 is a R^{44}-substituted or unsubstituted 5 to 6 membered heteroarylene. In embodiments, L^2 is a R^{44}-substituted or unsubstituted pyridinylene, pyridazinylene, pyrimidinylene, pyrazinylene, or triazinylene.

[0388] In embodiments, L^2 is R^{44}-substituted or unsubstituted indolinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted indazolylene. In embodiments, L^2 is R^{44}-substituted or

unsubstituted benzimidazolylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted benzoxazolylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted azaindolylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted purinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted indolylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted pyrazinylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted pyrrolylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted imidazolylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted pyrazolylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted triazolylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted tetrazolylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted azepanylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted azepinylene.

[0389] In embodiments, L^2 is R^{44}-substituted or unsubstituted C_3-C_8 cycloalkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted C_4-C_6 cycloalkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted C_5-C_6 cycloalkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted cycloalkylene (e.g., C_3-C_8 cycloalkylene, C_4-C_6 cycloalkylene, or C_5-C_6 cycloalkylene). In embodiments, L^2 is R^{44}-substituted C_3-C_8 cycloalkylene. In embodiments, L^2 is R^{44}-substituted C_4-C_6 cycloalkylene. In embodiments, L^2 is R^{44}-substituted C_5-C_6 cycloalkylene. In embodiments, L^2 is R^{44}-substituted cyclocalkylene (e.g., C_3-C_8 cycloalkylene, C_4-C_6 cycloalkylene, or C_5-C_6 cycloalkylene). In embodiments, L^2 is an unsubstituted C_3-C_8 cycloalkylene. In embodiments, L^2 is an unsubstituted C_4-C_6 cycloalkylene. In embodiments, L^2 is an unsubstituted C_5-C_6 cycloalkylene. In embodiments, L^2 is an unsubstituted cycloalkylene (e.g., C_3-C_8 cycloalkylene, C_4-C_6 cycloalkylene, or C_5-C_6 cycloalkylene). In embodiments, L^2 is R^{44}-substituted or unsubstituted arylene (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, L^2 is R^{44}-substituted arylene (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, L^2 is an unsubstituted arylene (e.g., C_6-C_{10}, C_{10}, or phenyl).

[0390] In embodiments, L^2 is R^{44}-substituted or unsubstituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, C_1-C_4 alkylene, C_1-C_2 alkylene). In embodiments, L^2 is R^{44}-substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted C_1-C_2 alkylene. In embodiments, L^2 is R^{44}-substituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, C_1-C_4 alkylene, C_1-C_2 alkylene). In embodiments, L^2 is R^{44}-substituted C_1-C_8 alkylene. In embodiments, L^2 is R^{44}-substituted C_1-C_6 alkylene. In embodiments, L^2 is R^{44}-substituted C_1-C_4 alkylene. In embodiments, L^2 is R^{44}-substituted C_1-C_2 alkylene. In embodiments, L^2 is an unsubstituted alkylene (e.g., C_1-C_8

alkylene, C_1-C_6 alkylene, C_1-C_4 alkylene, C_1-C_2 alkylene). In embodiments, L^2 is an unsubstituted C_1-C_8 alkylene. In embodiments, L^2 is an unsubstituted C_1-C_6 alkylene. In embodiments, L^2 is an unsubstituted C_1-C_4 alkylene. In embodiments, L^2 is an unsubstituted C_1-C_2 alkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted methylene. In embodiments, L^2 is an unsubstituted methylene.

[0391] In embodiments, L^2 is R^{44}-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, 2 to 4 membered heteroalkylene). In embodiments, L^2 is R^{44}-substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^2 is R^{44}-substituted or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^2 is R^{44}-substituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, 2 to 4 membered heteroalkylene). In embodiments, L^2 is R^{44}-substituted 2 to 8 membered heteroalkylene. In embodiments, L^2 is R^{44}-substituted 2 to 6 membered heteroalkylene. In embodiments, L^2 is R^{44}-substituted 2 to 4 membered heteroalkylene. In embodiments, L^2 is an unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, 2 to 4 membered heteroalkylene). In embodiments, L^2 is an unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^2 is an unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^2 is an unsubstituted 2 to 4 membered heteroalkylene.

[0392] In embodiments, R^7 is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^7 is hydrogen or unsubstituted C_1-C_3 alkyl. In embodiments, R^7 is hydrogen.

[0393] In embodiments, R^7 is independently hydrogen. In embodiments, R^7 is independently halogen. In embodiments, R^7 is independently $-CX^7_3$. In embodiments, R^7 is independently $-CHX^7_2$. In embodiments, R^7 is independently $-CH_2X^7$. In embodiments, R^7 is independently $-OCX^7_3$. In embodiments, R^7 is independently $-OCH_2X^7$. In embodiments, R^7 is independently $-OCHX^7_2$. In embodiments, R^7 is independently -CN. In embodiments, R^7 is independently $-SO_{n7}R^{7D}$. In embodiments, R^7 is independently $-SO_{v7}NR^{7A}R^{7B}$. In embodiments, R^7 is independently $-NHC(O)NR^{7A}R^{7B}$. In embodiments, R^7 is independently $-N(O)_{m7}$. In embodiments, R^7 is independently $-NR^{7A}R^{7B}$. In embodiments, R^7 is independently $-C(O)R^{7C}$. In embodiments, R^7 is independently $-C(O)-OR^{7C}$. In embodiments, R^7 is independently $-C(O)NR^{7A}R^{7B}$. In embodiments, R^7 is independently $-OR^{7D}$. In embodiments,

R^7 is independently $-NR^{7A}SO_2R^{7D}$. In embodiments, R^7 is independently $-NR^{7A}C(O)R^{7C}$. In embodiments, R^7 is independently $-NR^{7A}C(O)OR^{7C}$. In embodiments, R^7 is independently $-NR^{7A}OR^{7C}$. In embodiments, R^7 is independently -OH. In embodiments, R^7 is independently $-NH_2$. In embodiments, R^7 is independently -COOH. In embodiments, R^7 is independently $-CONH_2$. In embodiments, R^7 is independently $-NO_2$. In embodiments, R^7 is independently –SH.

[0394] In embodiments, R^7 is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^7 is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^7 is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^7 is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^7 is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^7 is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^7 is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^7 is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^7 is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^7 is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^7 is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^7 is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^7 is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^7 is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^7 is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^7 is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^7 is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^7 is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0395] In embodiments, R^{7A} is independently hydrogen. In embodiments, R^{7A} is independently $-CX^{7A}_3$. In embodiments, R^{7A} is independently $-CHX^{7A}_2$. In embodiments, R^{7A} is independently $-CH_2X^{7A}$. In embodiments, R^{7A} is independently -CN. In embodiments, R^{7A} is independently -COOH. In embodiments, R^{7A} is independently $-CONH_2$.

[0396] In embodiments, R^{7A} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7A} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7A} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7A} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7A} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7A} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7A} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7A} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7A} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7A} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7A} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7A} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7A} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7A} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7A} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7A} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7A} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7A} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7A} is independently unsubstituted methyl. In embodiments, R^{7A} is independently unsubstituted ethyl. In embodiments, R^{7A} is independently unsubstituted propyl. In embodiments, R^{7A} is independently unsubstituted isopropyl. In embodiments, R^{7A} is independently unsubstituted tert-butyl.

[0397] In embodiments, R^{7B} is independently hydrogen. In embodiments, R^{7B} is independently $-CX^{7B}_3$. In embodiments, R^{7B} is independently $-CHX^{7B}_2$. In embodiments, R^{7B} is independently $-CH_2X^{7B}$. In embodiments, R^{7B} is independently -CN. In embodiments, R^{7B} is independently -COOH. In embodiments, R^{7B} is independently $-CONH_2$.

[0398] In embodiments, R^{7B} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7B} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7B} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4).

In embodiments, R^{7B} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7B} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7B} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7B} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7B} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7B} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7B} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7B} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7B} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7B} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7B} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7B} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7B} is independently 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 substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7B} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7B} is independently unsubstituted methyl. In embodiments, R^{7B} is independently unsubstituted ethyl. In embodiments, R^{7B} is independently unsubstituted propyl. In embodiments, R^{7B} is independently unsubstituted isopropyl. In embodiments, R^{7B} is independently unsubstituted tert-butyl.

[0399] In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heterocycloalkyl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted or

unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 10 membered heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 6 membered heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 6 membered heteroaryl.

[0400] In embodiments, R^{7C} is independently hydrogen. In embodiments, R^{7C} is independently $-CX^{7C}_3$. In embodiments, R^{7C} is independently $-CHX^{7C}_2$. In embodiments, R^{7C} is independently $-CH_2X^{7C}$. In embodiments, R^{7C} is independently -CN. In embodiments, R^{7C} is independently -COOH. In embodiments, R^{7C} is independently $-CONH_2$.

[0401] In embodiments, R^{7C} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7C} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7C} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7C} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7C} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7C} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7C} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7C} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7C} is independently

unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7C} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7C} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7C} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7C} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7C} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7C} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7C} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7C} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7C} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7C} is independently unsubstituted methyl. In embodiments, R^{7C} is independently unsubstituted ethyl. In embodiments, R^{7C} is independently unsubstituted propyl. In embodiments, R^{7C} is independently unsubstituted isopropyl. In embodiments, R^{7C} is independently unsubstituted tert-butyl.

[0402] In embodiments, R^{7D} is independently hydrogen. In embodiments, R^{7D} is independently $-CX^{7D}_3$. In embodiments, R^{7D} is independently $-CHX^{7D}_2$. In embodiments, R^{7D} is independently $-CH_2X^{7D}$. In embodiments, R^{7D} is independently -CN. In embodiments, R^{7D} is independently -COOH. In embodiments, R^{7D} is independently $-CONH_2$.

[0403] In embodiments, R^{7D} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7D} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7D} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{7D} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7D} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7D} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{7D} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7D} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7D} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{7D} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7D} is independently substituted heterocycloalkyl (e.g., 3 to 8

membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7D} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{7D} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7D} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7D} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{7D} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7D} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7D} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7D} is independently unsubstituted methyl. In embodiments, R^{7D} is independently unsubstituted ethyl. In embodiments, R^{7D} is independently unsubstituted propyl. In embodiments, R^{7D} is independently unsubstituted isopropyl. In embodiments, R^{7D} is independently unsubstituted tert-butyl.

[0404] In embodiments, R^7 is independently hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, R^{38}-substituted or unsubstituted alkyl, R^{38}-substituted or unsubstituted heteroalkyl, R^{38}-substituted or unsubstituted cycloalkyl, R^{38}-substituted or unsubstituted heterocycloalkyl, R^{38}-substituted or unsubstituted aryl, or R^{38}-substituted or unsubstituted heteroaryl. In embodiments, R^7 is independently halogen, $-CX^7_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^7_3$, $-OCHX^7_2$, R^{38}-substituted or unsubstituted alkyl, R^{38}-substituted or unsubstituted heteroalkyl, R^{38}-substituted or unsubstituted cycloalkyl, R^{38}-substituted or unsubstituted heterocycloalkyl, R^{38}-substituted or unsubstituted aryl, or R^{38}-substituted or unsubstituted heteroaryl. In embodiments, R^7 is independently halogen, $-CX^7_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^7_3$, $-OCHX^7_2$, R^{38}-substituted or unsubstituted C_1-C_8 alkyl, R^{38}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{38}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{38}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{38}-substituted or unsubstituted phenyl, or R^{38}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^7 is –

F,-Cl, -Br, or –I. In embodiments, R^7 is independently hydrogen. In embodiments, R^7 is independently methyl. In embodiments, R^7 is independently ethyl.

[0405] R^{38} is independently oxo, halogen, $-CX^{38}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{38}_3$, $-OCHX^{38}_2$, R^{39}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{39}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{39}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{39}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{39}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{39}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{38} is –F, -Cl, -Br, or –I.

[0406] R^{39} is independently oxo, halogen, $-CX^{39}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{39}_3$, $-OCHX^{39}_2$, R^{40}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{40}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{40}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{40}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{40}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{40}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{39} is –F, -Cl, -Br, or –I.

[0407] In embodiments, R^{7A} is independently hydrogen, $-CX^{7A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{7A}_2$, $-CH_2X^{7A}$, R^{38A}-substituted or unsubstituted alkyl, R^{38A}-substituted or unsubstituted heteroalkyl, R^{38A}-substituted or unsubstituted cycloalkyl, R^{38A}-substituted or unsubstituted heterocycloalkyl, R^{38A}-substituted or unsubstituted aryl, or R^{38A}-substituted or unsubstituted heteroaryl. In embodiments, R^{7A} is independently hydrogen, $-CX^{7A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{7A}_2$, $-CH_2X^{7A}$, R^{38A}-substituted or unsubstituted C_1-C_8 alkyl, R^{38A}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{38A}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{38A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{38A}-substituted or unsubstituted phenyl, or R^{38A}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{7A} is –F, -Cl, -Br, or –I. In embodiments, R^{7A} is independently

hydrogen. In embodiments, R^{7A} is independently methyl. In embodiments, R^{7A} is independently ethyl.

[0408] In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{38A}-substituted or unsubstituted heterocycloalkyl or R^{38A}-substituted or unsubstituted heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{38A}-substituted or unsubstituted 3 to 6

[0409] R^{38A} is independently oxo, halogen, $-CX^{38A}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{38A}_3$, $-OCHX^{38A}_2$, R^{39A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{39A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{39A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{39A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{39A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{39A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{38A} is –F, -Cl, -Br, or –I.

[0410] R^{39A} is independently oxo, halogen, $-CX^{39A}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{39A}_3$, $-OCHX^{39A}_2$, R^{40A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{40A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{40A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{40A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{40A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{40A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{39A} is –F, -Cl, -Br, or –I.

[0411] In embodiments, R^{7B} is independently hydrogen, $-CX^{7B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{7B}_2$, $-CH_2X^{7B}$, R^{38B}-substituted or unsubstituted alkyl, R^{38B}-substituted or unsubstituted heteroalkyl, R^{38B}-substituted or unsubstituted cycloalkyl, R^{38B}-substituted or unsubstituted heterocycloalkyl, R^{38B}-substituted or unsubstituted aryl, or R^{38B}-substituted or unsubstituted heteroaryl. In embodiments, R^{7B} is independently hydrogen, $-CX^{7B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{7B}_2$, $-CH_2X^{7B}$, R^{38B}-substituted or unsubstituted

C_1-C_8 alkyl, R^{38B}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{38B}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{38B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{38B}-substituted or unsubstituted phenyl, or R^{38B}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{7B} is –F, -Cl, -Br, or –I. In embodiments, R^{7B} is independently hydrogen. In embodiments, R^{7B} is independently methyl. In embodiments, R^{7B} is independently ethyl.

[0412] In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{38B}-substituted or unsubstituted heterocycloalkyl or R^{38B}-substituted or unsubstituted heteroaryl. In embodiments, R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{38B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{38B}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0413] R^{38B} is independently oxo, halogen, $-CX^{38B}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{38B}_3$, $-OCHX^{38B}_2$, R^{39B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{39B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{39B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{39B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{39B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{39B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{38B} is –F, -Cl, -Br, or –I.

[0414] R^{39B} is independently oxo, halogen, $-CX^{39B}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{39B}_3$, $-OCHX^{39B}_2$, R^{40B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{40B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{40B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{40B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{40B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{40B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{39B} is –F, -Cl, -Br, or –I.

[0415] In embodiments, R^{7C} is independently hydrogen, $-CX^{7C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{7C}_2$, $-CH_2X^{7C}$, R^{38C}-substituted or unsubstituted alkyl, R^{38C}-substituted or unsubstituted heteroalkyl, R^{38C}-substituted or unsubstituted cycloalkyl, R^{38C}-substituted or unsubstituted heterocycloalkyl, R^{38C}-substituted or unsubstituted aryl, or R^{38C}-substituted or unsubstituted heteroaryl. In embodiments, R^{7C} is independently hydrogen, $-CX^{7C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{7C}_2$, $-CH_2X^{7C}$, R^{38C}-substituted or unsubstituted C_1-C_8 alkyl, R^{38C}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{38C}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{38C}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{38C}-substituted or unsubstituted phenyl, or R^{38C}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{7C} is –F, -Cl, -Br, or –I. In embodiments, R^{7C} is independently hydrogen. In embodiments, R^{7C} is independently methyl. In embodiments, R^{7C} is independently ethyl.

[0416] R^{38C} is independently oxo, halogen, $-CX^{38C}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{38C}_3$, $-OCHX^{38C}_2$, R^{39C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{39C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{39C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{39C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{39C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{39C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{38C} is –F, -Cl, -Br, or –I.

[0417] R^{39C} is independently oxo, halogen, $-CX^{39C}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{39C}_3$, $-OCHX^{39C}_2$, R^{40C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{40C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{40C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{40C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{40C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{40C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{39C} is –F, -Cl, -Br, or –I.

[0418] In embodiments, R^{7D} is independently hydrogen, $-CX^{7D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{7D}_2$, $-CH_2X^{7D}$, R^{38D}-substituted or unsubstituted alkyl, R^{38D}-substituted or unsubstituted heteroalkyl, R^{38D}-substituted or unsubstituted cycloalkyl, R^{38D}-substituted or unsubstituted heterocycloalkyl, R^{38D}-substituted or unsubstituted aryl, or R^{38D}-substituted or unsubstituted heteroaryl. In embodiments, R^{7D} is independently hydrogen, $-CX^{7D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{7D}_2$, $-CH_2X^{7D}$, R^{38D}-substituted or unsubstituted C_1-C_8 alkyl, R^{38D}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{38D}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{38D}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{38D}-substituted or unsubstituted phenyl, or R^{38D}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{7D} is –F, -Cl, -Br, or –I. In embodiments, R^{7D} is independently hydrogen. In embodiments, R^{7D} is independently methyl. In embodiments, R^{7D} is independently ethyl.

[0419] R^{38D} is independently oxo, halogen, $-CX^{38D}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{38D}_3$, $-OCHX^{38D}_2$, R^{39D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{39D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{39D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{39D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{39D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{39D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{38D} is –F, -Cl, -Br, or –I.

[0420] R^{39D} is independently oxo, halogen, $-CX^{39D}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{39D}_3$, $-OCHX^{39D}_2$, R^{40D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{40D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{40D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{40D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{40D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{40D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{39D} is –F, -Cl, -Br, or –I.

[0421] R^{40}, R^{40A}, R^{40B}, R^{40C}, and R^{40D} are independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0422] In embodiments, L^3 is a bond. In embodiments, L^3 is $-S(O)_2-$. In embodiments, L^3 is $-NR^8-$. In embodiments, L^3 is -O-. In embodiments, L^3 is -S-. In embodiments, L^3 is -C(O)- . In embodiments, L^3 is $-C(O)NR^8-$. In embodiments, L^3 is $-NR^8C(O)-$. In embodiments, L^3 is $-NR^8C(O)NH-$. In embodiments, L^3 is $-NHC(O)NR^8-$. In embodiments, L^3 is -C(O)O-. In embodiments, L^3 is -OC(O)-. In embodiments, L^3 is -NH-. In embodiments, L^3 is -C(O)NH-. In embodiments, L^3 is -NHC(O)- . In embodiments, L^3 is -NHC(O)NH-.

[0423] In embodiments, L^3 is a substituted or unsubstituted alkylene. In embodiments, L^3 is a substituted or unsubstituted heteroalkylene. In embodiments, L^3 is a substituted alkylene. In embodiments, L^3 is a substituted heteroalkylene. In embodiments, L^3 is an unsubstituted alkylene. In embodiments, L^3 is an unsubstituted heteroalkylene. In embodiments, L^3 is a substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^3 is a substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^3 is a substituted C_1-C_8 alkylene. In embodiments, L^3 is a substituted 2 to 8 membered heteroalkylene. In embodiments, L^3 is an unsubstituted C_1-C_8 alkylene. In embodiments, L^3 is an unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^3 is a substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^3 is a substituted or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^3 is a substituted C_1-C_4 alkylene. In embodiments, L^3 is a substituted 2 to 4 membered heteroalkylene. In embodiments, L^3 is an unsubstituted C_1-C_4 alkylene. In embodiments, L^3 is an unsubstituted 2 to 4 membered heteroalkylene.

[0424] In embodiments, L^3 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^8-$, -O-, -S-, -C(O)-, $-C(O)NR^8-$, $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-NHC(O)NR^8-$, -C(O)O-, -OC(O)-, R^{50}-substituted or unsubstituted alkylene, or R^{50}-substituted or

unsubstituted heteroalkylene. In embodiments, L^3 is a bond, -$S(O)_2$-, -$S(O)_2$-Ph-, -NH-, -O-, -S-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, R^{50}-substituted or unsubstituted alkylene, or R^{50}-substituted or unsubstituted heteroalkylene. In embodiments, L^3 is a bond, -$S(O)_2$-, -$S(O)_2$-Ph-, -NH-, -O-, -S-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, R^{50}-substituted or unsubstituted C_1-C_8 alkylene, or R^{50}-substituted or unsubstituted 2 to 8 membered heteroalkylene.

[0425] R^{50} is independently oxo, halogen, -CX^{50}_3, -CHX^{50}_2, -CH_2X^{50}, -OCX^{50}_3, -$OCHX^{50}_2$, -OCH_2X^{50}, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{51}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{51}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{51}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{51}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{51}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{51}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{50} is –F, -Cl, -Br, or –I.

[0426] R^{51} is independently oxo, halogen, -CX^{51}_3, -CHX^{51}_2, -CH_2X^{51}, -OCX^{51}_3, -$OCHX^{51}_2$, -OCH_2X^{51}, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{52}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{52}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{52}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{52}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{52}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{52}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{51} is –F, -Cl, -Br, or –I.

[0427] R^{52} is independently oxo, halogen, -CF_3, -CCl_3, -CBr_3, -CI_3, -CHF_2, -$CHCl_2$, -$CHBr_2$, -CHI_2, -CH_2F, -CH_2Cl, -CH_2Br, -CH_2I, -OCF_3, -$OCCl_3$, -$OCBr_3$, -OCI_3, -$OCHF_2$, -$OCHCl_2$, -$OCHBr_2$, -$OCHI_2$, -OCH_2F, -OCH_2Cl, -OCH_2Br, -OCH_2I, -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, -$NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered),

unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0428] In embodiments, L^3 is R^{50}-substituted or unsubstituted C_1-C_2 alkylene. In embodiments, L^3 is R^{50}-substituted or unsubstituted C_1-C_4 alkylene. In embodiments, L^3 is R^{50}-substituted or unsubstituted C_1-C_6 alkylene. In embodiments, L^3 is R^{50}-substituted or unsubstituted C_1-C_8 alkylene. In embodiments, L^3 is R^{50}-substituted or unsubstituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, C_1-C_4 alkylene, C_1-C_2 alkylene). In embodiments, L^3 is R^{50}-substituted C_1-C_2 alkylene. In embodiments, L^3 is R^{50}-substituted C_1-C_4 alkylene. In embodiments, L^3 is R^{50}-substituted C_1-C_6 alkylene. In embodiments, L^3 is R^{50}-substituted C_1-C_8 alkylene. In embodiments, L^3 is R^{50}-substituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, C_1-C_4 alkylene, C_1-C_2 alkylene). In embodiments, L^3 is R^{50}-substituted methylene. In embodiments, L^3 is an unsubstituted C_1-C_2 alkylene. In embodiments, L^3 is an unsubstituted C_1-C_4 alkylene. In embodiments, L^3 is an unsubstituted C_1-C_6 alkylene. In embodiments, L^3 is an unsubstituted C_1-C_8 alkylene. In embodiments, L^3 is an unsubstituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, C_1-C_4 alkylene, C_1-C_2 alkylene). In embodiments, L^3 is R^{50}-substituted or unsubstituted methylene. In embodiments, L^3 is R^{50}-substituted methylene. In embodiments, L^3 is an unsubstituted methylene. In embodiments, L^3 is a bond.

[0429] In embodiments, L^3 is R^{50}-substituted or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^3 is R^{50}-substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^3 is R^{50}-substituted or unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^3 is R^{50}-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, 2 to 4 membered heteroalkylene). In embodiments, L^3 is R^{50}-substituted 2 to 4 membered heteroalkylene. In embodiments, L^3 is R^{50}-substituted 2 to 6 membered heteroalkylene. In embodiments, L^3 is R^{50}-substituted 2 to 8 membered heteroalkylene. In embodiments, L^3 is R^{50}-substituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, 2 to 4 membered heteroalkylene). In embodiments, L^3 is an unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^3 is an unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^3 is an unsubstituted 2 to 8 membered heteroalkylene. In embodiments, L^3 is an unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, 2 to 4 membered heteroalkylene).

[0430] In embodiments, R^8 is substituted or unsubstituted C_1-C_6 alkyl. In embodiments, R^8 is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^8 is substituted or unsubstituted C_3-C_6 cycloalkyl. In embodiments, R^8 is substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^8 is substituted or unsubstituted phenyl. In embodiments, R^8 is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^8 is substituted C_1-C_6 alkyl. In embodiments, R^8 is substituted 2 to 6 membered heteroalkyl. In embodiments, R^8 is substituted C_3-C_6 cycloalkyl. In embodiments, R^8 is substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^8 is substituted phenyl. In embodiments, R^8 is substituted 5 to 6 membered heteroaryl. In embodiments, R^8 is an unsubstituted C_1-C_6 alkyl. In embodiments, R^8 is an unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^8 is an unsubstituted C_3-C_6 cycloalkyl. In embodiments, R^8 is an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^8 is an unsubstituted phenyl. In embodiments, R^8 is an unsubstituted 5 to 6 membered heteroaryl.

[0431] In embodiments, R^8 is substituted or unsubstituted C_1-C_4 alkyl. In embodiments, R^8 is substituted or unsubstituted C_3-C_5 cycloalkyl. In embodiments, R^8 is substituted or unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, R^8 is substituted or unsubstituted 5 membered heteroaryl. In embodiments, R^8 is substituted C_1-C_4 alkyl. In embodiments, R^8 is substituted C_3-C_5 cycloalkyl. In embodiments, R^8 is substituted 3 to 5 membered heterocycloalkyl. In embodiments, R^8 is substituted 5 membered heteroaryl. In embodiments, R^8 is substituted 6 membered heteroaryl. In embodiments, R^8 is an unsubstituted C_1-C_4 alkyl. In embodiments, R^8 is an unsubstituted C_3-C_5 cycloalkyl. In embodiments, R^8 is an unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, R^8 is an unsubstituted 5 membered heteroaryl. In embodiments, R^8 is an unsubstituted 6 membered heteroaryl. In embodiments, R^8 is substituted C_1-C_3 alkyl. In embodiments, R^8 is an unsubstituted C_1-C_3 alkyl.

[0432] In embodiments, R^8 is independently hydrogen. In embodiments, R^8 is independently halogen. In embodiments, R^8 is independently $-CX^8_3$. In embodiments, R^8 is independently $-CHX^8_2$. In embodiments, R^8 is independently $-CH_2X^8$. In embodiments, R^8 is independently $-OCX^8_3$. In embodiments, R^8 is independently $-OCH_2X^8$. In embodiments, R^8 is independently $-OCHX^8_2$. In embodiments, R^8 is independently $-CN$. In embodiments, R^8 is independently $-SO_{n8}R^{8D}$. In embodiments, R^8 is independently $-SO_{v8}NR^{8A}R^{8B}$. In embodiments, R^8 is independently $-NHC(O)NR^{8A}R^{8B}$. In embodiments, R^8 is independently $-N(O)_{m8}$. In embodiments, R^8 is independently $-NR^{8A}R^{8B}$. In embodiments, R^8 is independently $-C(O)R^{8C}$. In embodiments, R^8 is independently $-C(O)-OR^{8C}$. In embodiments, R^8 is

independently -C(O)$NR^{8A}R^{8B}$. In embodiments, R^8 is independently -OR^{8D}. In embodiments, R^8 is independently -$NR^{8A}SO_2R^{8D}$. In embodiments, R^8 is independently -$NR^{8A}C(O)R^{8C}$. In embodiments, R^8 is independently -$NR^{8A}C(O)OR^{8C}$. In embodiments, R^8 is independently -$NR^{8A}OR^{8C}$. In embodiments, R^8 is independently -OH. In embodiments, R^8 is independently -NH_2. In embodiments, R^8 is independently -COOH. In embodiments, R^8 is independently -$CONH_2$. In embodiments, R^8 is independently -NO_2. In embodiments, R^8 is independently –SH.

[0433] In embodiments, R^8 is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^8 is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^8 is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^8 is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^8 is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^8 is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^8 is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^8 is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^8 is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^8 is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^8 is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^8 is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^8 is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^8 is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^8 is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^8 is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^8 is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^8 is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0434] In embodiments, R^{8A} is independently hydrogen. In embodiments, R^{8A} is independently -CX^{8A}_3. In embodiments, R^{8A} is independently -CHX^{8A}_2. In embodiments, R^{8A} is

independently $-CH_2X^{8A}$. In embodiments, R^{8A} is independently -CN. In embodiments, R^{8A} is independently -COOH. In embodiments, R^{8A} is independently $-CONH_2$.

[0435] In embodiments, R^{8A} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8A} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8A} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8A} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8A} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8A} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8A} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8A} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8A} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8A} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8A} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8A} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8A} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8A} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8A} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8A} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8A} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8A} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8A} is independently unsubstituted methyl. In embodiments, R^{8A} is independently unsubstituted ethyl. In embodiments, R^{8A} is independently unsubstituted propyl. In embodiments, R^{8A} is independently unsubstituted isopropyl. In embodiments, R^{8A} is independently unsubstituted tert-butyl.

[0436] In embodiments, R^{8B} is independently hydrogen. In embodiments, R^{8B} is independently $-CX^{8B}_3$. In embodiments, R^{8B} is independently $-CHX^{8B}_2$. In embodiments, R^{8B} is independently $-CH_2X^{8B}$. In embodiments, R^{8B} is independently -CN. In embodiments, R^{8B} is independently -COOH. In embodiments, R^{8B} is independently $-CONH_2$.

[0437] In embodiments, R^{8B} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8B} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8B} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8B} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8B} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8B} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8B} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8B} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8B} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8B} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8B} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8B} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8B} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8B} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8B} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8B} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8B} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8B} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8B} is independently unsubstituted methyl. In embodiments, R^{8B} is independently unsubstituted ethyl. In embodiments, R^{8B} is independently unsubstituted propyl. In embodiments, R^{8B} is independently unsubstituted isopropyl. In embodiments, R^{8B} is independently unsubstituted tert-butyl.

[0438] In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form

an unsubstituted heterocycloalkyl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 10 membered heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 6 membered heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 6 membered heteroaryl.

[0439] In embodiments, R^{8C} is independently hydrogen. In embodiments, R^{8C} is independently $-CX^{8C}_3$. In embodiments, R^{8C} is independently $-CHX^{8C}_2$. In embodiments, R^{8C} is independently $-CH_2X^{8C}$. In embodiments, R^{8C} is independently -CN. In embodiments, R^{8C} is independently -COOH. In embodiments, R^{8C} is independently $-CONH_2$.

[0440] In embodiments, R^{8C} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8C} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8C} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8C} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8C} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8C} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6

membered, or 2 to 4 membered). In embodiments, R^{8C} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8C} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8C} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8C} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8C} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8C} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8C} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8C} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8C} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8C} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8C} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8C} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8C} is independently unsubstituted methyl. In embodiments, R^{8C} is independently unsubstituted ethyl. In embodiments, R^{8C} is independently unsubstituted propyl. In embodiments, R^{8C} is independently unsubstituted isopropyl. In embodiments, R^{8C} is independently unsubstituted tert-butyl.

[0441] In embodiments, R^{8D} is independently hydrogen. In embodiments, R^{8D} is independently $-CX^{8D}_3$. In embodiments, R^{8D} is independently $-CHX^{8D}_2$. In embodiments, R^{8D} is independently $-CH_2X^{8D}$. In embodiments, R^{8D} is independently -CN. In embodiments, R^{8D} is independently -COOH. In embodiments, R^{8D} is independently $-CONH_2$.

[0442] In embodiments, R^{8D} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8D} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8D} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{8D} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8D} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8D} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{8D} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8D} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8D} is independently

unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{8D} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8D} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8D} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{8D} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8D} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8D} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{8D} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8D} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8D} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{8D} is independently unsubstituted methyl. In embodiments, R^{8D} is independently unsubstituted ethyl. In embodiments, R^{8D} is independently unsubstituted propyl. In embodiments, R^{8D} is independently unsubstituted isopropyl. In embodiments, R^{8D} is independently unsubstituted tert-butyl.

[0443] In embodiments, R^8 is independently hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, -CN, $-SO_{n8}R^{8D}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-C(O)R^{8C}$, $-C(O)OR^{8C}$, $-C(O)NR^{8A}R^{8B}$, $-OR^{8D}$, $-NR^{8A}SO_2R^{8D}$, $-NR^{8A}C(O)R^{8C}$, $-NR^{8A}C(O)OR^{8C}$, $-NR^{8A}OR^{8C}$, R^{47}-substituted or unsubstituted alkyl, R^{47}-substituted or unsubstituted heteroalkyl, R^{47}-substituted or unsubstituted cycloalkyl, R^{47}-substituted or unsubstituted heterocycloalkyl, R^{47}-substituted or unsubstituted aryl, or R^{47}-substituted or unsubstituted heteroaryl. In embodiments, R^8 is independently hydrogen, halogen, $-CX^8_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^8_3$, $-OCHX^8_2$, R^{47}-substituted or unsubstituted alkyl, R^{47}-substituted or unsubstituted heteroalkyl, R^{47}-substituted or unsubstituted cycloalkyl, R^{47}-substituted or unsubstituted heterocycloalkyl, R^{47}-substituted or unsubstituted aryl, or R^{47}-substituted or unsubstituted heteroaryl.

[0444] In embodiments, R^8 is independently hydrogen, halogen, $-CX^8_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^8_3$, $-OCHX^8_2$, R^{47}-substituted or unsubstituted C_1-C_8 alkyl, R^{47}-substituted or

unsubstituted 2 to 8 membered heteroalkyl, R^{47}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{47}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{47}-substituted or unsubstituted phenyl, or R^{47}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^8 is –F,-Cl, -Br, or –I. In embodiments, R^8 is independently methyl. In embodiments, R^8 is independently ethyl.

[0445] R^{47} is independently oxo, halogen, $-CX^{47}_3$, $-CHX^{47}_2$, $-CH_2X^{47}$, $-OCX^{47}_3$, $-OCHX^{47}_2$, $-OCH_2X^{47}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{48}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{48}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{48}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{48}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{48}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{47} is –F, -Cl, -Br, or –I.

[0446] R^{48} is independently oxo, halogen, $-CX^{48}_3$, $-CHX^{48}_2$, $-CH_2X^{48}$, $-OCX^{48}_3$, $-OCHX^{48}_2$, $-OCH_2X^{48}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{49}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{49}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{49}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{49}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{49}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{49}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{48} is –F, -Cl, -Br, or –I.

[0447] In embodiments, R^{8A} is independently hydrogen, $-CX^{8A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{8A}_2$, $-CH_2X^{8A}$, R^{47A}-substituted or unsubstituted alkyl, R^{47A}-substituted or unsubstituted heteroalkyl, R^{47A}-substituted or unsubstituted cycloalkyl, R^{47A}-substituted or unsubstituted heterocycloalkyl, R^{47A}-substituted or unsubstituted aryl, or R^{47A}-substituted or unsubstituted heteroaryl. In embodiments, R^{8A} is independently hydrogen, $-CX^{8A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{8A}_2$, $-CH_2X^{8A}$, R^{47A}-substituted or unsubstituted C_1-C_8 alkyl, R^{47A}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{47A}-substituted or

unsubstituted C_3-C_8 cycloalkyl, R^{47A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{47A}-substituted or unsubstituted phenyl, or R^{47A}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{8A} is –F, -Cl, -Br, or –I. In embodiments, R^{8A} is independently hydrogen. In embodiments, R^{8A} is independently methyl. In embodiments, R^{8A} is independently ethyl.

[0448] In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{47A}-substituted or unsubstituted heterocycloalkyl or R^{47A}-substituted or unsubstituted heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{47A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{47A}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0449] R^{47A} is independently oxo, halogen, $-CX^{47A}_3$, $-CHX^{47A}_2$, $-CH_2X^{47A}$, $-OCX^{47A}_3$, $-OCHX^{47A}_2$, $-OCH_2X^{47A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{48A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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^{47A} is –F, -Cl, -Br, or –I.

[0450] R^{48A} is independently oxo, halogen, $-CX^{48A}_3$, $-CHX^{48A}_2$, $-CH_2X^{48A}$, $-OCX^{48A}_3$, $-OCHX^{48A}_2$, $-OCH_2X^{48A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{49A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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 –F, -Cl, -Br, or –I.

[0451] In embodiments, R^{8B} is independently hydrogen, $-CX^{8B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{8B}_2$, $-CH_2X^{8B}$, R^{47B}-substituted or unsubstituted

alkyl, R^{47B}-substituted or unsubstituted heteroalkyl, R^{47B}-substituted or unsubstituted cycloalkyl, R^{47B}-substituted or unsubstituted heterocycloalkyl, R^{47B}-substituted or unsubstituted aryl, or R^{47B}-substituted or unsubstituted heteroaryl. In embodiments, R^{8B} is independently hydrogen, $-CX^{8B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{8B}_2$, $-CH_2X^{8B}$, R^{47B}-substituted or unsubstituted C_1-C_8 alkyl, R^{47B}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{47B}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{47B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{47B}-substituted or unsubstituted phenyl, or R^{47B}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{8B} is –F, -Cl, -Br, or –I. In embodiments, R^{8B} is independently hydrogen. In embodiments, R^{8B} is independently methyl. In embodiments, R^{8B} is independently ethyl.

[0452] In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{47B}-substituted or unsubstituted heterocycloalkyl or R^{47B}-substituted or unsubstituted heteroaryl. In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{47B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{47B}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0453] R^{47B} is independently oxo, halogen, $-CX^{47B}_3$, $-CHX^{47B}_2$, $-CH_2X^{47B}$, $-OCX^{47B}_3$, $-OCHX^{47B}_2$, $-OCH_2X^{47B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{48B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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^{47B} is –F, -Cl, -Br, or –I.

[0454] R^{48B} is independently oxo, halogen, $-CX^{48B}_3$, $-CHX^{48B}_2$, $-CH_2X^{48B}$, $-OCX^{48B}_3$, $-OCHX^{48B}_2$, $-OCH_2X^{48B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{49B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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 –F, -Cl, -Br, or –I.

[0455] In embodiments, R^{8C} is independently hydrogen, $-CX^{8C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{8C}_2$, $-CH_2X^{8C}$, R^{47C}-substituted or unsubstituted alkyl, R^{47C}-substituted or unsubstituted heteroalkyl, R^{47C}-substituted or unsubstituted cycloalkyl, R^{47C}-substituted or unsubstituted heterocycloalkyl, R^{47C}-substituted or unsubstituted aryl, or R^{47C}-substituted or unsubstituted heteroaryl. In embodiments, R^{8C} is independently hydrogen, $-CX^{8C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{8C}_2$, $-CH_2X^{8C}$, R^{47C}-substituted or unsubstituted C_1-C_8 alkyl, R^{47C}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{47C}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{47C}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{47C}-substituted or unsubstituted phenyl, or R^{47C}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{8C} is –F, -Cl, -Br, or –I. In embodiments, R^{8C} is independently hydrogen. In embodiments, R^{8C} is independently methyl. In embodiments, R^{8C} is independently ethyl.

[0456] R^{47C} is independently oxo, halogen, $-CX^{47C}_3$, $-CHX^{47C}_2$, $-CH_2X^{47C}$, $-OCX^{47C}_3$, $-OCHX^{47C}_2$, $-OCH_2X^{47C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{48C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{48C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{48C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{48C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{48C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{47C} is –F, -Cl, -Br, or –I.

[0457] R^{48C} is independently oxo, halogen, $-CX^{48C}_3$, $-CHX^{48C}_2$, $-CH_2X^{48C}$, $-OCX^{48C}_3$, $-OCHX^{48C}_2$, $-OCH_2X^{48C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{49C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{49C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{49C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{49C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

membered, 3 to 6 membered, or 5 to 6 membered), R^{49C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{49C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{48C} is –F, -Cl, -Br, or –I.

[0458] In embodiments, R^{8D} is independently hydrogen, $-CX^{8D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{8D}_2$, $-CH_2X^{8D}$, R^{47D}-substituted or unsubstituted alkyl, R^{47D}-substituted or unsubstituted heteroalkyl, R^{47D}-substituted or unsubstituted cycloalkyl, R^{47D}-substituted or unsubstituted heterocycloalkyl, R^{47D}-substituted or unsubstituted aryl, or R^{47D}-substituted or unsubstituted heteroaryl. In embodiments, R^{8D} is independently hydrogen, $-CX^{8D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{8D}_2$, $-CH_2X^{8D}$, R^{47D}-substituted or unsubstituted C_1-C_8 alkyl, R^{47D}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{47D}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{47D}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{47D}-substituted or unsubstituted phenyl, or R^{47D}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{8D} is –F, -Cl, -Br, or –I. In embodiments, R^{8D} is independently hydrogen. In embodiments, R^{8D} is independently methyl. In embodiments, R^{8D} is independently ethyl.

[0459] R^{47D} is independently oxo, halogen, $-CX^{47D}_3$, $-CHX^{47D}_2$, $-CH_2X^{47D}$, $-OCX^{47D}_3$, $-OCHX^{47D}_2$, $-OCH_2X^{47D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{48D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{48D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{48D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{48D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{48D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{47D} is –F, -Cl, -Br, or –I.

[0460] R^{48D} is independently oxo, halogen, $-CX^{48D}_3$, $-CHX^{48D}_2$, $-CH_2X^{48D}$, $-OCX^{48D}_3$, $-OCHX^{48D}_2$, $-OCH_2X^{48D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{49D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{49D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{49D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{49D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

membered, 3 to 6 membered, or 5 to 6 membered), R^{49D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{49D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{48D} is –F, -Cl, -Br, or –I.

[0461] R^{49}, R^{49A}, R^{49B}, R^{49C}, and R^{49D} are independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $–NHNH_2$, $–ONH_2$, $–NHC(O)NHNH_2$, $–NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0462] In embodiments, R^9 is an unsubstituted methoxy. In embodiments, R^9 is –OH. In embodiments, R^9 is an unsubstituted ethoxy. In embodiments, R^9 is $-N(CH_3)_2$. In embodiments, R^9 is –SH. In embodiments, R^9 is $-SCH_3$. In embodiments, R^9 is $–SCH_2CH_3$. In embodiments, R^9 is $–NH_2$. In embodiments, R^9 is $-NHCH_3$. In embodiments, R^9 is $–NHCH_2CH_3$. In embodiments, R^9 is $-N(CH_2CH_3)_2$. In embodiments, R^9 is $-N(CH_3)(CH_2CH_3)$. In embodiments, R^9 is hydrogen.

[0463] In embodiments, R^9 is substituted or unsubstituted C_1-C_6 alkyl. In embodiments, R^9 is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^9 is substituted or unsubstituted C_3-C_6 cycloalkyl. In embodiments, R^9 is substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^9 is substituted or unsubstituted phenyl. In embodiments, R^9 is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^9 is substituted C_1-C_6 alkyl. In embodiments, R^9 is substituted 2 to 6 membered heteroalkyl. In embodiments, R^9 is substituted C_3-C_6 cycloalkyl. In embodiments, R^9 is substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^9 is substituted phenyl. In embodiments, R^9 is substituted 5 to 6 membered heteroaryl. In embodiments, R^9 is an unsubstituted C_1-C_6 alkyl. In embodiments, R^9 is an unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^9 is an unsubstituted C_3-C_6 cycloalkyl. In embodiments, R^9 is an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^9 is an unsubstituted phenyl. In embodiments, R^9 is an unsubstituted 5 to 6 membered heteroaryl.

[0464] In embodiments, R^9 is substituted or unsubstituted C_1-C_4 alkyl. In embodiments, R^9 is substituted or unsubstituted C_3-C_5 cycloalkyl. In embodiments, R^9 is substituted or unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, R^9 is substituted or unsubstituted 5 membered heteroaryl. In embodiments, R^9 is substituted C_1-C_4 alkyl. In embodiments, R^9 is substituted C_3-C_5 cycloalkyl. In embodiments, R^9 is substituted 3 to 5 membered heterocycloalkyl. In embodiments, R^9 is substituted 5 membered heteroaryl. In embodiments, R^9 is substituted 6 membered heteroaryl. In embodiments, R^9 is an unsubstituted C_1-C_4 alkyl. In embodiments, R^9 is an unsubstituted C_3-C_5 cycloalkyl. In embodiments, R^9 is an unsubstituted 3 to 5 membered heterocycloalkyl. In embodiments, R^9 is an unsubstituted 5 membered heteroaryl. In embodiments, R^9 is an unsubstituted 6 membered heteroaryl. In embodiments, R^9 is substituted C_1-C_3 alkyl. In embodiments, R^9 is an unsubstituted C_1-C_3 alkyl.

[0465] In embodiments, R^9 is independently hydrogen. In embodiments, R^9 is independently halogen. In embodiments, R^9 is independently $-CX^9_3$. In embodiments, R^9 is independently $-CHX^9_2$. In embodiments, R^9 is independently $-CH_2X^9$. In embodiments, R^9 is independently $-OCX^9_3$. In embodiments, R^9 is independently $-OCH_2X^9$. In embodiments, R^9 is independently $-OCHX^9_2$. In embodiments, R^9 is independently -CN. In embodiments, R^9 is independently $-SO_{n9}R^{9D}$. In embodiments, R^9 is independently $-SO_{v9}NR^{9A}R^{9B}$. In embodiments, R^9 is independently $-NHC(O)NR^{9A}R^{9B}$. In embodiments, R^9 is independently $-N(O)_{m9}$. In embodiments, R^9 is independently $-NR^{9A}R^{9B}$. In embodiments, R^9 is independently $-C(O)R^{9C}$. In embodiments, R^9 is independently $-C(O)-OR^{9C}$. In embodiments, R^9 is independently $-C(O)NR^{9A}R^{9B}$. In embodiments, R^9 is independently $-OR^{9D}$. In embodiments, R^9 is independently $-NR^{9A}SO_2R^{9D}$. In embodiments, R^9 is independently $-NR^{9A}C(O)R^{9C}$. In embodiments, R^9 is independently $-NR^{9A}C(O)OR^{9C}$. In embodiments, R^9 is independently $-NR^{9A}OR^{9C}$. In embodiments, R^9 is independently -OH. In embodiments, R^9 is independently $-NH_2$. In embodiments, R^9 is independently -COOH. In embodiments, R^9 is independently $-CONH_2$. In embodiments, R^9 is independently $-NO_2$. In embodiments, R^9 is independently –SH.

[0466] In embodiments, R^9 is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^9 is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^9 is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^9 is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^9 is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In

embodiments, R^9 is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^9 is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^9 is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^9 is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^9 is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^9 is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^9 is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^9 is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^9 is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^9 is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^9 is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^9 is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^9 is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0467] In embodiments, R^{9A} is independently hydrogen. In embodiments, R^{9A} is independently $-CX^{9A}_3$. In embodiments, R^{9A} is independently $-CHX^{9A}_2$. In embodiments, R^{9A} is independently $-CH_2X^{9A}$. In embodiments, R^{9A} is independently -CN. In embodiments, R^{9A} is independently -COOH. In embodiments, R^{9A} is independently $-CONH_2$.

[0468] In embodiments, R^{9A} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9A} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9A} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9A} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9A} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9A} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9A} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9A} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9A} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9A} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6

membered). In embodiments, R^{9A} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9A} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9A} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9A} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9A} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9A} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9A} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9A} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9A} is independently unsubstituted methyl. In embodiments, R^{9A} is independently unsubstituted ethyl. In embodiments, R^{9A} is independently unsubstituted propyl. In embodiments, R^{9A} is independently unsubstituted isopropyl. In embodiments, R^{9A} is independently unsubstituted tert-butyl.

[0469] In embodiments, R^{9B} is independently hydrogen. In embodiments, R^{9B} is independently $-CX^{9B}_3$. In embodiments, R^{9B} is independently $-CHX^{9B}_2$. In embodiments, R^{9B} is independently $-CH_2X^{9B}$. In embodiments, R^{9B} is independently -CN. In embodiments, R^{9B} is independently -COOH. In embodiments, R^{9B} is independently $-CONH_2$.

[0470] In embodiments, R^{9B} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9B} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9B} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9B} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9B} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9B} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9B} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9B} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9B} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9B} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9B} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9B} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered).

In embodiments, R^{9B} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9B} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9B} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9B} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9B} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9B} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9B} is independently unsubstituted methyl. In embodiments, R^{9B} is independently unsubstituted ethyl. In embodiments, R^{9B} is independently unsubstituted propyl. In embodiments, R^{9B} is independently unsubstituted isopropyl. In embodiments, R^{9B} is independently unsubstituted tert-butyl.

[0471] In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heteroaryl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heterocycloalkyl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heteroaryl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 10 membered heteroaryl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted 5 to 6 membered heteroaryl.

In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form a substituted 5 to 6 membered heteroaryl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted 5 to 6 membered heteroaryl.

[0472] In embodiments, R^{9C} is independently hydrogen. In embodiments, R^{9C} is independently $-CX^{9C}_3$. In embodiments, R^{9C} is independently $-CHX^{9C}_2$. In embodiments, R^{9C} is independently $-CH_2X^{9C}$. In embodiments, R^{9C} is independently -CN. In embodiments, R^{9C} is independently -COOH. In embodiments, R^{9C} is independently $-CONH_2$.

[0473] In embodiments, R^{9C} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9C} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9C} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9C} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9C} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9C} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9C} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9C} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9C} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9C} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9C} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9C} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9C} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9C} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9C} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9C} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9C} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9C} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9

membered, or 5 to 6 membered). In embodiments, R^{9C} is independently unsubstituted methyl. In embodiments, R^{9C} is independently unsubstituted ethyl. In embodiments, R^{9C} is independently unsubstituted propyl. In embodiments, R^{9C} is independently unsubstituted isopropyl. In embodiments, R^{9C} is independently unsubstituted tert-butyl.

[0474] In embodiments, R^{9D} is independently hydrogen. In embodiments, R^{9D} is independently $-CX^{9D}_3$. In embodiments, R^{9D} is independently $-CHX^{9D}_2$. In embodiments, R^{9D} is independently $-CH_2X^{9D}$. In embodiments, R^{9D} is independently -CN. In embodiments, R^{9D} is independently -COOH. In embodiments, R^{9D} is independently $-CONH_2$.

[0475] In embodiments, R^{9D} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9D} is independently substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9D} is independently unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{9D} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9D} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9D} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{9D} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9D} is independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9D} is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{9D} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9D} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9D} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{9D} is independently substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9D} is independently substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9D} is independently unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{9D} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9D} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9D} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{9D} is independently unsubstituted methyl. In embodiments, R^{9D} is independently unsubstituted ethyl. In embodiments, R^{9D} is

independently unsubstituted propyl. In embodiments, R^{9D} is independently unsubstituted isopropyl. In embodiments, R^{9D} is independently unsubstituted tert-butyl.

[0476] In embodiments, R^9 is independently hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, R^{53}-substituted or unsubstituted alkyl, R^{53}-substituted or unsubstituted heteroalkyl, R^{53}-substituted or unsubstituted cycloalkyl, R^{53}-substituted or unsubstituted heterocycloalkyl, R^{53}-substituted or unsubstituted aryl, or R^{53}-substituted or unsubstituted heteroaryl. In embodiments, R^9 is independently hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{53}-substituted or unsubstituted alkyl, R^{53}-substituted or unsubstituted heteroalkyl, R^{53}-substituted or unsubstituted cycloalkyl, R^{53}-substituted or unsubstituted heterocycloalkyl, R^{53}-substituted or unsubstituted aryl, or R^{53}-substituted or unsubstituted heteroaryl. In embodiments, R^9 is independently hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{53}-substituted or unsubstituted C_1-C_8 alkyl, R^{53}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{53}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{53}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{53}-substituted or unsubstituted phenyl, or R^{53}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^9 is –F,-Cl, -Br, or –I. In embodiments, R^9 is independently hydrogen. In embodiments, R^9 is independently methyl. In embodiments, R^9 is independently ethyl.

[0477] R^{53} is independently oxo, halogen, $-CX^{53}_3$, $-CHX^{53}_2$, $-CH_2X^{53}$, $-OCX^{53}_3$, $-OCHX^{53}_2$, $-OCH_2X^{53}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{54}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{54}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{54}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{54}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{54}-substituted or unsubstituted aryl (e.g., C_6-

C_{10}, C_{10}, or phenyl), or R^{54}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{53} is –F, -Cl, -Br, or –I.

[0478] R^{54} is independently oxo, halogen, $-CX^{54}_3$, $-CHX^{54}_2$, $-CH_2X^{54}$, $-OCX^{54}_3$, $-OCHX^{54}_2$, $-OCH_2X^{54}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{55}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{55}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{55}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{55}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{55}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{55}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{54} is –F, -Cl, -Br, or –I.

[0479] In embodiments, R^{9A} is independently hydrogen, $-CX^{9A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{9A}_2$, $-CH_2X^{9A}$, R^{53A}-substituted or unsubstituted alkyl, R^{53A}-substituted or unsubstituted heteroalkyl, R^{53A}-substituted or unsubstituted cycloalkyl, R^{53A}-substituted or unsubstituted heterocycloalkyl, R^{53A}-substituted or unsubstituted aryl, or R^{53A}-substituted or unsubstituted heteroaryl. In embodiments, R^{9A} is independently hydrogen, $-CX^{9A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{9A}_2$, $-CH_2X^{9A}$, R^{53A}-substituted or unsubstituted C_1-C_8 alkyl, R^{53A}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{53A}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{53A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{53A}-substituted or unsubstituted phenyl, or R^{53A}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{9A} is –F, -Cl, -Br, or –I. In embodiments, R^{9A} is independently hydrogen. In embodiments, R^{9A} is independently methyl. In embodiments, R^{9A} is independently ethyl.

[0480] In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{53A}-substituted or unsubstituted heterocycloalkyl or R^{53A}-substituted or unsubstituted heteroaryl. In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{53A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{53A}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0481] R^{53A} is independently oxo, halogen, $-CX^{53A}_3$, $-CHX^{53A}_2$, $-CH_2X^{53A}$, $-OCX^{53A}_3$, $-OCHX^{53A}_2$, $-OCH_2X^{53A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$,

–$NHC(O)NH_2$, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{54A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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^{53A} is –F, -Cl, -Br, or –I.

[0482] R^{54A} is independently oxo, halogen, -CX^{54A}_3, -CHX^{54A}_2, -CH_2X^{54A}, -OCX^{54A}_3, -$OCHX^{54A}_2$, -OCH_2X^{54A}, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –$NHC(O)NHNH_2$, –$NHC(O)NH_2$, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{55A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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 –F, -Cl, -Br, or –I.

[0483] In embodiments, R^{9B} is independently hydrogen, -CX^{9B}_3, -CN, -COOH, -$CONH_2$, -CHX^{9B}_2, -CH_2X^{9B}, R^{53B}-substituted or unsubstituted alkyl, R^{53B}-substituted or unsubstituted heteroalkyl, R^{53B}-substituted or unsubstituted cycloalkyl, R^{53B}-substituted or unsubstituted heterocycloalkyl, R^{53B}-substituted or unsubstituted aryl, or R^{53B}-substituted or unsubstituted heteroaryl. In embodiments, R^{9B} is independently hydrogen, -CX^{9B}_3, -CN, -COOH, -$CONH_2$, -CHX^{9B}_2, -CH_2X^{9B}, R^{53B}-substituted or unsubstituted C_1-C_8 alkyl, R^{53B}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{53B}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{53B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{53B}-substituted or unsubstituted phenyl, or R^{53B}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{9B} is –F, -Cl, -Br, or –I. In embodiments, R^{9B} is independently hydrogen. In embodiments, R^{9B} is independently methyl. In embodiments, R^{9B} is independently ethyl.

[0484] In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{53B}-substituted or unsubstituted heterocycloalkyl or R^{53B}-substituted or unsubstituted heteroaryl. In embodiments, R^{9A} and R^{9B} substituents bonded to the

same nitrogen atom may optionally be joined to form a R^{53B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{53B}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0485] R^{53B} is independently oxo, halogen, $-CX^{53B}_3$, $-CHX^{53B}_2$, $-CH_2X^{53B}$, $-OCX^{53B}_3$, $-OCHX^{53B}_2$, $-OCH_2X^{53B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{54B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, or phenyl), or R^{54B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{53B} is –F, -Cl, -Br, or –I.

[0486] R^{54B} is independently oxo, halogen, $-CX^{54B}_3$, $-CHX^{54B}_2$, $-CH_2X^{54B}$, $-OCX^{54B}_3$, $-OCHX^{54B}_2$, $-OCH_2X^{54B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{55B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), R^{55B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{55B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, 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 –F, -Cl, -Br, or –I.

[0487] In embodiments, R^{9C} is independently hydrogen, $-CX^{9C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{9C}_2$, $-CH_2X^{9C}$, R^{53C}-substituted or unsubstituted alkyl, R^{53C}-substituted or unsubstituted heteroalkyl, R^{53C}-substituted or unsubstituted cycloalkyl, R^{53C}-substituted or unsubstituted heterocycloalkyl, R^{53C}-substituted or unsubstituted aryl, or R^{53C}-substituted or unsubstituted heteroaryl. In embodiments, R^{9C} is independently hydrogen, $-CX^{9C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{9C}_2$, $-CH_2X^{9C}$, R^{53C}-substituted or unsubstituted C_1-C_8 alkyl, R^{53C}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{53C}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{53C}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{53C}-substituted or unsubstituted phenyl, or R^{53C}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{9C} is –F, -Cl, -Br, or –I. In embodiments, R^{9C} is independently

hydrogen. In embodiments, R^{9C} is independently methyl. In embodiments, R^{9C} is independently ethyl.

[0488] R^{53C} is independently oxo, halogen, $-CX^{53C}_3$, $-CHX^{53C}_2$, $-CH_2X^{53C}$, $-OCX^{53C}_3$, $-OCHX^{53C}_2$, $-OCH_2X^{53C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{54C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{54C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{54C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{54C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{54C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{54C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{53C} is –F, -Cl, -Br, or –I.

[0489] R^{54C} is independently oxo, halogen, $-CX^{54C}_3$, $-CHX^{54C}_2$, $-CH_2X^{54C}$, $-OCX^{54C}_3$, $-OCHX^{54C}_2$, $-OCH_2X^{54C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{55C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{55C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{55C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{55C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{55C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{55C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{54C} is –F, -Cl, -Br, or –I.

[0490] In embodiments, R^{9D} is independently hydrogen, $-CX^{9D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{9D}_2$, $-CH_2X^{9D}$, R^{53D}-substituted or unsubstituted alkyl, R^{53D}-substituted or unsubstituted heteroalkyl, R^{53D}-substituted or unsubstituted cycloalkyl, R^{53D}-substituted or unsubstituted heterocycloalkyl, R^{53D}-substituted or unsubstituted aryl, or R^{53D}-substituted or unsubstituted heteroaryl. In embodiments, R^{9D} is independently hydrogen, $-CX^{9D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{9D}_2$, $-CH_2X^{9D}$, R^{53D}-substituted or unsubstituted C_1-C_8 alkyl, R^{53D}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{53D}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{53D}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{53D}-substituted or unsubstituted phenyl, or R^{53D}-substituted or unsubstituted 5 to 6 membered heteroaryl. X^{9D} is –F, -Cl, -Br, or –I. In embodiments, R^{9D} is independently

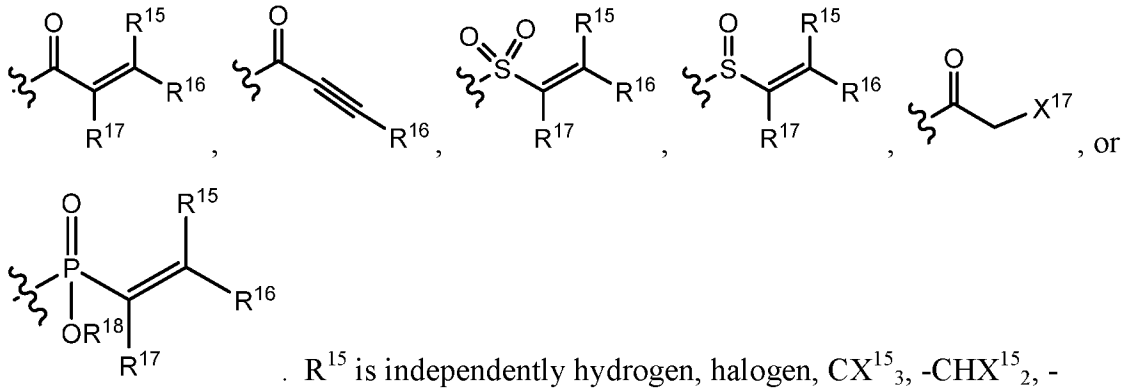
hydrogen. In embodiments, R^{9D} is independently methyl. In embodiments, R^{9D} is independently ethyl.

[0491] R^{53D} is independently oxo, halogen, $-CX^{53D}_3$, $-CHX^{53D}_2$, $-CH_2X^{53D}$, $-OCX^{53D}_3$, $-OCHX^{53D}_2$, $-OCH_2X^{53D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{54D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{54D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{54D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{54D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{54D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{54D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{53D} is –F, -Cl, -Br, or –I.

[0492] R^{54D} is independently oxo, halogen, $-CX^{54D}_3$, $-CHX^{54D}_2$, $-CH_2X^{54D}$, $-OCX^{54D}_3$, $-OCHX^{54D}_2$, $-OCH_2X^{54D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, R^{55D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{55D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{55D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{55D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{55D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{55D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{54D} is –F, -Cl, -Br, or –I.

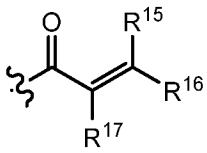
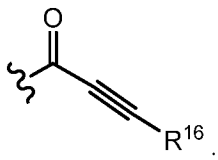
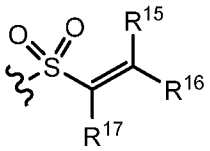
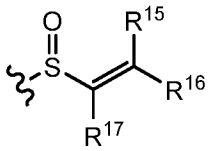
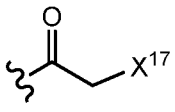
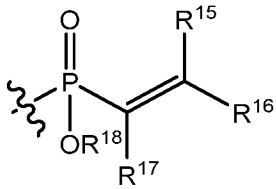
[0493] R^{55}, R^{55A}, R^{55B}, R^{55C}, and R^{55D} are independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)\ NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0494] In embodiments, E is a covalent cysteine modifier moiety. In embodiments, E is:



. R^{15} is independently hydrogen, halogen, CX^{15}_3, $-CHX^{15}_2$, $-CH_2X^{15}$, -CN, $-SO_{n15}R^{15D}$, $-SO_{v15}NR^{15A}R^{15B}$, $-NHNR^{15A}R^{15B}$, $-ONR^{15A}R^{15B}$, $-NHC=(O)NHNR^{15A}R^{15B}$, $-NHC(O)NR^{15A}R^{15B}$, $-N(O)_{m15}$, $-NR^{15A}R^{15B}$, $-C(O)R^{15C}$, $-C(O)-OR^{15C}$, $-C(O)NR^{15A}R^{15B}$, $-OR^{15D}$, $-NR^{15A}SO_2R^{15D}$, $-NR^{15A}C(O)R^{15C}$, $-NR^{15A}C(O)OR^{15C}$, $-NR^{15A}OR^{15C}$, $-OCX^{15}_3$, $-OCHX^{15}_2$, 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^{16} is independently hydrogen, halogen, CX^{16}_3, $-CHX^{16}_2$, $-CH_2X^{16}$, -CN, $-SO_{n16}R^{16D}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHNR^{16A}R^{16B}$, $-ONR^{16A}R^{16B}$, $-NHC=(O)NHNR^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16C}$, $-C(O)-OR^{16C}$, $-C(O)NR^{16A}R^{16B}$, $-OR^{16D}$, $-NR^{16A}SO_2R^{16D}$, $-NR^{16A}C(O)R^{16C}$, $-NR^{16A}C(O)OR^{16C}$, $-NR^{16A}OR^{16C}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, 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^{17} is independently hydrogen, halogen, CX^{17}_3, $-CHX^{17}_2$, $-CH_2X^{17}$, -CN, $-SO_{n17}R^{17D}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC=(O)NHNR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17C}$, $-C(O)-OR^{17C}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17D}$, $-NR^{17A}SO_2R^{17D}$, $-NR^{17A}C(O)R^{17C}$, $-NR^{17A}C(O)OR^{17C}$, $-NR^{17A}OR^{17C}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{18} is independently hydrogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-C(O)R^{18C}$, $-C(O)OR^{18C}$, $-C(O)NR^{18A}R^{18B}$, 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^{15A}, R^{15B}, R^{15C}, R^{15D}, R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B}, R^{17C}, R^{17D}, R^{18A}, R^{18B}, R^{18C}, R^{18D}, are independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{15A} and R^{15B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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;. Each X, X^{15}, X^{16}, X^{17} and X^{18} is independently –F, -Cl, -Br, or –I. n15, n16, n17, v15, v16, and v17, are independently an integer from 0 to 4. m15, m16, and m17 are independently and integer from 1 to 2.

[0495] In embodiments, E is:  . In embodiments, E is:  . In embodiments, E is:  . In embodiments, E is:  . In embodiments, E is:  . In embodiments, E is:  .

[0496] X may independently be –F. X may independently be –Cl. X may independently be –Br. X may independently be –I. X^{15} may independently be –F. X^{15} may independently be –Cl. X^{15} may independently be –Br. X^{15} may independently be –I. X^{16} may independently be –F. X^{16} may independently be –Cl. X^{16} may independently be –Br. X^{16} may independently be –I. X^{17} may independently be –F. X^{17} may independently be –Cl. X^{17} may independently be –Br. X^{17} may independently be –I. X^{18} may independently be –F. X^{18} may independently be –Cl.

X^{18} may independently be –Br. X^{18} may independently be –I. n15 may independently be 0. n15 may independently be 1. n15 may independently be 2. n15 may independently be 3. n15 may independently be 4. 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. n17 may independently be 1. n17 may independently be 2. n17 may independently be 3. n17 may independently be 4. v15 may independently be 0. v15 may independently be 1. v15 may independently be 2. v15 may independently be 3. v15 may independently be 4. 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. m15 may independently be 1. m15 may independently be 2. m16 may independently be 1. m16 may independently be 2. m17 may independently be 1. m17 may independently be 2.

[0497] In embodiments, R^{15} is hydrogen. In embodiments, R^{15} is halogen. In embodiments, R^{15} is CX^{15}_3. In embodiments, R^{15} is $-CHX^{15}_2$. In embodiments, R^{15} is $-CH_2X^{15}$. In embodiments, R^{15} is –CN. In embodiments, R^{15} is $-SO_{n15}R^{15D}$. In embodiments, R^{15} is $-SO_{v15}NR^{15A}R^{15B}$. In embodiments, R^{15} is $–NHNR^{15A}R^{15B}$. In embodiments, R^{15} is $–ONR^{15A}R^{15B}$. In embodiments, R^{15} is $–NHC=(O)NHNR^{15A}R^{15B}$. In embodiments, R^{15} is $–NHC(O)NR^{15A}R^{15B}$. In embodiments, R^{15} is $-N(O)_{m15}$. In embodiments, R^{15} is $-NR^{15A}R^{15B}$. In embodiments, R^{15} is $-C(O)R^{15C}$. In embodiments, R^{15} is $-C(O)-OR^{15C}$. In embodiments, R^{15} is $-C(O)NR^{15A}R^{15B}$. In embodiments, R^{15} is $-OR^{15D}$. In embodiments, R^{15} is $-NR^{15A}SO_2R^{15D}$. In embodiments, R^{15} is $-NR^{15A}C(O)R^{15C}$. In embodiments, R^{15} is $-NR^{15A}C(O)OR^{15C}$. In embodiments, R^{15} is $-NR^{15A}OR^{15C}$. In embodiments, R^{15} is $-OCX^{15}_3$. In embodiments, R^{15} is $-OCHX^{15}_2$. In embodiments, R^{15} is substituted or unsubstituted alkyl. In embodiments, R^{15} is substituted or unsubstituted heteroalkyl. In embodiments, R^{15} is substituted or unsubstituted cycloalkyl. In embodiments, R^{15} is substituted or unsubstituted heterocycloalkyl. In embodiments, R^{15} is substituted or unsubstituted aryl. In embodiments, R^{15} is substituted or unsubstituted heteroaryl. In embodiments, R^{15} is substituted alkyl. In embodiments, R^{15} is substituted heteroalkyl. In embodiments, R^{15} is substituted cycloalkyl. In embodiments, R^{15} is substituted heterocycloalkyl. In embodiments, R^{15} is substituted aryl. In embodiments, R^{15} is substituted heteroaryl. In embodiments, R^{15} is an unsubstituted alkyl. In embodiments, R^{15} is an unsubstituted heteroalkyl. In embodiments, R^{15} is an unsubstituted cycloalkyl. In embodiments, R^{15} is an unsubstituted heterocycloalkyl. In embodiments, R^{15} is an unsubstituted aryl. In embodiments, R^{15} is an unsubstituted heteroaryl. In embodiments, R^{15} is an unsubstituted methyl. In embodiments, R^{15} is an unsubstituted ethyl. In embodiments, R^{15} is an unsubstituted

propyl. In embodiments, R^{15} is an unsubstituted isopropyl. In embodiments, R^{15} is an unsubstituted butyl. In embodiments, R^{15} is an unsubstituted tert-butyl.

[0498] In embodiments, R^{15} is substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{15} is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{15} is substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{15} is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{15} is substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{15} is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0499] In embodiments, R^{15} is substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{15} is substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{15} is substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{15} is substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{15} is substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{15} is substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{15} is an unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{15} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{15} is an unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{15} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{15} is an unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{15} is an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0500] In embodiments, R^{15A} is hydrogen. In embodiments, R^{15A} is $-CX_3$. In embodiments, R^{15A} is -CN. In embodiments, R^{15A} is -COOH. In embodiments, R^{15A} is $-CONH_2$. In embodiments, R^{15A} is $-CHX_2$. In embodiments, R^{15A} is $-CH_2X$. In embodiments, R^{15A} is an unsubstituted methyl. In embodiments, R^{15A} is an unsubstituted ethyl. In embodiments, R^{15A} is an unsubstituted propyl. In embodiments, R^{15A} is an unsubstituted isopropyl. In embodiments, R^{15A} is an unsubstituted butyl. In embodiments, R^{15A} is an unsubstituted tert-butyl.

[0501] In embodiments, R^{15B} is hydrogen. In embodiments, R^{15B} is $-CX_3$. In embodiments, R^{15B} is -CN. In embodiments, R^{15B} is -COOH. In embodiments, R^{15B} is $-CONH_2$. In embodiments, R^{15B} is $-CHX_2$. In embodiments, R^{15B} is $-CH_2X$. In embodiments, R^{15B} is an

unsubstituted methyl. In embodiments, R^{15B} is an unsubstituted ethyl. In embodiments, R^{15B} is an unsubstituted propyl. In embodiments, R^{15B} is an unsubstituted isopropyl. In embodiments, R^{15B} is an unsubstituted butyl. In embodiments, R^{15B} is an unsubstituted tert-butyl.

[0502] In embodiments, R^{15C} is hydrogen. In embodiments, R^{15C} is $-CX_3$. In embodiments, R^{15C} is -CN. In embodiments, R^{15C} is -COOH. In embodiments, R^{15C} is $-CONH_2$. In embodiments, R^{15C} is $-CHX_2$. In embodiments, R^{15C} is $-CH_2X$. In embodiments, R^{15C} is an unsubstituted methyl. In embodiments, R^{15C} is an unsubstituted ethyl. In embodiments, R^{15C} is an unsubstituted propyl. In embodiments, R^{15C} is an unsubstituted isopropyl. In embodiments, R^{15C} is an unsubstituted butyl. In embodiments, R^{15C} is an unsubstituted tert-butyl.

[0503] In embodiments, R^{15D} is hydrogen. In embodiments, R^{15D} is $-CX_3$. In embodiments, R^{15D} is -CN. In embodiments, R^{15D} is -COOH. In embodiments, R^{15D} is $-CONH_2$. In embodiments, R^{15D} is $-CHX_2$. In embodiments, R^{15D} is $-CH_2X$. In embodiments, R^{15D} is an unsubstituted methyl. In embodiments, R^{15D} is an unsubstituted ethyl. In embodiments, R^{15D} is an unsubstituted propyl. In embodiments, R^{15D} is an unsubstituted isopropyl. In embodiments, R^{15D} is an unsubstituted butyl. In embodiments, R^{15D} is an unsubstituted tert-butyl.

[0504] In embodiments, R^{15} is independently hydrogen, oxo, halogen, $-CX^{15}_3$, $-CHX^{15}_2$, $-OCH_2X^{15}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, -NHC(=O)H, -NHC(O)-OH, -NHOH, $-OCX^{15}_3$, $-OCHX^{15}_2$, R^{72}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{72}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{72}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{72}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{72}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{72}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{15} is halogen. In embodiments, X^{15} is F.

[0505] R^{72} is independently oxo, halogen, $-CX^{72}_3$, $-CHX^{72}_2$, $-OCH_2X^{72}$, $-OCHX^{72}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, -NHC(=O)H, -NHC(O)-OH, -NHOH, $-OCX^{72}_3$, $-OCHX^{72}_2$, R^{73}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{73}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{73}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{73}-substituted or unsubstituted heterocycloalkyl (e.g.,

3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{73}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{73}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{72} is halogen. In embodiments, X^{72} is F.

[0506] R^{73} is independently oxo, halogen, $-CX^{73}_3$, $-CHX^{73}_2$, $-OCH_2X^{73}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, -NHC(=O)H, -NHC(O)-OH, -NHOH, $-OCX^{73}_3$, $-OCHX^{73}_2$, R^{74}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{74}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{74}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{74}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{74}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{74}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{73} is halogen. In embodiments, X^{73} is F.

[0507] In embodiments, R^{15A} is independently hydrogen, oxo, halogen, $-CX^{15A}_3$, $-CHX^{15A}_2$, $-OCH_2X^{15A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, -NHC(=O)H, -NHC(O)-OH, -NHOH, $-OCX^{15A}_3$, $-OCHX^{15A}_2$, R^{72A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{72A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{72A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{72A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{72A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{72A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{15A} is halogen. In embodiments, X^{15A} is F.

[0508] R^{72A} is independently oxo, halogen, $-CX^{72A}_3$, $-CHX^{72A}_2$, $-OCH_2X^{72A}$, $-OCHX^{72A}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, -NHC(=O)H, -NHC(O)-OH, -NHOH, $-OCX^{72A}_3$, $-OCHX^{72A}_2$, R^{73A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{73A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{73A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{73A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{73A}-substituted or unsubstituted aryl

(e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{73A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{72A} is halogen. In embodiments, X^{72A} is F.

[0509] R^{73A} is independently oxo, halogen, $-CX^{73A}_3$, $-CHX^{73A}_2$, $-OCH_2X^{73A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCX^{73A}_3$, $-OCHX^{73A}_2$, R^{74A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{74A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{74A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{74A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{74A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{74A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{73A} is halogen. In embodiments, X^{73A} is F.

[0510] In embodiments, R^{15B} is independently hydrogen, oxo, halogen, $-CX^{15B}_3$, $-CHX^{15B}_2$, $-OCH_2X^{15B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCX^{15B}_3$, $-OCHX^{15B}_2$, R^{72B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{72B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{72B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{72B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{72B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{72B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{15B} is halogen. In embodiments, X^{15B} is F.

[0511] R^{72B} is independently oxo, halogen, $-CX^{72B}_3$, $-CHX^{72B}_2$, $-OCH_2X^{72B}$, $-OCHX^{72B}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCX^{72B}_3$, $-OCHX^{72B}_2$, R^{73B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{73B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{73B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{73B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{73B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{73B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{72B} is halogen. In embodiments, X^{72B} is F.

[0512] R^{73B} is independently oxo, halogen, $-CX^{73B}_3$, $-CHX^{73B}_2$, $-OCH_2X^{73B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{73B}_3$, $-OCHX^{73B}_2$, R^{74B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{74B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{74B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{74B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{74B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{74B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{73B} is halogen. In embodiments, X^{73B} is F.

[0513] In embodiments, R^{15C} is independently hydrogen, oxo, halogen, $-CX^{15C}_3$, $-CHX^{15C}_2$, $-OCH_2X^{15C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{15C}_3$, $-OCHX^{15C}_2$, R^{72C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{72C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{72C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{72C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{72C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{72C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{15C} is halogen. In embodiments, X^{15C} is F.

[0514] R^{72C} is independently oxo, halogen, $-CX^{72C}_3$, $-CHX^{72C}_2$, $-OCH_2X^{72C}$, $-OCHX^{72C}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{72C}_3$, $-OCHX^{72C}_2$, R^{73C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{73C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{73C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{73C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{73C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{73C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{72C} is halogen. In embodiments, X^{72C} is F.

[0515] R^{73C} is independently oxo, halogen, $-CX^{73C}_3$, $-CHX^{73C}_2$, $-OCH_2X^{73C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, -

SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{73C}_3$, $-OCHX^{73C}_2$, R^{74C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{74C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{74C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{74C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{74C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{74C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{73C} is halogen. In embodiments, X^{73C} is F.

[0516] In embodiments, R^{15D} is independently hydrogen, oxo, halogen, $-CX^{15D}_3$, $-CHX^{15D}_2$, $-OCH_2X^{15D}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{15D}_3$, $-OCHX^{15D}_2$, R^{72D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{72D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{72D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{72D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{72D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{72D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{15D} is halogen. In embodiments, X^{15D} is F.

[0517] R^{72D} is independently oxo, halogen, $-CX^{72D}_3$, $-CHX^{72D}_2$, $-OCH_2X^{72D}$, $-OCHX^{72D}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{72D}_3$, $-OCHX^{72D}_2$, R^{73D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{73D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{73D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{73D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{73D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{73D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{72D} is halogen. In embodiments, X^{72D} is F.

[0518] R^{73D} is independently oxo, halogen, $-CX^{73D}_3$, $-CHX^{73D}_2$, $-OCH_2X^{73D}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{73D}_3$, $-OCHX^{73D}_2$, R^{74D}-substituted or unsubstituted

alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{74D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{74D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{74D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{74D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{74D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{73D} is halogen. In embodiments, X^{73D} is F.

[0519] 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, R^{16} is substituted or unsubstituted aryl. In embodiments, R^{16} is substituted or unsubstituted heteroaryl. In embodiments, R^{16} is substituted alkyl. In embodiments, R^{16} is substituted heteroalkyl. In embodiments, R^{16} is substituted cycloalkyl. In embodiments, R^{16} is substituted heterocycloalkyl. In embodiments, R^{16} is substituted aryl. In embodiments, R^{16} is substituted heteroaryl. In embodiments, R^{16} is an unsubstituted alkyl. In embodiments, R^{16} is an unsubstituted heteroalkyl. In embodiments, R^{16} is an unsubstituted cycloalkyl. In embodiments, R^{16} is an unsubstituted heterocycloalkyl. In embodiments, R^{16} is an unsubstituted aryl. In embodiments, R^{16} is an unsubstituted heteroaryl. In embodiments, R^{16} is an unsubstituted methyl. In embodiments, R^{16} is an unsubstituted ethyl. In embodiments, R^{16} is an unsubstituted propyl. In embodiments, R^{16} is an unsubstituted isopropyl. In embodiments, R^{16} is an unsubstituted butyl. In embodiments, R^{16} is an unsubstituted tert-butyl.

[0520] In embodiments, R^{16} is substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{16} is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{16} is substituted or unsubstituted cycloalkyl

(e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{16} is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{16} is substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{16} is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0521] In embodiments, R^{16} is substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{16} is substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{16} is substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{16} is substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{16} is substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{16} is substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{16} is an unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{16} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{16} is an unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{16} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{16} is an unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{16} is an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0522] In embodiments, R^{16A} is hydrogen. In embodiments, R^{16A} is $-CX_3$. In embodiments, R^{16A} is -CN. In embodiments, R^{16A} is -COOH. In embodiments, R^{16A} is $-CONH_2$. In embodiments, R^{16A} is $-CHX_2$. In embodiments, R^{16A} is $-CH_2X$. In embodiments, R^{16A} is an unsubstituted methyl. In embodiments, R^{16A} is an unsubstituted ethyl. In embodiments, R^{16A} is an unsubstituted propyl. In embodiments, R^{16A} is an unsubstituted isopropyl. In embodiments, R^{16A} is an unsubstituted butyl. In embodiments, R^{16A} is an unsubstituted tert-butyl.

[0523] In embodiments, R^{16B} is hydrogen. In embodiments, R^{16B} is $-CX_3$. In embodiments, R^{16B} is -CN. In embodiments, R^{16B} is -COOH. In embodiments, R^{16B} is $-CONH_2$. In embodiments, R^{16B} is $-CHX_2$. In embodiments, R^{16B} is $-CH_2X$. In embodiments, R^{16B} is an unsubstituted methyl. In embodiments, R^{16B} is an unsubstituted ethyl. In embodiments, R^{16B} is an unsubstituted propyl. In embodiments, R^{16B} is an unsubstituted isopropyl. In embodiments, R^{16B} is an unsubstituted butyl. In embodiments, R^{16B} is an unsubstituted tert-butyl.

[0524] In embodiments, R^{16C} is hydrogen. In embodiments, R^{16C} is $-CX_3$. In embodiments, R^{16C} is -CN. In embodiments, R^{16C} is -COOH. In embodiments, R^{16C} is $-CONH_2$. In

embodiments, R^{16C} is $-CHX_2$. In embodiments, R^{16C} is $-CH_2X$. In embodiments, R^{16C} is an unsubstituted methyl. In embodiments, R^{16C} is an unsubstituted ethyl. In embodiments, R^{16C} is an unsubstituted propyl. In embodiments, R^{16C} is an unsubstituted isopropyl. In embodiments, R^{16C} is an unsubstituted butyl. In embodiments, R^{16C} is an unsubstituted tert-butyl.

[0525] In embodiments, R^{16D} is hydrogen. In embodiments, R^{16D} is $-CX_3$. In embodiments, R^{16D} is -CN. In embodiments, R^{16D} is -COOH. In embodiments, R^{16D} is $-CONH_2$. In embodiments, R^{16D} is $-CHX_2$. In embodiments, R^{16D} is $-CH_2X$. In embodiments, R^{16D} is an unsubstituted methyl. In embodiments, R^{16D} is an unsubstituted ethyl. In embodiments, R^{16D} is an unsubstituted propyl. In embodiments, R^{16D} is an unsubstituted isopropyl. In embodiments, R^{16D} is an unsubstituted butyl. In embodiments, R^{16D} is an unsubstituted tert-butyl.

[0526] In embodiments, R^{16} is independently hydrogen, oxo, halogen, $-CX^{16}_3$, $-CHX^{16}_2$, $-OCH_2X^{16}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{16}_3$, $-OCHX^{16}_2$, R^{75}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{75}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{75}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{75}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{75}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{75}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{16} is halogen. In embodiments, X^{16} is F.

[0527] R^{75} is independently oxo, halogen, $-CX^{75}_3$, $-CHX^{75}_2$, $-OCH_2X^{75}$, $-OCHX^{75}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{75}_3$, $-OCHX^{75}_2$, R^{76}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{76}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{76}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{76}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{76}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{75} is halogen. In embodiments, X^{75} is F.

[0528] R^{76} is independently oxo, halogen, $-CX^{76}_3$, $-CHX^{76}_2$, $-OCH_2X^{76}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, -

SO_4H, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{76}_3$, $-OCHX^{76}_2$, R^{77}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{77}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{77}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{77}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{77}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{77}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{76} is halogen. In embodiments, X^{76} is F.

[0529] In embodiments, R^{16A} is independently hydrogen, oxo, halogen, $-CX^{16A}_3$, $-CHX^{16A}_2$, $-OCH_2X^{16A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{16A}_3$, $-OCHX^{16A}_2$, R^{75A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{75A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{75A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), 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.

[0530] R^{75A} is independently oxo, halogen, $-CX^{75A}_3$, $-CHX^{75A}_2$, $-OCH_2X^{75A}$, $-OCHX^{75A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{75A}_3$, $-OCHX^{75A}_2$, 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., 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.

[0531] R^{76A} is independently oxo, halogen, $-CX^{76A}_3$, $-CHX^{76A}_2$, $-OCH_2X^{76A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{76A}_3$, $-OCHX^{76A}_2$, 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 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.

[0532] In embodiments, R^{16B} is independently hydrogen, oxo, halogen, $-CX^{16B}_3$, $-CHX^{16B}_2$, $-OCH_2X^{16B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{16B}_3$, $-OCHX^{16B}_2$, R^{75B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0533] R^{75B} is independently oxo, halogen, $-CX^{75B}_3$, $-CHX^{75B}_2$, $-OCH_2X^{75B}$, $-OCHX^{75B}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{75B}_3$, $-OCHX^{75B}_2$, R^{76B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0534] R^{76B} is independently oxo, halogen, $-CX^{76B}_3$, $-CHX^{76B}_2$, $-OCH_2X^{76B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{76B}_3$, $-OCHX^{76B}_2$, R^{77B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0535] In embodiments, R^{16C} is independently hydrogen, oxo, halogen, $-CX^{16C}_3$, $-CHX^{16C}_2$, $-OCH_2X^{16C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{16C}_3$, $-OCHX^{16C}_2$, R^{75C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0536] R^{75C} is independently oxo, halogen, $-CX^{75C}_3$, $-CHX^{75C}_2$, $-OCH_2X^{75C}$, $-OCHX^{75C}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{75C}_3$, $-OCHX^{75C}_2$, R^{76C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0537] R^{76C} is independently oxo, halogen, $-CX^{76C}_3$, $-CHX^{76C}_2$, $-OCH_2X^{76C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{76C}_3$, $-OCHX^{76C}_2$, R^{77C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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.,

C_6-C_{10}, C_{10}, 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.

[0538] In embodiments, R^{16D} is independently hydrogen, oxo, halogen, $-CX^{16D}_3$, $-CHX^{16D}_2$, $-OCH_2X^{16D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCX^{16D}_3$, $-OCHX^{16D}_2$, R^{75D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0539] R^{75D} is independently oxo, halogen, $-CX^{75D}_3$, $-CHX^{75D}_2$, $-OCH_2X^{75D}$, $-OCHX^{75D}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCX^{75D}_3$, $-OCHX^{75D}_2$, R^{76D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{76D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0540] R^{76D} is independently oxo, halogen, $-CX^{76D}_3$, $-CHX^{76D}_2$, $-OCH_2X^{76D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCX^{76D}_3$, $-OCHX^{76D}_2$, R^{77D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{77D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{77D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0541] In embodiments, R^{17} is hydrogen. In embodiments, R^{17} is halogen. In embodiments, R^{17} is CX^{17}_3. In embodiments, R^{17} is $-CHX^{17}_2$. In embodiments, R^{17} is $-CH_2X^{17}$. In embodiments, R^{17} is –CN. In embodiments, R^{17} is $-SO_{n17}R^{17D}$. In embodiments, R^{17} is $-SO_{v17}NR^{17A}R^{17B}$. In embodiments, R^{17} is $-NHNR^{17A}R^{17B}$. In embodiments, R^{17} is $-ONR^{17A}R^{17B}$. In embodiments, R^{17} is $-NHC{=}(O)NHNR^{17A}R^{17B}$. In embodiments, R^{17} is $-NHC(O)NR^{17A}R^{17B}$. In embodiments, R^{17} is $-N(O)_{m17}$. In embodiments, R^{17} is $-NR^{17A}R^{17B}$. In embodiments, R^{17} is $-C(O)R^{17C}$. In embodiments, R^{17} is $-C(O)-OR^{17C}$. In embodiments, R^{17} is $-C(O)NR^{17A}R^{17B}$. In embodiments, R^{17} is $-OR^{17D}$. In embodiments, R^{17} is $-NR^{17A}SO_2R^{17D}$. In embodiments, R^{17} is $-NR^{17A}C(O)R^{17C}$. In embodiments, R^{17} is $-NR^{17A}C(O)OR^{17C}$. In embodiments, R^{17} is $-NR^{17A}OR^{17C}$. In embodiments, R^{17} is $-OCX^{17}_3$. In embodiments, R^{17} is $-OCHX^{17}_2$. In embodiments, R^{17} is substituted or unsubstituted alkyl. In embodiments, R^{17} is substituted or unsubstituted heteroalkyl. In embodiments, R^{17} is substituted or unsubstituted cycloalkyl. In embodiments, R^{17} is substituted or unsubstituted heterocycloalkyl. In embodiments, R^{17} is substituted or unsubstituted aryl. In embodiments, R^{17} is substituted or unsubstituted heteroaryl. In embodiments, R^{17} is substituted alkyl. In embodiments, R^{17} is substituted heteroalkyl. In embodiments, R^{17} is substituted cycloalkyl. In embodiments, R^{17} is substituted heterocycloalkyl. In embodiments, R^{17} is substituted aryl. In embodiments, R^{17} is substituted heteroaryl. In embodiments, R^{17} is an unsubstituted alkyl. In embodiments, R^{17} is an unsubstituted heteroalkyl. In embodiments, R^{17} is an unsubstituted cycloalkyl. In embodiments, R^{17} is an unsubstituted heterocycloalkyl. In embodiments, R^{17} is an unsubstituted aryl. In embodiments, R^{17} is an unsubstituted heteroaryl. In embodiments, R^{17} is an unsubstituted methyl. In embodiments, R^{17} is an unsubstituted ethyl. In embodiments, R^{17} is an unsubstituted propyl. In embodiments, R^{17} is an unsubstituted isopropyl. In embodiments, R^{17} is an unsubstituted butyl. In embodiments, R^{17} is an unsubstituted tert-butyl.

[0542] In embodiments, R^{17A} is hydrogen. In embodiments, R^{17A} is $-CX_3$. In embodiments, R^{17A} is -CN. In embodiments, R^{17A} is -COOH. In embodiments, R^{17A} is $-CONH_2$. In embodiments, R^{17A} is $-CHX_2$. In embodiments, R^{17A} is $-CH_2X$. In embodiments, R^{17A} is an unsubstituted methyl. In embodiments, R^{17A} is an unsubstituted ethyl. In embodiments, R^{17A} is an unsubstituted propyl. In embodiments, R^{17A} is an unsubstituted isopropyl. In embodiments, R^{17A} is an unsubstituted butyl. In embodiments, R^{17A} is an unsubstituted tert-butyl.

[0543] In embodiments, R^{17} is substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{17} is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{17} is substituted or unsubstituted cycloalkyl

(e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{17} is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{17} is substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{17} is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0544] In embodiments, R^{17} is substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{17} is substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{17} is substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{17} is substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{17} is substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{17} is substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{17} is an unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{17} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{17} is an unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{17} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{17} is an unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{17} is an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0545] In embodiments, R^{17B} is hydrogen. In embodiments, R^{17B} is $-CX_3$. In embodiments, R^{17B} is -CN. In embodiments, R^{17B} is -COOH. In embodiments, R^{17B} is $-CONH_2$. In embodiments, R^{17B} is $-CHX_2$. In embodiments, R^{17B} is $-CH_2X$. In embodiments, R^{17B} is an unsubstituted methyl. In embodiments, R^{17B} is an unsubstituted ethyl. In embodiments, R^{17B} is an unsubstituted propyl. In embodiments, R^{17B} is an unsubstituted isopropyl. In embodiments, R^{17B} is an unsubstituted butyl. In embodiments, R^{17B} is an unsubstituted tert-butyl.

[0546] In embodiments, R^{17C} is hydrogen. In embodiments, R^{17C} is $-CX_3$. In embodiments, R^{17C} is -CN. In embodiments, R^{17C} is -COOH. In embodiments, R^{17C} is $-CONH_2$. In embodiments, R^{17C} is $-CHX_2$. In embodiments, R^{17C} is $-CH_2X$. In embodiments, R^{17C} is an unsubstituted methyl. In embodiments, R^{17C} is an unsubstituted ethyl. In embodiments, R^{17C} is an unsubstituted propyl. In embodiments, R^{17C} is an unsubstituted isopropyl. In embodiments, R^{17C} is an unsubstituted butyl. In embodiments, R^{17C} is an unsubstituted tert-butyl.

[0547] In embodiments, R^{17D} is hydrogen. In embodiments, R^{17D} is $-CX_3$. In embodiments, R^{17D} is -CN. In embodiments, R^{17D} is -COOH. In embodiments, R^{17D} is $-CONH_2$. In

embodiments, R^{17D} is $-CHX_2$. In embodiments, R^{17D} is $-CH_2X$. In embodiments, R^{17D} is an unsubstituted methyl. In embodiments, R^{17D} is an unsubstituted ethyl. In embodiments, R^{17D} is an unsubstituted propyl. In embodiments, R^{17D} is an unsubstituted isopropyl. In embodiments, R^{17D} is an unsubstituted butyl. In embodiments, R^{17D} is an unsubstituted tert-butyl.

[0548] In embodiments, R^{17} is independently hydrogen, oxo, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-OCH_2X^{17}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{17}_3$, $-OCHX^{17}_2$, R^{78}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{78}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{78}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{78}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{78}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{78}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{17} is halogen. In embodiments, X^{17} is F.

[0549] R^{78} is independently oxo, halogen, $-CX^{78}_3$, $-CHX^{78}_2$, $-OCH_2X^{78}$, $-OCHX^{78}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{78}_3$, $-OCHX^{78}_2$, R^{79}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{79}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{79}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{79}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{78} is halogen. In embodiments, X^{78} is F.

[0550] R^{79} is independently oxo, halogen, $-CX^{79}_3$, $-CHX^{79}_2$, $-OCH_2X^{79}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{79}_3$, $-OCHX^{79}_2$, R^{80}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{80}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{80}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80}-substituted or unsubstituted aryl (e.g., C_6-

C_{10}, C_{10}, or phenyl), or R^{80}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79} is halogen. In embodiments, X^{79} is F.

[0551] In embodiments, R^{17A} is independently hydrogen, oxo, halogen, $-CX^{17A}_3$, $-CHX^{17A}_2$, $-OCH_2X^{17A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -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 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.

[0552] R^{78A} is independently oxo, halogen, $-CX^{78A}_3$, $-CHX^{78A}_2$, $-OCH_2X^{78A}$, $-OCHX^{78A}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{78A}_3$, $-OCHX^{78A}_2$, R^{79A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0553] R^{79A} is independently oxo, halogen, $-CX^{79A}_3$, $-CHX^{79A}_2$, $-OCH_2X^{79A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{79A}_3$, $-OCHX^{79A}_2$, R^{80A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0554] In embodiments, R^{17B} is independently hydrogen, oxo, halogen, $-CX^{17B}_3$, $-CHX^{17B}_2$, $-OCH_2X^{17B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{17B}_3$, $-OCHX^{17B}_2$, R^{78B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0555] R^{78B} is independently oxo, halogen, $-CX^{78B}_3$, $-CHX^{78B}_2$, $-OCH_2X^{78B}$, $-OCHX^{78B}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{78B}_3$, $-OCHX^{78B}_2$, R^{79B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0556] R^{79B} is independently oxo, halogen, $-CX^{79B}_3$, $-CHX^{79B}_2$, $-OCH_2X^{79B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, $-NHC{=}(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{79B}_3$, $-OCHX^{79B}_2$, R^{80B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0557] In embodiments, R^{17C} is independently hydrogen, oxo, halogen, $-CX^{17C}_3$, $-CHX^{17C}_2$, $-OCH_2X^{17C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, -

SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{17C}_3$, $-OCHX^{17C}_2$, R^{78C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), R^{78C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{78C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, 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.

[0558] R^{78C} is independently oxo, halogen, $-CX^{78C}_3$, $-CHX^{78C}_2$, $-OCH_2X^{78C}$, $-OCHX^{78C}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{78C}_3$, $-OCHX^{78C}_2$, R^{79C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), R^{79C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, 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.

[0559] R^{79C} is independently oxo, halogen, $-CX^{79C}_3$, $-CHX^{79C}_2$, $-OCH_2X^{79C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{79C}_3$, $-OCHX^{79C}_2$, R^{80C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), R^{80C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, 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.

[0560] In embodiments, R^{17D} is independently hydrogen, oxo, halogen, $-CX^{17D}_3$, $-CHX^{17D}_2$, $-OCH_2X^{17D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, -NHC(O)-OH, -NHOH, $-OCX^{17D}_3$, $-OCHX^{17D}_2$, R^{78D}-substituted or unsubstituted

alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{78D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{78D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), 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.

[0561] R^{78D} is independently oxo, halogen, $-CX^{78D}_3$, $-CHX^{78D}_2$, $-OCH_2X^{78D}$, $-OCHX^{78D}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -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., 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.

[0562] R^{79D} is independently oxo, halogen, $-CX^{79D}_3$, $-CHX^{79D}_2$, $-OCH_2X^{79D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -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 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.

[0563] In embodiments, R^{18} is hydrogen. In embodiments, R^{18} is halogen. In embodiments, R^{18} is CX^{18}_3. In embodiments, R^{18} is $-CHX^{18}_2$. In embodiments, R^{18} is $-CH_2X^{18}$. In embodiments, R^{18} is –CN. In embodiments, R^{18} is $-SO_{n18}R^{18D}$. In embodiments, R^{18} is $-SO_{v18}NR^{18A}R^{18B}$. In embodiments, R^{18} is $-NHNR^{18A}R^{18B}$. In embodiments, R^{18} is $-ONR^{18A}R^{18B}$. In embodiments, R^{18} is $-NHC{=}(O)NHNR^{18A}R^{18B}$. In embodiments, R^{18} is $-NHC(O)NR^{18A}R^{18B}$. In embodiments, R^{18} is $-N(O)_{m18}$. In embodiments, R^{18} is $-NR^{18A}R^{18B}$. In

embodiments, R^{18} is $-C(O)R^{18C}$. In embodiments, R^{18} is $-C(O)-OR^{18C}$. In embodiments, R^{18} is $-C(O)NR^{18A}R^{18B}$. In embodiments, R^{18} is $-OR^{18D}$. In embodiments, R^{18} is $-NR^{18A}SO_2R^{18D}$. In embodiments, R^{18} is $-NR^{18A}C(O)R^{18C}$. In embodiments, R^{18} is $-NR^{18A}C(O)OR^{18C}$. In embodiments, R^{18} is $-NR^{18A}OR^{18C}$. In embodiments, R^{18} is $-OCX^{18}_3$. In embodiments, R^{18} is $-OCHX^{18}_2$. In embodiments, R^{18} is substituted or unsubstituted alkyl. In embodiments, R^{18} is substituted or unsubstituted heteroalkyl. In embodiments, R^{18} is substituted or unsubstituted cycloalkyl. In embodiments, R^{18} is substituted or unsubstituted heterocycloalkyl. In embodiments, R^{18} is substituted or unsubstituted aryl. In embodiments, R^{18} is substituted or unsubstituted heteroaryl. In embodiments, R^{18} is substituted alkyl. In embodiments, R^{18} is substituted heteroalkyl. In embodiments, R^{18} is substituted cycloalkyl. In embodiments, R^{18} is substituted heterocycloalkyl. In embodiments, R^{18} is substituted aryl. In embodiments, R^{18} is substituted heteroaryl. In embodiments, R^{18} is an unsubstituted alkyl. In embodiments, R^{18} is an unsubstituted heteroalkyl. In embodiments, R^{18} is an unsubstituted cycloalkyl. In embodiments, R^{18} is an unsubstituted heterocycloalkyl. In embodiments, R^{18} is an unsubstituted aryl. In embodiments, R^{18} is an unsubstituted heteroaryl. In embodiments, R^{18} is an unsubstituted methyl. In embodiments, R^{18} is an unsubstituted ethyl. In embodiments, R^{18} is an unsubstituted propyl. In embodiments, R^{18} is an unsubstituted isopropyl. In embodiments, R^{18} is an unsubstituted butyl. In embodiments, R^{18} is an unsubstituted tert-butyl.

[0564] In embodiments, R^{17} is substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{17} is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{17} is substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{17} is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{17} is substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{17} is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0565] In embodiments, R^{17} is substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{17} is substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{17} is substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{17} is substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{17} is substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{17} is substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{17} is an unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In

embodiments, R^{17} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{17} is an unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{17} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{17} is an unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{17} is an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0566] In embodiments, R^{18A} is hydrogen. In embodiments, R^{18A} is $-CX_3$. In embodiments, R^{18A} is -CN. In embodiments, R^{18A} is -COOH. In embodiments, R^{18A} is $-CONH_2$. In embodiments, R^{18A} is $-CHX_2$. In embodiments, R^{18A} is $-CH_2X$. In embodiments, R^{18A} is an unsubstituted methyl. In embodiments, R^{18A} is an unsubstituted ethyl. In embodiments, R^{18A} is an unsubstituted propyl. In embodiments, R^{18A} is an unsubstituted isopropyl. In embodiments, R^{18A} is an unsubstituted butyl. In embodiments, R^{18A} is an unsubstituted tert-butyl.

[0567] In embodiments, R^{18B} is hydrogen. In embodiments, R^{18B} is $-CX_3$. In embodiments, R^{18B} is -CN. In embodiments, R^{18B} is -COOH. In embodiments, R^{18B} is $-CONH_2$. In embodiments, R^{18B} is $-CHX_2$. In embodiments, R^{18B} is $-CH_2X$. In embodiments, R^{18B} is an unsubstituted methyl. In embodiments, R^{18B} is an unsubstituted ethyl. In embodiments, R^{18B} is an unsubstituted propyl. In embodiments, R^{18B} is an unsubstituted isopropyl. In embodiments, R^{18B} is an unsubstituted butyl. In embodiments, R^{18B} is an unsubstituted tert-butyl.

[0568] In embodiments, R^{18C} is hydrogen. In embodiments, R^{18C} is $-CX_3$. In embodiments, R^{18C} is -CN. In embodiments, R^{18C} is -COOH. In embodiments, R^{18C} is $-CONH_2$. In embodiments, R^{18C} is $-CHX_2$. In embodiments, R^{18C} is $-CH_2X$. In embodiments, R^{18C} is an unsubstituted methyl. In embodiments, R^{18C} is an unsubstituted ethyl. In embodiments, R^{18C} is an unsubstituted propyl. In embodiments, R^{18C} is an unsubstituted isopropyl. In embodiments, R^{18C} is an unsubstituted butyl. In embodiments, R^{18C} is an unsubstituted tert-butyl.

[0569] In embodiments, R^{18D} is hydrogen. In embodiments, R^{18D} is $-CX_3$. In embodiments, R^{18D} is -CN. In embodiments, R^{18D} is -COOH. In embodiments, R^{18D} is $-CONH_2$. In embodiments, R^{18D} is $-CHX_2$. In embodiments, R^{18D} is $-CH_2X$. In embodiments, R^{18D} is an unsubstituted methyl. In embodiments, R^{18D} is an unsubstituted ethyl. In embodiments, R^{18D} is an unsubstituted propyl. In embodiments, R^{18D} is an unsubstituted isopropyl. In embodiments, R^{18D} is an unsubstituted butyl. In embodiments, R^{18D} is an unsubstituted tert-butyl.

[0570] In embodiments, R^{18} is independently hydrogen, oxo, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-OCH_2X^{18}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, -

SO_4H, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{18}{}_3$, $-OCHX^{18}{}_2$, R^{81}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{81}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{81}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{81}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{81}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{81}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18} is halogen. In embodiments, X^{18} is F.

[0571] R^{81} is independently oxo, halogen, $-CX^{81}{}_3$, $-CHX^{81}{}_2$, $-OCH_2X^{81}$, $-OCHX^{81}{}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{81}{}_3$, $-OCHX^{81}{}_2$, R^{82}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{82}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{82}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{82}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{82}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81} is halogen. In embodiments, X^{81} is F.

[0572] R^{82} is independently oxo, halogen, $-CX^{82}{}_3$, $-CHX^{82}{}_2$, $-OCH_2X^{82}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{82}{}_3$, $-OCHX^{82}{}_2$, R^{83}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{83}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{83}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{83}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{83}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{83}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{82} is halogen. In embodiments, X^{82} is F.

[0573] In embodiments, R^{18A} is independently hydrogen, oxo, halogen, $-CX^{18A}{}_3$, $-CHX^{18A}{}_2$, $-OCH_2X^{18A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{18A}{}_3$, $-OCHX^{18A}{}_2$, R^{81A}-substituted or unsubstituted

alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0574] R^{81A} is independently oxo, halogen, $-CX^{81A}_3$, $-CHX^{81A}_2$, $-OCH_2X^{81A}$, $-OCHX^{81A}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{81A}_3$, $-OCHX^{81A}_2$, R^{82A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), R^{82A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, 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.

[0575] R^{82A} is independently oxo, halogen, $-CX^{82A}_3$, $-CHX^{82A}_2$, $-OCH_2X^{82A}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{82A}_3$, $-OCHX^{82A}_2$, R^{83A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0576] In embodiments, R^{18B} is independently hydrogen, oxo, halogen, $-CX^{18B}_3$, $-CHX^{18B}_2$, $-OCH_2X^{18B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{18B}_3$, $-OCHX^{18B}_2$, R^{81B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0577] R^{81B} is independently oxo, halogen, $-CX^{81B}_3$, $-CHX^{81B}_2$, $-OCH_2X^{81B}$, $-OCHX^{81B}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{81B}_3$, $-OCHX^{81B}_2$, R^{82B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0578] R^{82B} is independently oxo, halogen, $-CX^{82B}_3$, $-CHX^{82B}_2$, $-OCH_2X^{82B}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{82B}_3$, $-OCHX^{82B}_2$, R^{83B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0579] In embodiments, R^{18C} is independently hydrogen, oxo, halogen, $-CX^{18C}_3$, $-CHX^{18C}_2$, $-OCH_2X^{18C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{18C}_3$, $-OCHX^{18C}_2$, R^{81C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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.,

C_6-C_{10}, C_{10}, 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.

[0580] R^{81C} is independently oxo, halogen, $-CX^{81C}_3$, $-CHX^{81C}_2$, $-OCH_2X^{81C}$, $-OCHX^{81C}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{81C}_3$, $-OCHX^{81C}_2$, R^{82C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0581] R^{82C} is independently oxo, halogen, $-CX^{82C}_3$, $-CHX^{82C}_2$, $-OCH_2X^{82C}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{82C}_3$, $-OCHX^{82C}_2$, R^{83C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, 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.

[0582] In embodiments, R^{18D} is independently hydrogen, oxo, halogen, $-CX^{18D}_3$, $-CHX^{18D}_2$, $-OCH_2X^{18D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC{=}(O)NHNH_2$, $-NHC{=}(O)NH_2$, $-NHSO_2H$, -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 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.

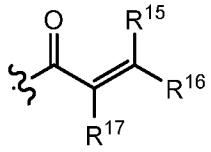
[0583] R^{81D} is independently oxo, halogen, $-CX^{81D}_3$, $-CHX^{81D}_2$, $-OCH_2X^{81D}$, $-OCHX^{81D}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{81D}_3$, $-OCHX^{81D}_2$, R^{82D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, or phenyl), or R^{82D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81D} is halogen. In embodiments, X^{81D} is F.

[0584] R^{82D} is independently oxo, halogen, $-CX^{82D}_3$, $-CHX^{82D}_2$, $-OCH_2X^{82D}$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCX^{82D}_3$, $-OCHX^{82D}_2$, R^{83D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), 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., C_3-C_8, C_3-C_6, or C_5-C_6), 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., C_6-C_{10}, C_{10}, or phenyl), or R^{83D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{82D} is halogen. In embodiments, X^{82D} is F.

[0585] R^{74}, R^{77}, R^{80}, R^{83}, R^{74A}, R^{77A}, R^{80A}, R^{83A}, R^{74B}, R^{77B}, R^{80B}, R^{83B}, R^{74C}, R^{77C}, R^{80C}, R^{83C}, R^{74D}, R^{77D}, R^{80D}, and R^{83D} are independently hydrogen, oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. In embodiments, R^{74}, R^{77}, R^{80}, R^{83}, R^{74A}, R^{77A}, R^{80A}, R^{83A}, R^{74B}, R^{77B}, R^{80B}, R^{83B}, R^{74C}, R^{77C}, R^{80C}, R^{83C}, R^{74D}, R^{77D}, R^{80D}, and R^{83D} are independently oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. In embodiments, R^{74}, R^{77}, R^{80}, R^{83}, R^{74A}, R^{77A}, R^{80A}, R^{83A}, R^{74B}, R^{77B}, R^{80B}, R^{83B}, R^{74C}, R^{77C}, R^{80C},

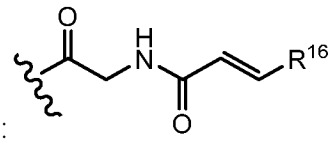
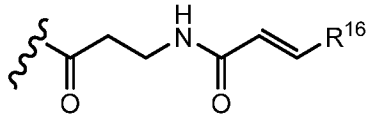
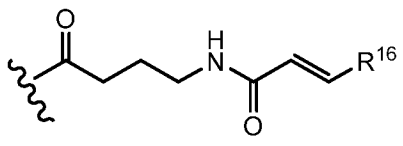
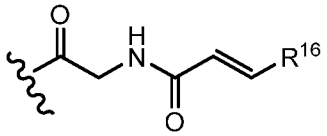
R^{83C}, R^{74D}, R^{77D}, R^{80D}, and R^{83D} are independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-CHF_2$, $-CHCl_2$, $-CHBr_2$, $-CHI_2$, $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, unsubstituted C_1-C_8 alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

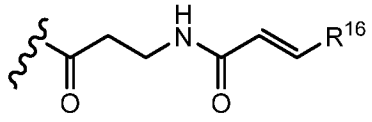
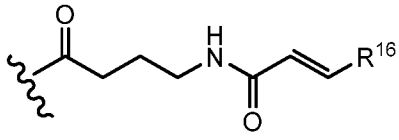
[0586] In embodiments, E is:



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[0587] In embodiments, R^{15}, R^{16}, R^{17}, and R^{18} are hydrogen. In embodiments, R^{15} is hydrogen; R^{16} is hydrogen, $-CH_3$, or $-CH_2NR^{16A}R^{16B}$; R^{17} is hydrogen; and R^{16A} and R^{16B} are independently hydrogen or unsubstituted alkyl. In embodiments, R^{16A} and R^{16B} are independently unsubstituted methyl. In embodiments, R^{15} is hydrogen; R^{16} is hydrogen; R^{17} is hydrogen, $-CH_3$, or $-CH_2NR^{17A}R^{17B}$; and R^{17A} and R^{17B} are independently hydrogen or unsubstituted alkyl. In embodiments, R^{17A} and R^{17B} are independently unsubstituted methyl. In embodiments, R^{15} is hydrogen, $-CH_3$, or $-CH_2NR^{15A}R^{15B}$; R^{16} is hydrogen; R^{17} is hydrogen; and R^{15A} and R^{15B} are independently hydrogen or unsubstituted alkyl. In embodiments, R^{15A} and R^{15B} are independently unsubstituted methyl.

[0588] In embodiments, $-L^1-L^2$-E is:  . In embodiments, $-L^1-L^2$-E is:  . In embodiments, $-L^1-L^2$-E is:  . In embodiments, -E is:  . In embodiments, --E is:


. In embodiments, -E is: 
. In embodiments R^{16} is $–CH_2N(CH_3)_2$. In embodiments R^{16} is $– CH_2CH_2N(CH_3)_2$.

[0589] In embodiments, X is –F. In embodiments, X is –Cl. In embodiments, X is –Br. In embodiments, X is –I. In embodiments, X^1 is –F. In embodiments, X^1 is –Cl. In embodiments, X^1 is –Br. In embodiments, X^1 is –I. In embodiments, X^2 is –F. In embodiments, X^2 is –Cl. In embodiments, X^2 is –Br. In embodiments, X^2 is –I. In embodiments, X^3 is –F. In embodiments, X^3 is –Cl. In embodiments, X^3 is –Br. In embodiments, X^3 is –I. In embodiments, X^4 is –F. In embodiments, X^4 is –Cl. In embodiments, X^4 is –Br. In embodiments, X^4 is –I. In embodiments, X^6 is –F. In embodiments, X^6 is –Cl. In embodiments, X^6 is –Br. In embodiments, X^6 is –I. In embodiments, X^7 is –F. In embodiments, X^7 is –Cl. In embodiments, X^7 is –Br. In embodiments, X^7 is –I. In embodiments, X^8 is –F. In embodiments, X^8 is –Cl. In embodiments, X^8 is –Br. In embodiments, X^8 is –I. In embodiments, X^9 is –F. In embodiments, X^9 is –Cl. In embodiments, X^9 is –Br. In embodiments, X^9 is –I. $X^{4.1}$ is –F, -Cl, -Br, or –I. $X^{4.2}$ is –F, -Cl, -Br, or –I. $X^{4.3}$ is –F, -Cl, -Br, or –I. $X^{4.4}$ is –F, -Cl, -Br, or –I. $X^{4.5}$ is –F, -Cl, -Br, or –I. In embodiments, $X^{4.1}$ is –F. In embodiments, $X^{4.1}$ is –Cl. In embodiments, $X^{4.1}$ is –Br. In embodiments, $X^{4.1}$ is –I. In embodiments, $X^{4.2}$ is –F. In embodiments, $X^{4.2}$ is –Cl. In embodiments, $X^{4.2}$ is –Br. In embodiments, $X^{4.2}$ is –I. In embodiments, $X^{4.3}$ is –F. In embodiments, $X^{4.3}$ is –Cl. In embodiments, $X^{4.3}$ is –Br. In embodiments, $X^{4.3}$ is –I. In embodiments, $X^{4.4}$ is –F. In embodiments, $X^{4.4}$ is –Cl. In embodiments, $X^{4.4}$ is –Br. In embodiments, $X^{4.4}$ is –I. In embodiments, $X^{4.5}$ is –F. In embodiments, $X^{4.5}$ is –Cl. In embodiments, $X^{4.5}$ is –Br. In embodiments, $X^{4.5}$ is –I.

[0590] In embodiments, n1 is 0. In embodiments, n1 is 1. In embodiments, n1 is 2. In embodiments, n1 is 3. In embodiments, n1 is 4. In embodiments, n2 is 0. In embodiments, n2 is 1. In embodiments, n2 is 2. In embodiments, n2 is 3. In embodiments, n2 is 4. In embodiments, n3 is 0. In embodiments, n3 is 1. In embodiments, n3 is 2. In embodiments, n3 is 3. In embodiments, n3 is 4. In embodiments, n4 is 0. In embodiments, n4 is 1. In embodiments, n4 is 2. In embodiments, n4 is 3. In embodiments, n4 is 4. In embodiments, n6 is 0. In embodiments, n6 is 1. In embodiments, n6 is 2. In embodiments, n6 is 3. In embodiments, n6 is 4. In embodiments, n7 is 0. In embodiments, n7 is 1. In embodiments, n7 is 2. In embodiments, n7 is 3. In embodiments, n7 is 4. In embodiments, n8 is 0. In embodiments, n8 is 1. In embodiments, n8 is 2. In embodiments, n8 is 3. In embodiments, n8 is

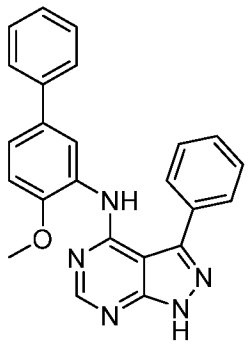
4. In embodiments, n9 is 0. In embodiments, n9 is 1. In embodiments, n9 is 2. In embodiments, n9 is 3. In embodiments, n9 is 4.

[0591] In embodiments, m1 is 1. In embodiments, m1 is 2. In embodiments, m2 is 1. In embodiments, m2 is 2. In embodiments, m3 is 1. In embodiments, m3 is 2. In embodiments, m4 is 1. In embodiments, m4 is 2. In embodiments, m6 is 1. In embodiments, m6 is 2. In embodiments, m7 is 1. In embodiments, m7 is 2. In embodiments, m8 is 1. In embodiments, m8 is 2. In embodiments, m9 is 1. In embodiments, m9 is 2.

[0592] In embodiments, v3 is 1. In embodiments, v3 is 2. In embodiments, v4 is 1. In embodiments, v4 is 2. In embodiments, v6 is 1. In embodiments, v6 is 2. In embodiments, v7 is 1. In embodiments, v7 is 2. In embodiments, v8 is 1. In embodiments, v8 is 2. In embodiments, v9 is 1. In embodiments, v9 is 2.

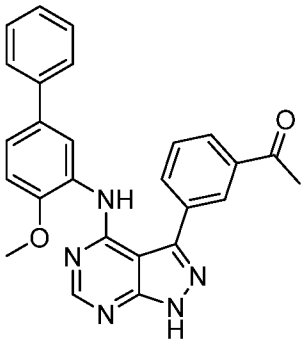
[0593] In embodiments, z3 is 0. In embodiments, z3 is 1. In embodiments, z3 is 2. In embodiments, z3 is 3. In embodiments, z3 is 4. In embodiments z4 is an integer from 0 to 2. In embodiments, z4 is 0 or 1. In embodiments, z4 is 0. In embodiments, z4 is 1. In embodiments, z4 is 2. In embodiments, z4 is 3. In embodiments, z4 is 4. In embodiments, z4 is 5. In embodiments, z20 is 0. In embodiments, z20 is 1. In embodiments, z20 is 2. In embodiments, z20 is 3. In embodiments, z20 is 4. In embodiments, z20 is 5.

[0594] In embodiments, the compound name may be written with a dash (e.g., 8-091) or without a dash (e.g., 8091) and it is understood both of these labels refer to the same compound.

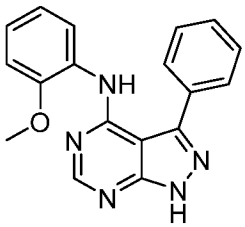


184

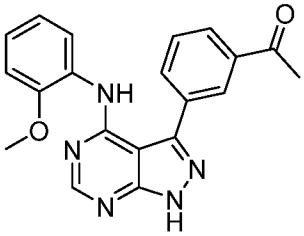
[0595] In embodiments, the compound has the formula:



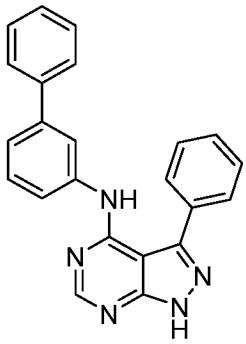
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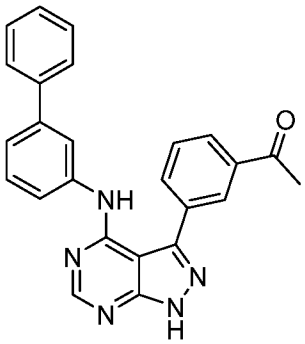
187A



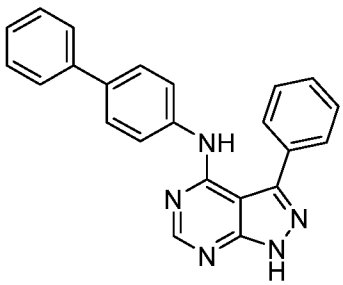
187B



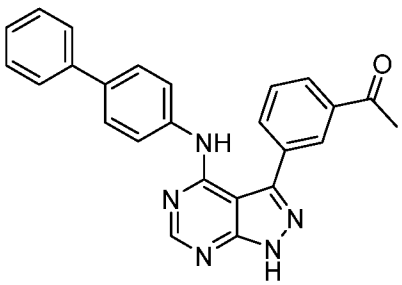
186A



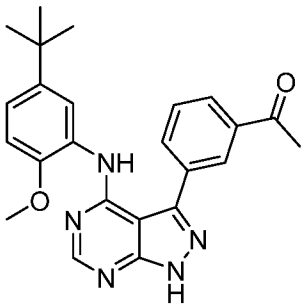
186B



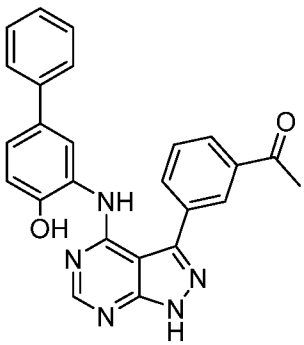
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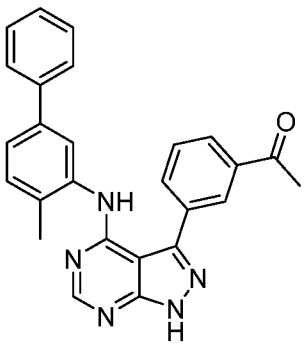
188B



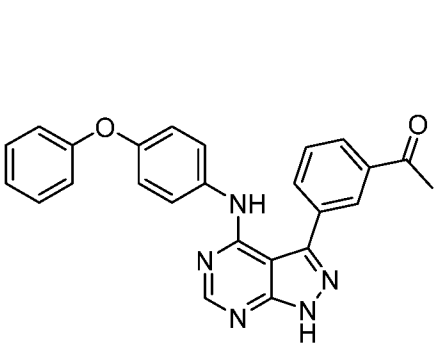
190D



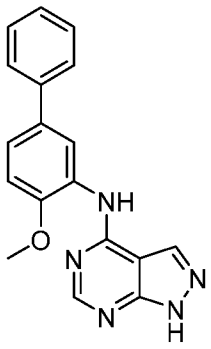
191A



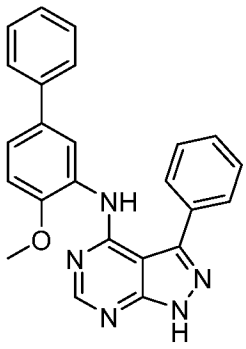
5-001A



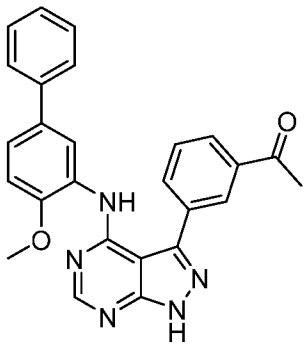
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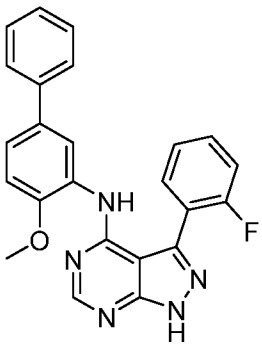
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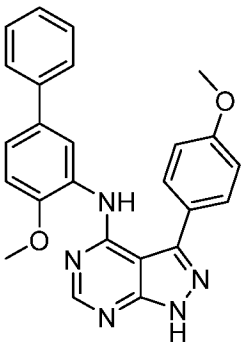
184 ,



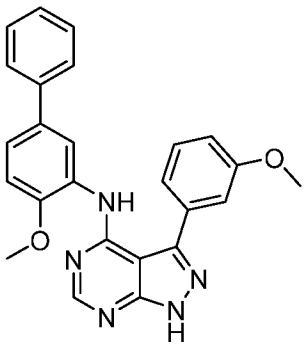
185 ,



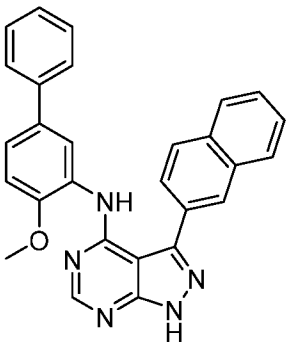
189A ,



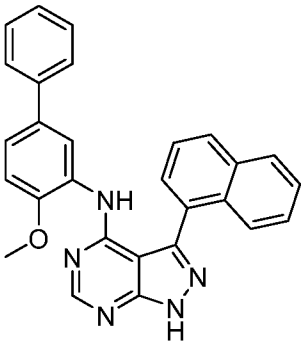
189B ,



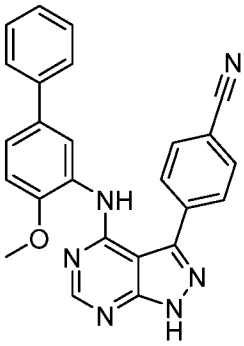
190A ,



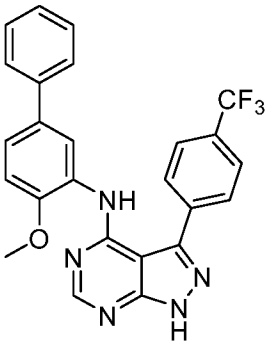
190C ,



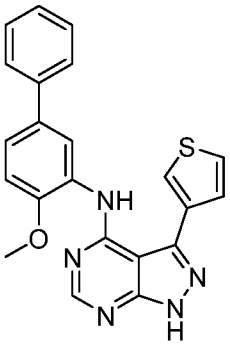
191B ,



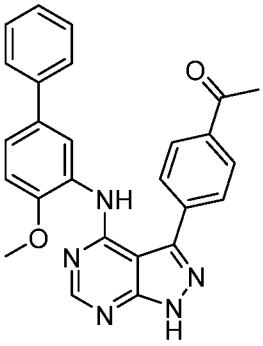
191D ,



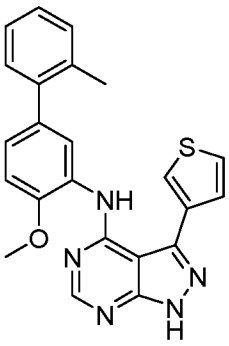
191E ,



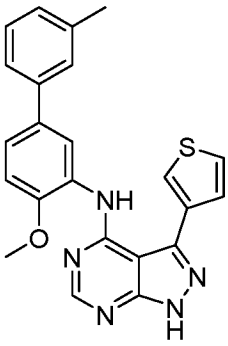
191F ,



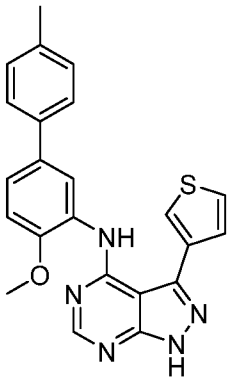
191H ,



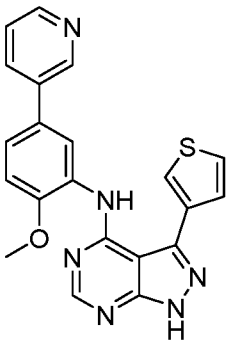
39A ,



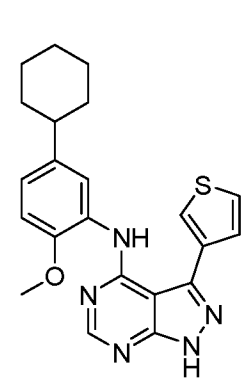
39B ,

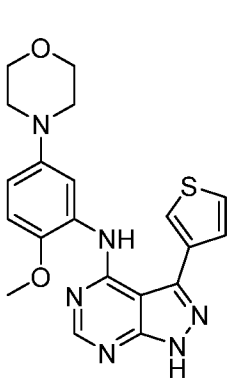


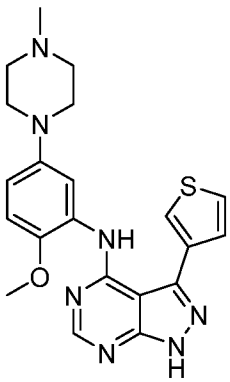
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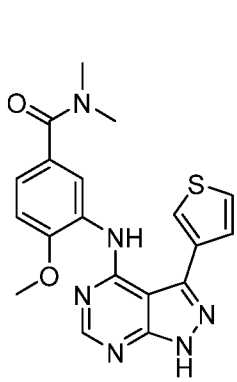


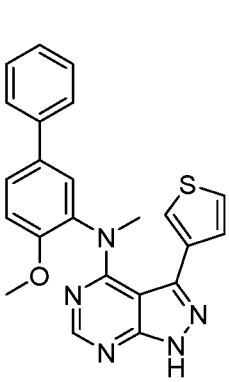
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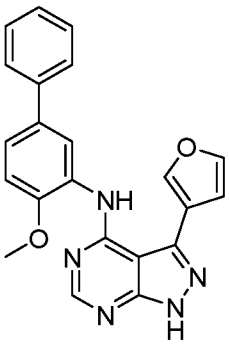

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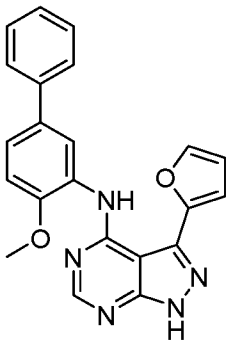

41A

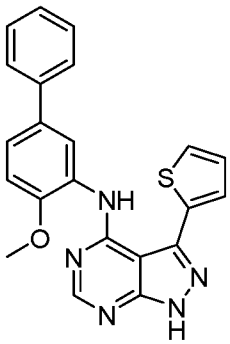

41B

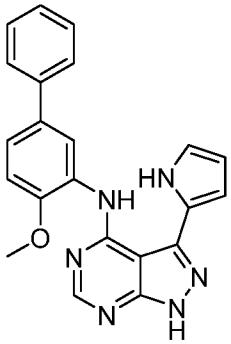

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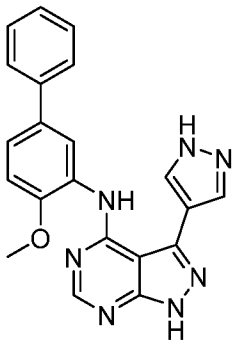

43

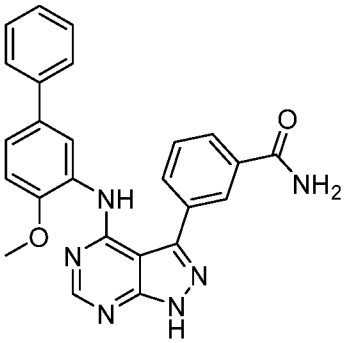

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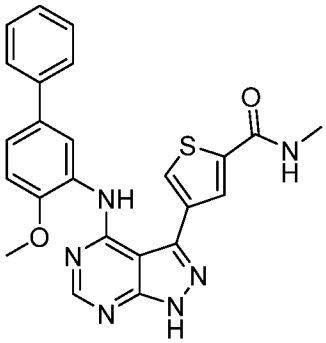

45A

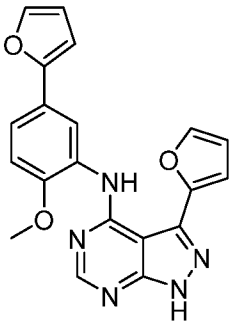

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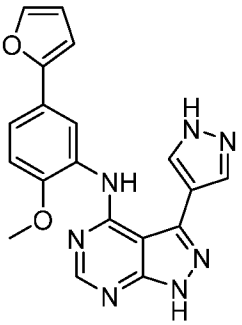

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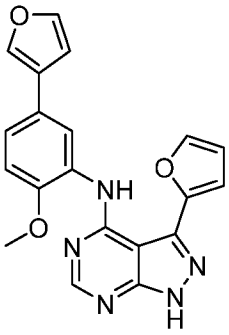

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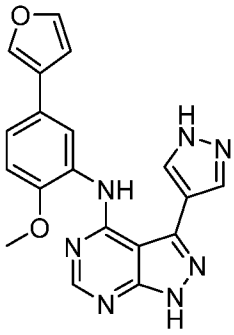

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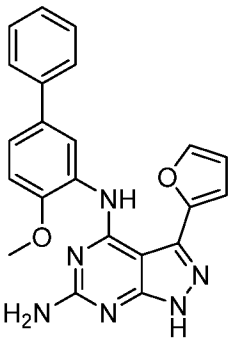

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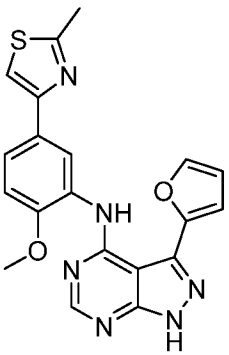

55A

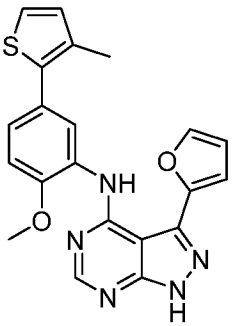

53B

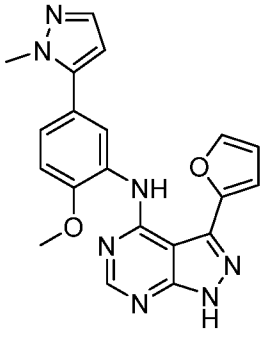

57A


57B

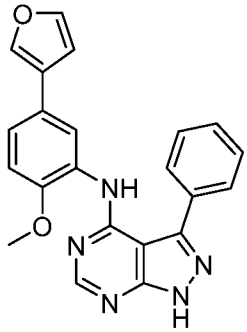

65


66A

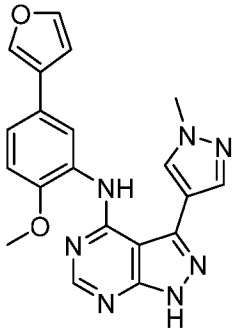

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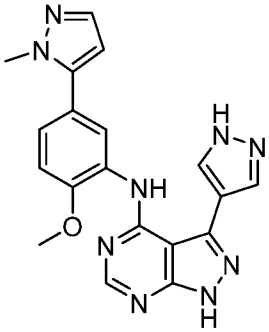
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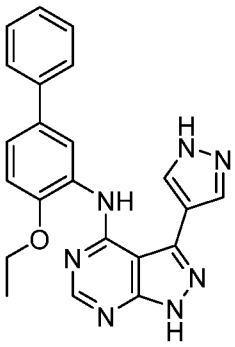
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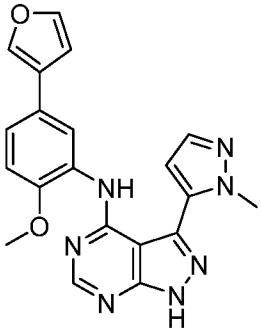
144B ,



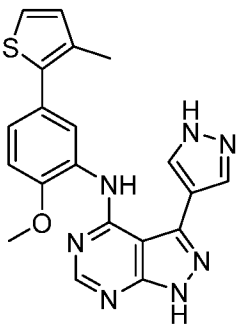
154A ,



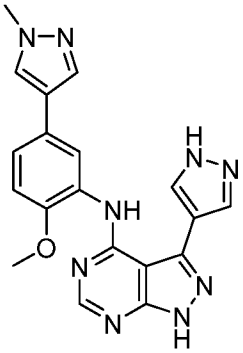
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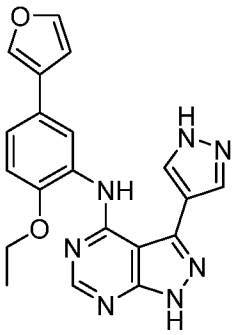
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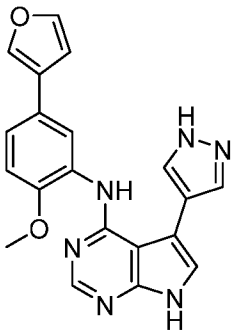
154B ,



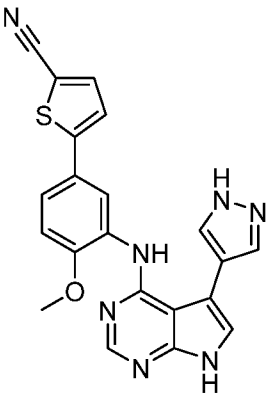
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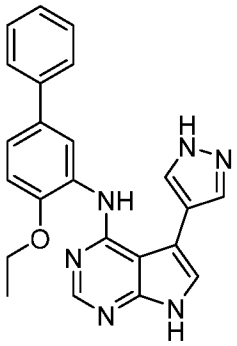
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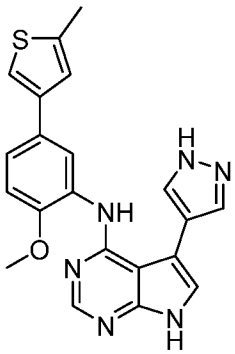
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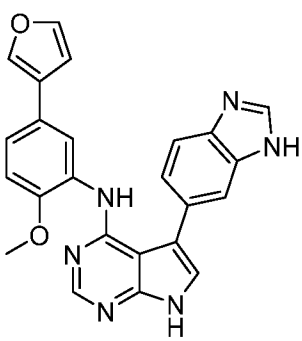
170 ,



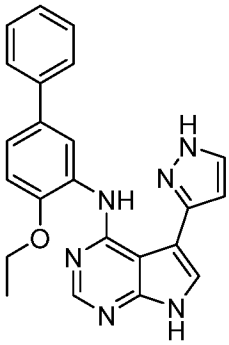
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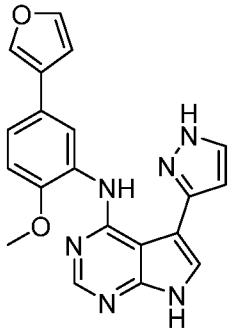
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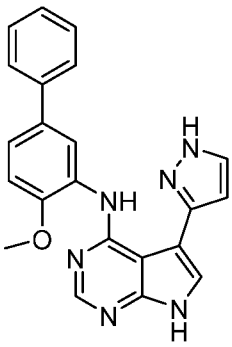
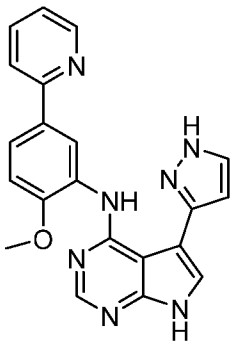
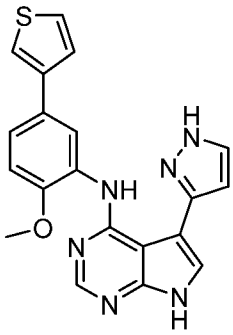
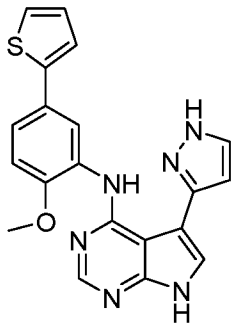
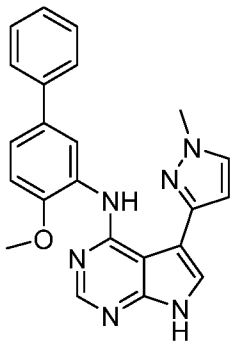
173B ,

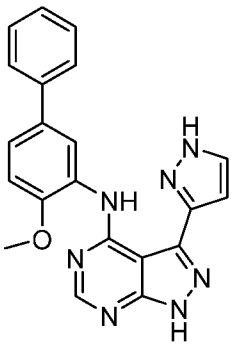
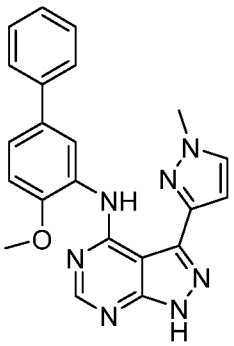
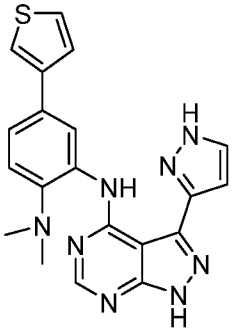
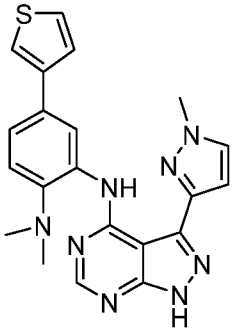


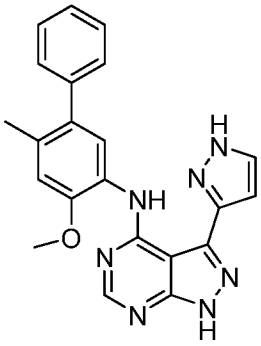
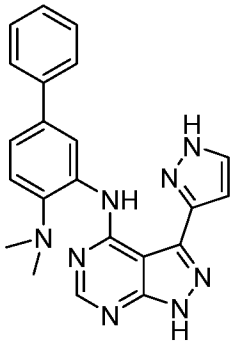
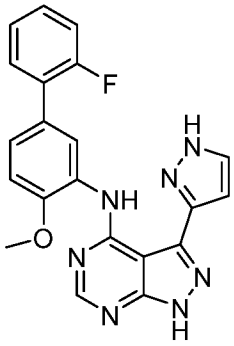
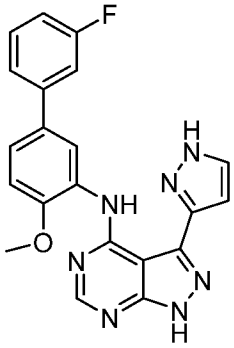
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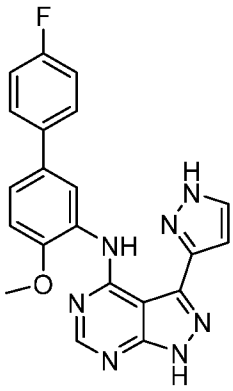
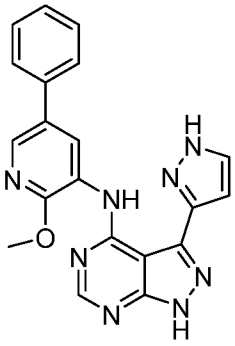
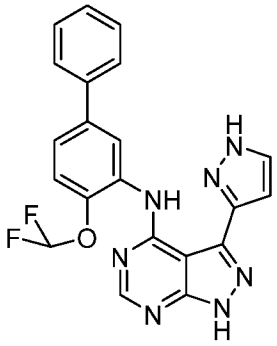
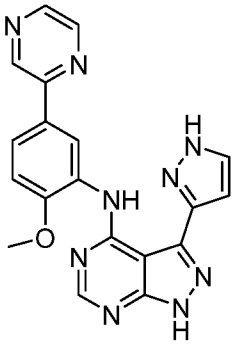


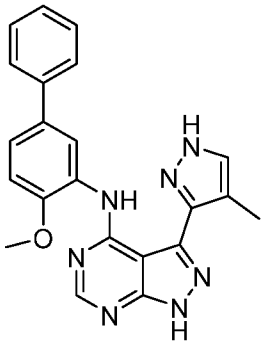
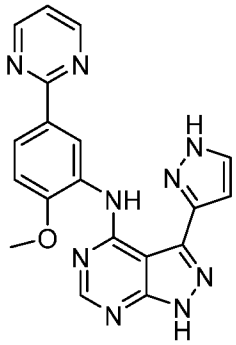
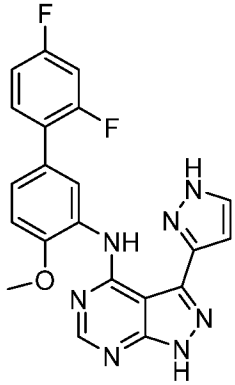
178 ,

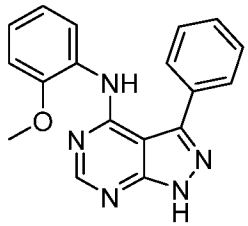

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8-091,

8-092,

8-095,


8-096,

8-097,

104A,

104B,

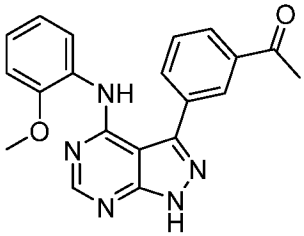
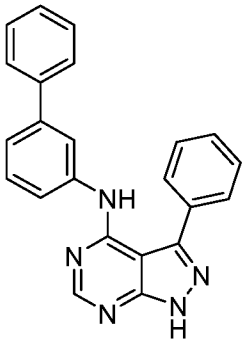
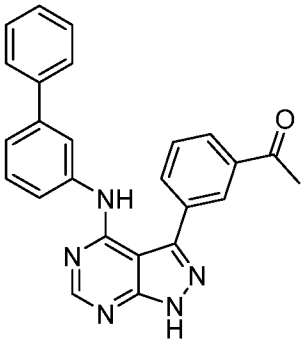
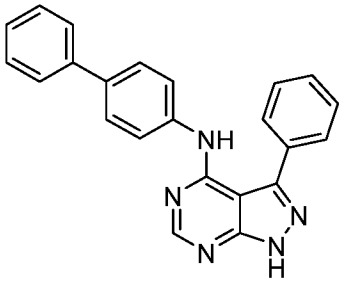

8134,

8164,

8168A,

8168B,

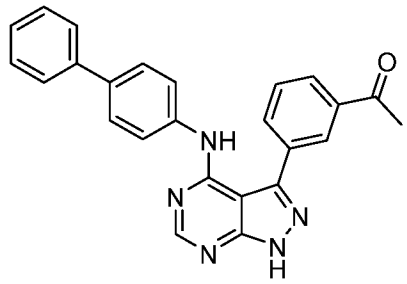

8168C ,

8177 ,

8179 ,

8184 ,


8186 ,

8185 , or

8168A8168C .

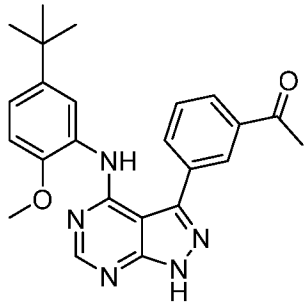

187A ,

[0596] In embodiments, the compound has the formula:

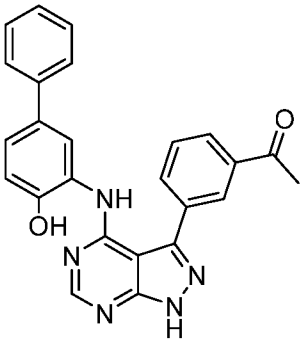

187B ,

186A ,

186B ,

188A



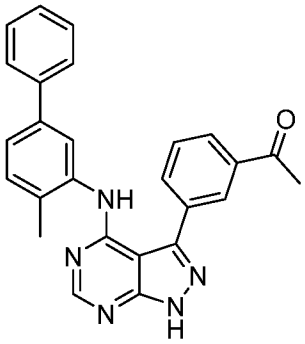
188B ,



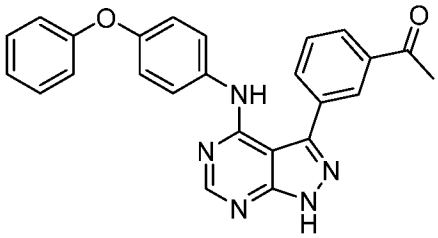
190D ,



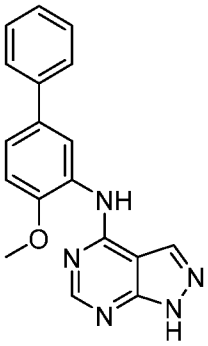
191A ,



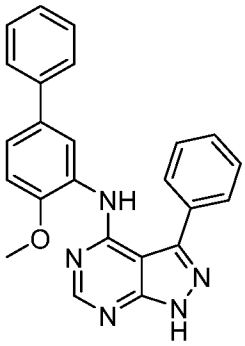
5-001A ,



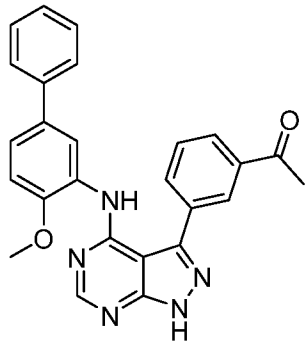
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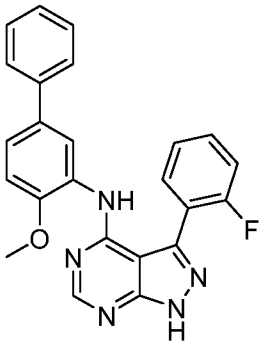
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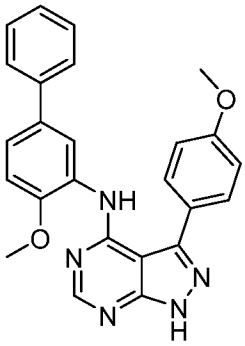
184 ,



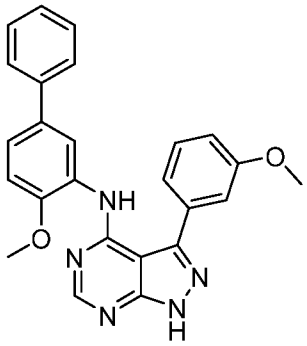
185 ,



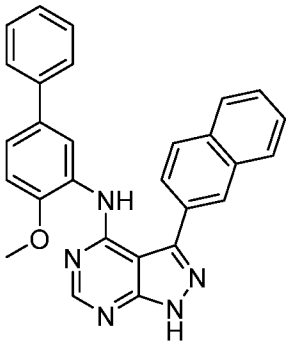
189A ,



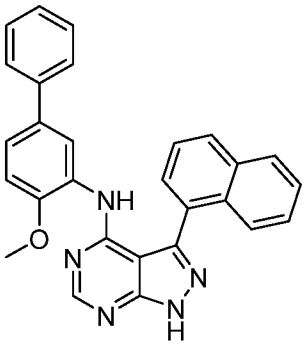
189B ,



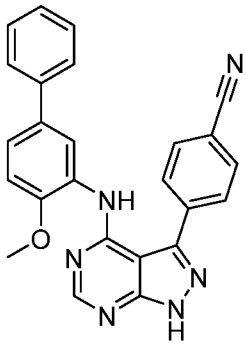
190A ,



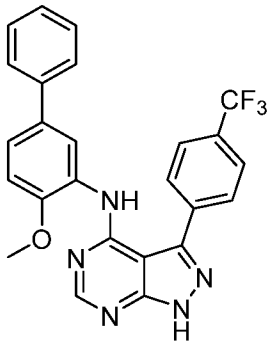
190C ,



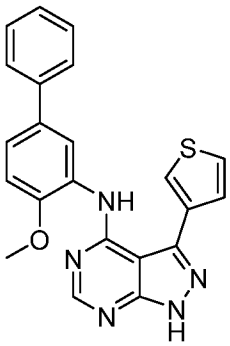
191B ,



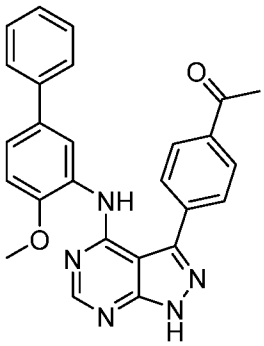
191D ,



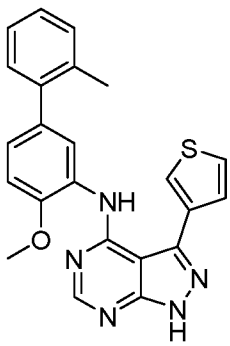
191E ,



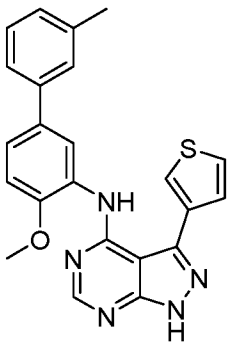
191F ,



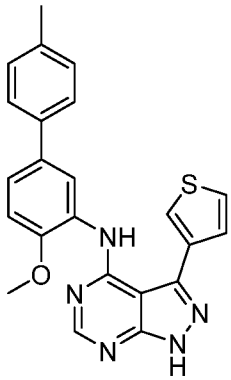
191H ,



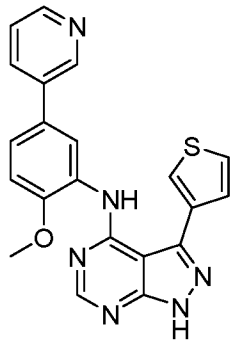
39A ,



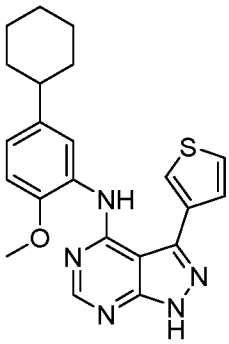
39B ,



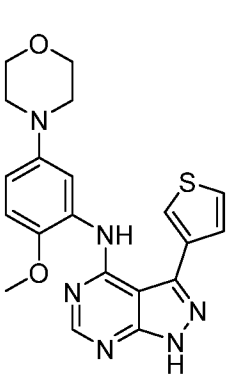
39C ,



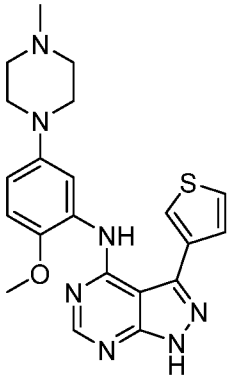
39D ,



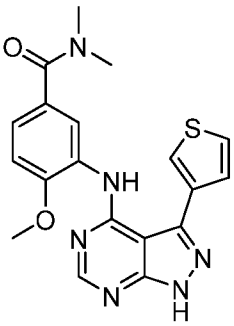
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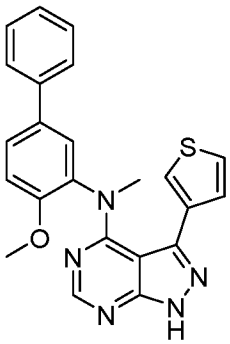
41A ,



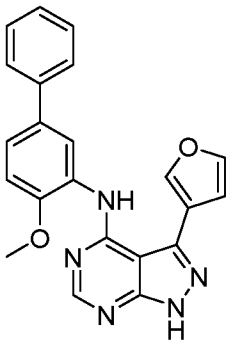
41B ,



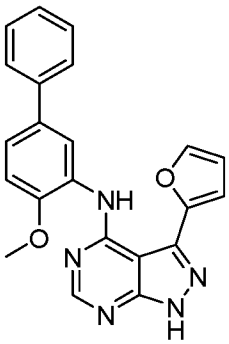
42 ,



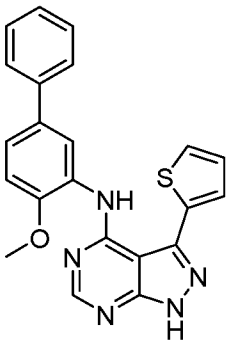
43 ,



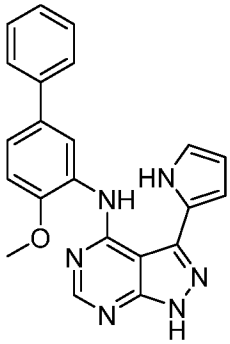
13 ,



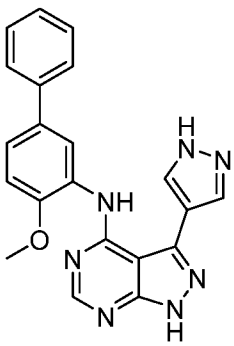
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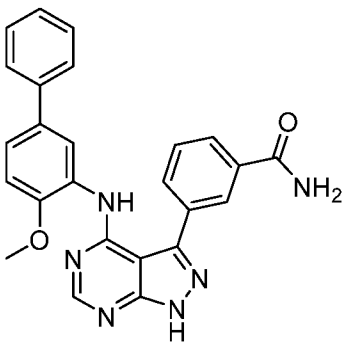
45B ,



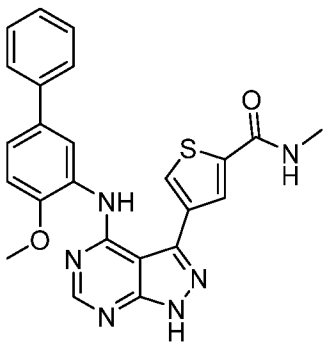
45C ,



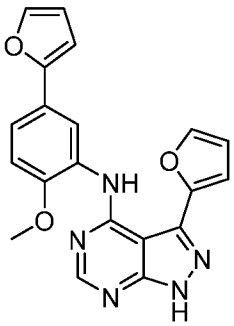
45E ,



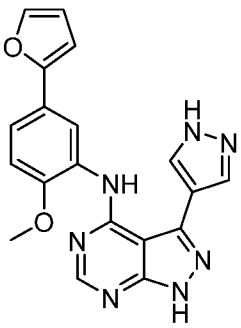
45D ,



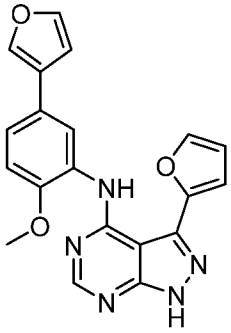
45F ,



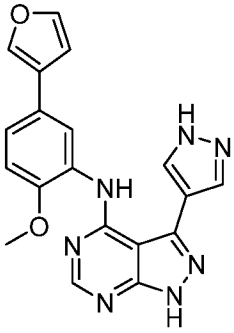
55A ,



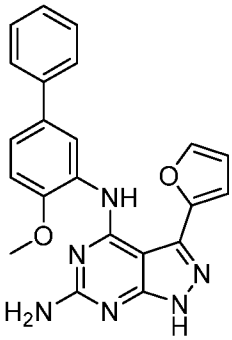
53B ,



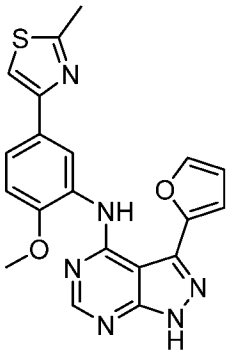
57A ,



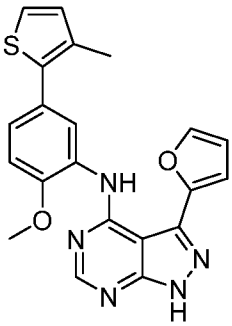
57B ,



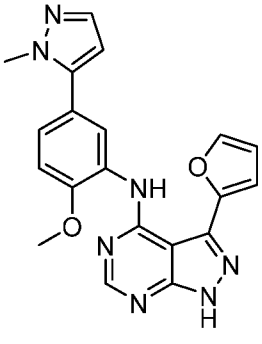
65 ,



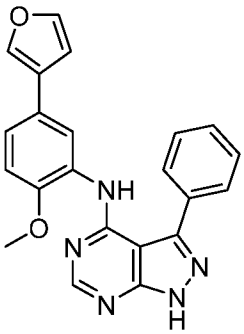
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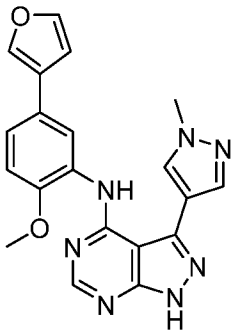
66B ,



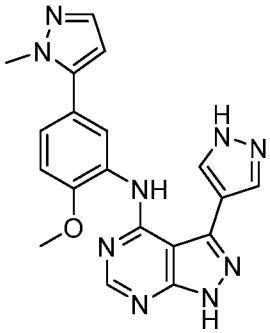
66C ,



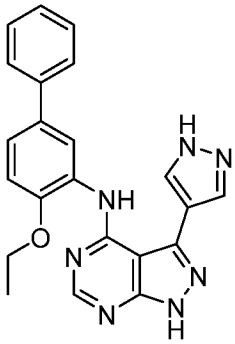
144A ,



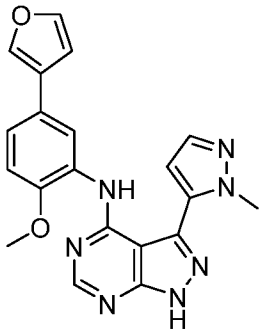
144B ,



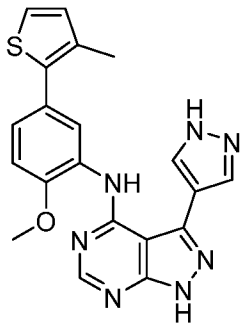
154A ,



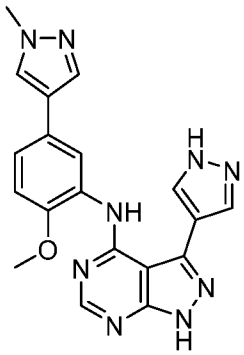
147 ,



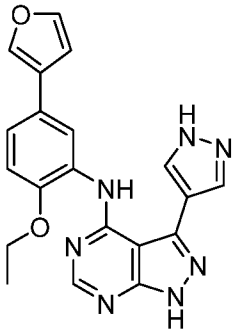
152 ,



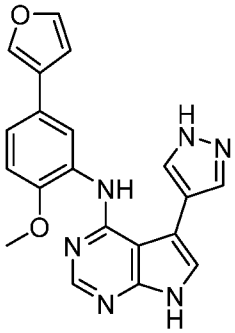
154B ,



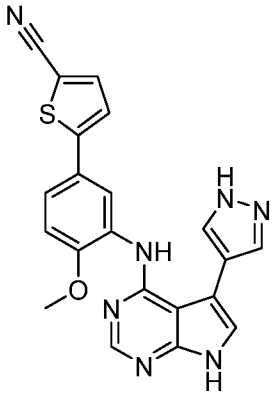
154C ,



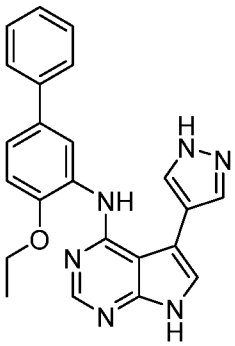
153 ,



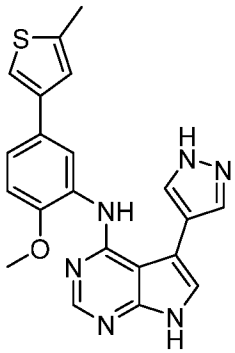
155 ,



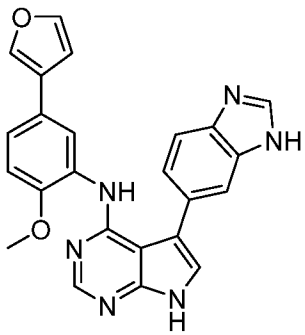
170 ,



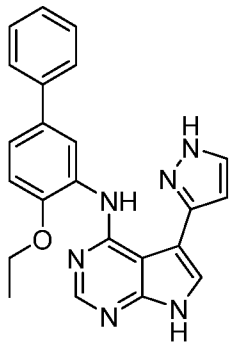
171 ,



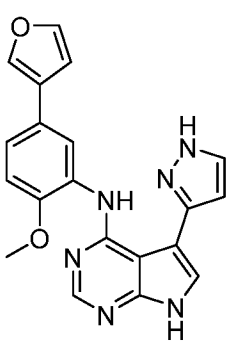
172 ,



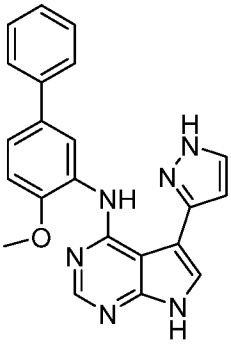
173B ,



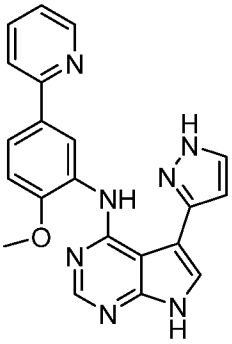
176 ,



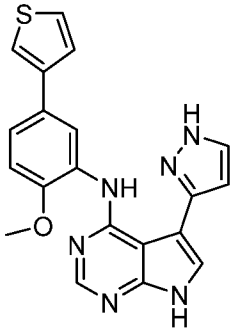
178 ,



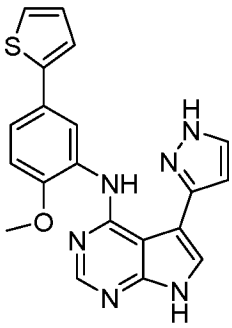
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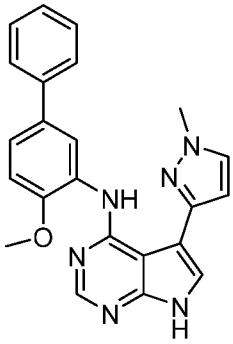
8-090 ,



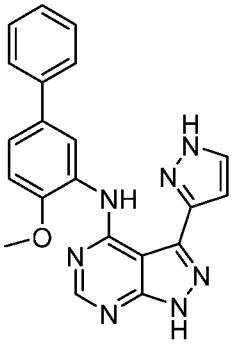
8-091 ,



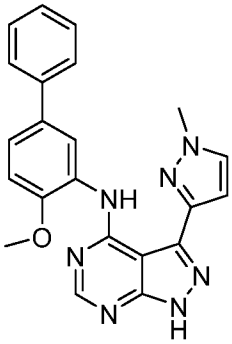
8-092 ,



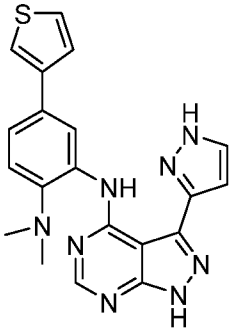
8-095 ,



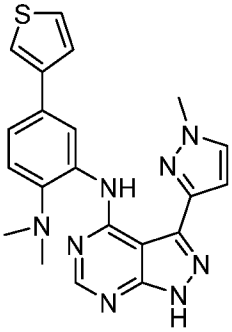
8-096 ,



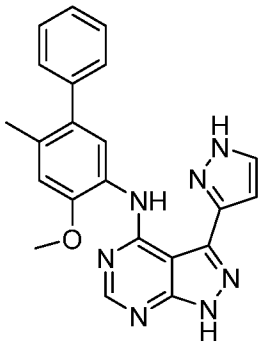
8-097 ,



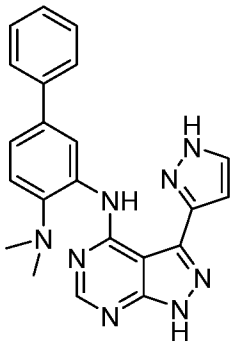
104A ,



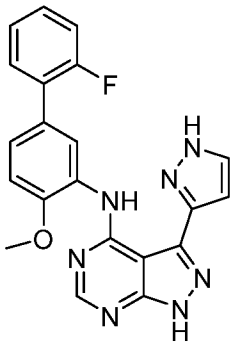
104B ,



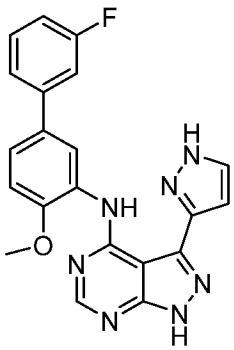
8134 ,



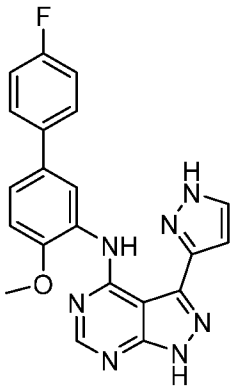
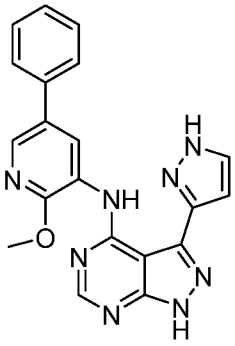
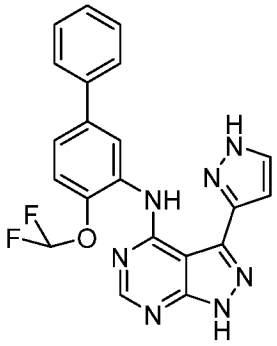
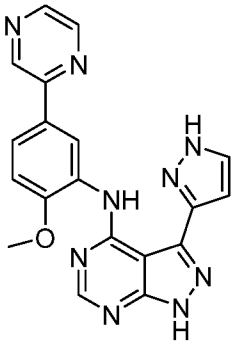
8164 ,

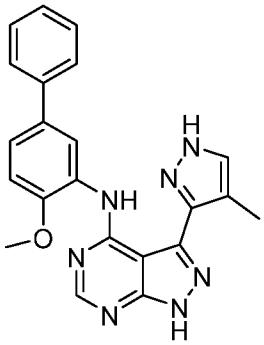
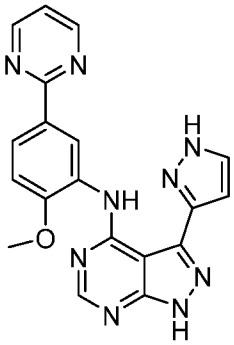
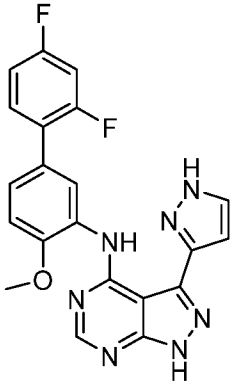


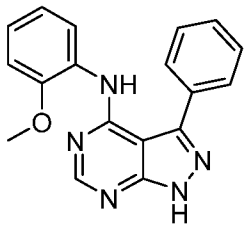
8168A ,



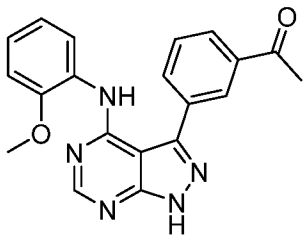
8168B ,


8168C ,

8177 ,

8179 ,

8184 ,

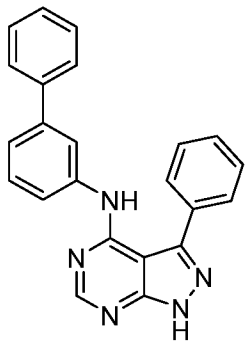

8186 ,

8185 , or

8168A8168C .


187A .

[0597] In embodiments, the compound has the formula:

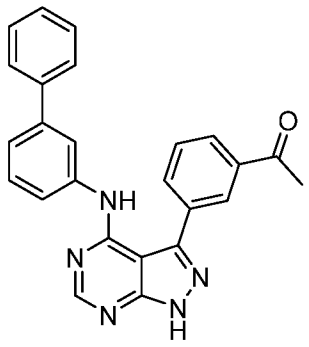

187B .

[0598] In embodiments, the compound has the formula:



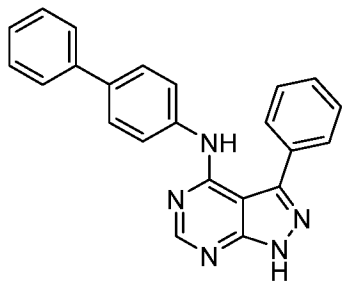
186A

[0599] In embodiments, the compound has the formula: .



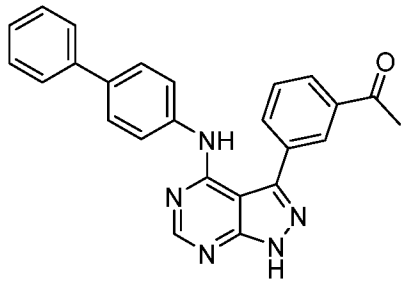
186B

[0600] In embodiments, the compound has the formula: .



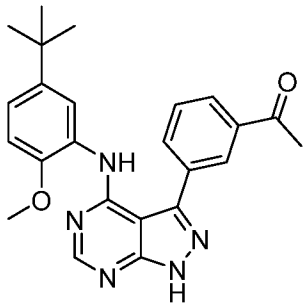
188A

[0601] In embodiments, the compound has the formula: .



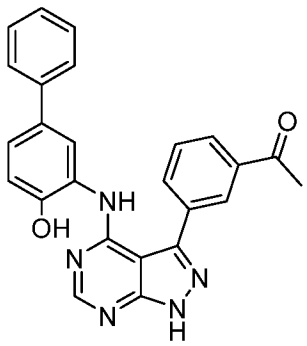
188B

[0602] In embodiments, the compound has the formula: .



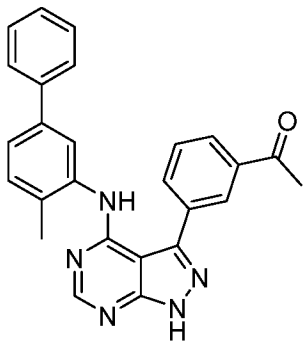
190D

[0603] In embodiments, the compound has the formula: .



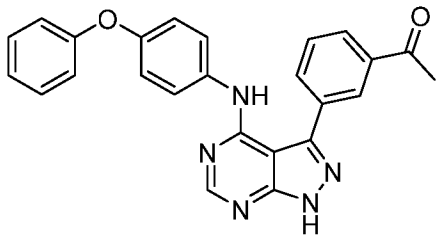
191A

[0604] In embodiments, the compound has the formula: .



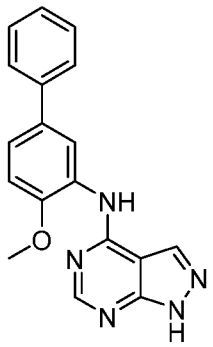
5-001A

[0605] In embodiments, the compound has the formula: .



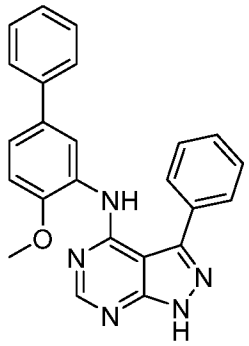
5-001B

[0606] In embodiments, the compound has the formula: .



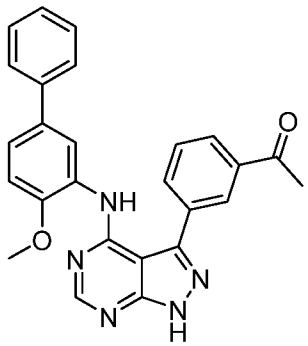
5-004

[0607] In embodiments, the compound has the formula: .



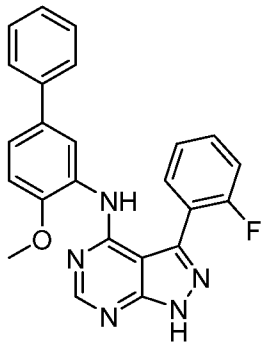
184

[0608] In embodiments, the compound has the formula: .



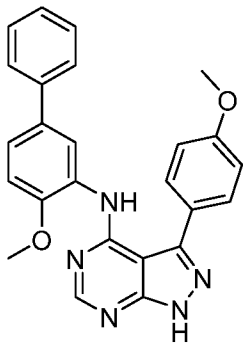
185

[0609] In embodiments, the compound has the formula: .



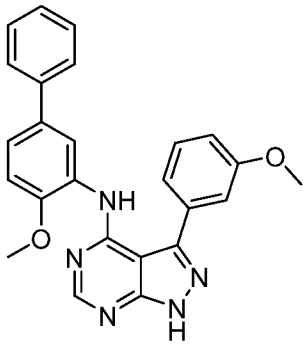
189A

[0610] In embodiments, the compound has the formula: .



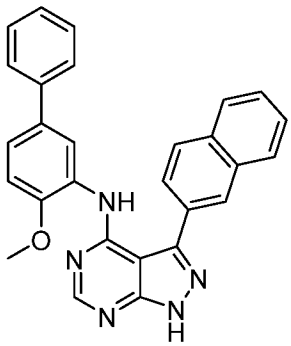
189B

[0611] In embodiments, the compound has the formula: .



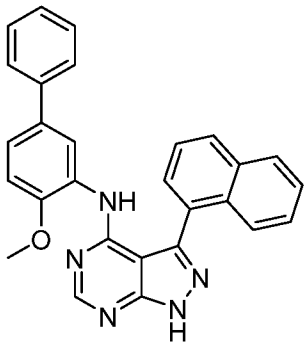
190A

[0612] In embodiments, the compound has the formula: .



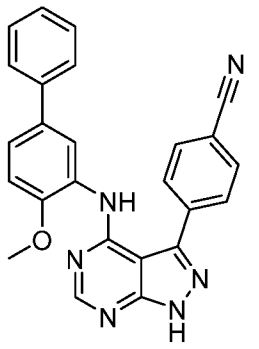
190C

[0613] In embodiments, the compound has the formula: .



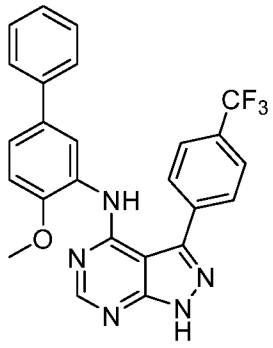
191B

[0614] In embodiments, the compound has the formula: .



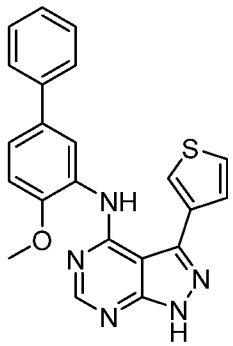
191D

[0615] In embodiments, the compound has the formula: .



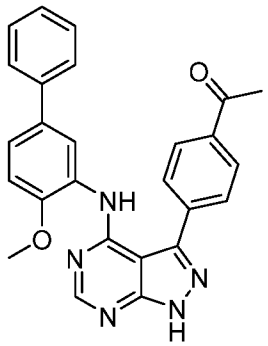
191E

[0616] In embodiments, the compound has the formula: .



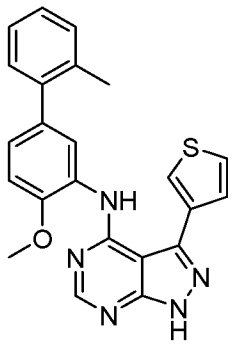
191F

[0617] In embodiments, the compound has the formula: .



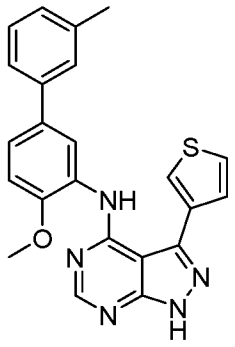
191H

[0618] In embodiments, the compound has the formula: .



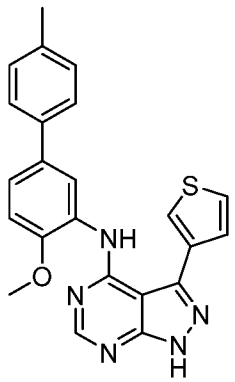
39A

[0619] In embodiments, the compound has the formula: .



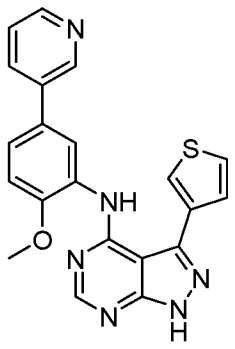
39B

[0620] In embodiments, the compound has the formula: .



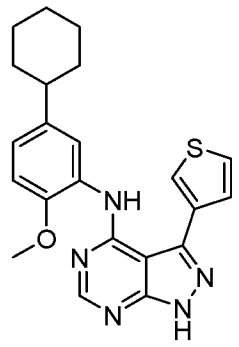
39C

[0621] In embodiments, the compound has the formula: .



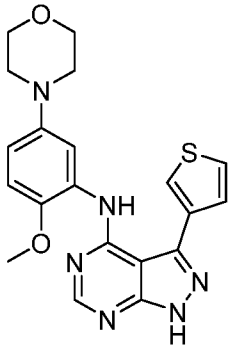
39D

[0622] In embodiments, the compound has the formula: .



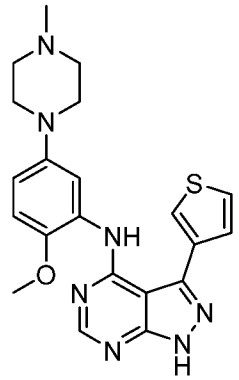
6

[0623] In embodiments, the compound has the formula: .



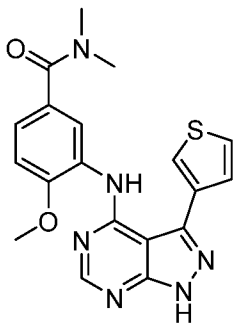
41A

[0624] In embodiments, the compound has the formula: .



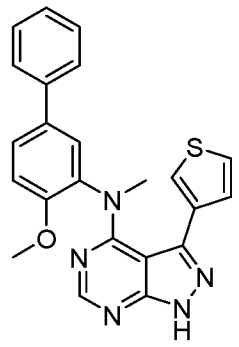
41B

[0625] In embodiments, the compound has the formula: .



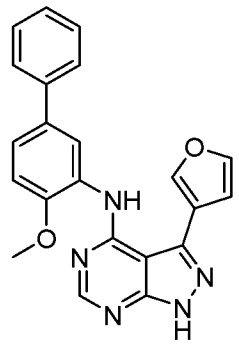
42

[0626] In embodiments, the compound has the formula: .



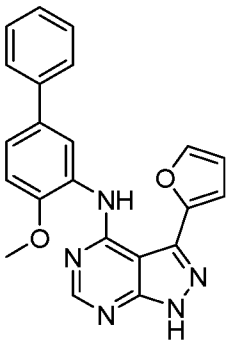
43

[0627] In embodiments, the compound has the formula: .



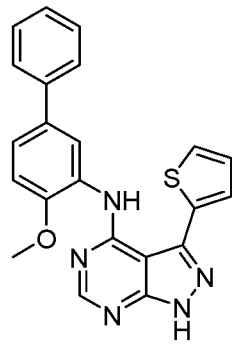
13

[0628] In embodiments, the compound has the formula: .



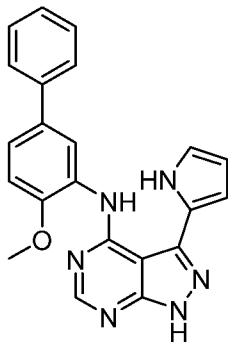
45A

[0629] In embodiments, the compound has the formula: .



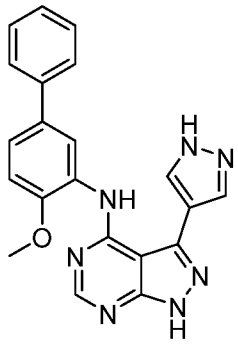
45B

[0630] In embodiments, the compound has the formula: .



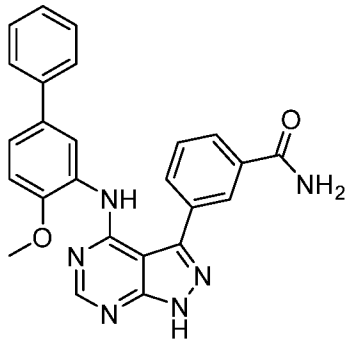
45C

[0631] In embodiments, the compound has the formula: .



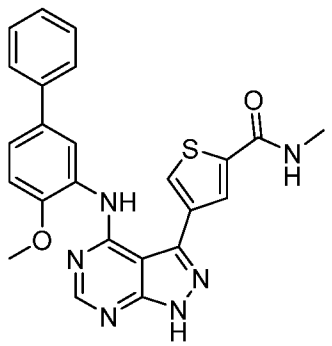
45E

[0632] In embodiments, the compound has the formula: .



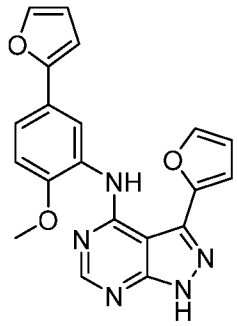
45D

[0633] In embodiments, the compound has the formula: .



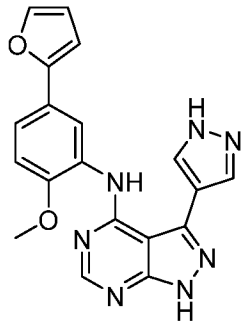
45F

[0634] In embodiments, the compound has the formula: .



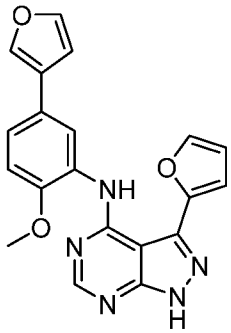
55A

[0635] In embodiments, the compound has the formula: .



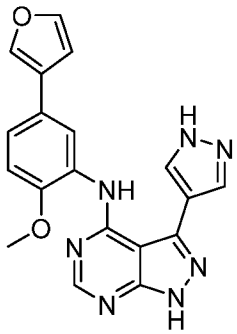
53B

[0636] In embodiments, the compound has the formula: .



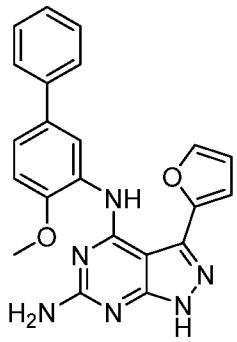
57A

[0637] In embodiments, the compound has the formula: .

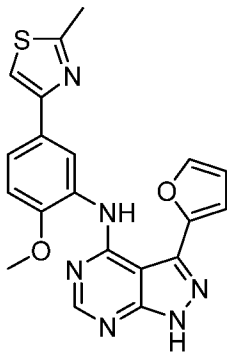


57B

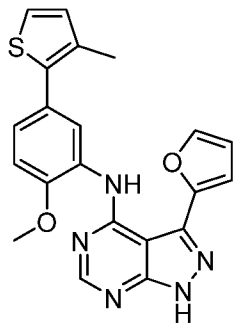
[0638] In embodiments, the compound has the formula: .



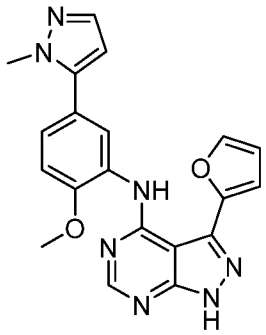
[0639] In embodiments, the compound has the formula: 65 .



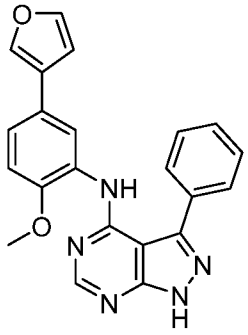
[0640] In embodiments, the compound has the formula: 66A .



[0641] In embodiments, the compound has the formula: 66B .

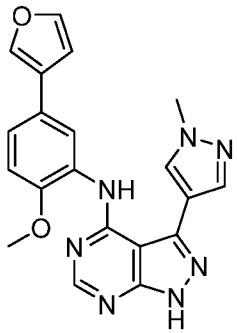


[0642] In embodiments, the compound has the formula: 66C .



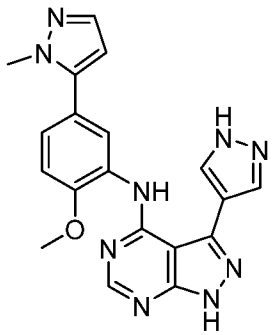
144A

[0643] In embodiments, the compound has the formula: .



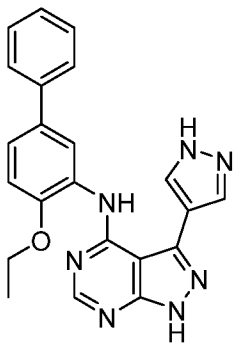
144B

[0644] In embodiments, the compound has the formula: .



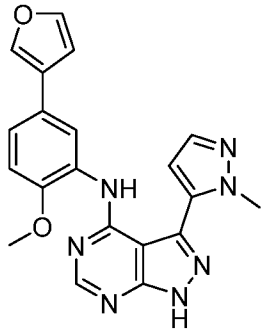
154A

[0645] In embodiments, the compound has the formula: .



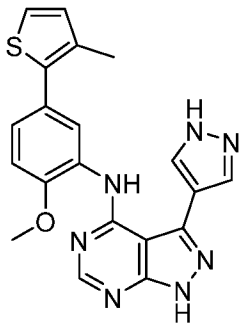
147

[0646] In embodiments, the compound has the formula: .



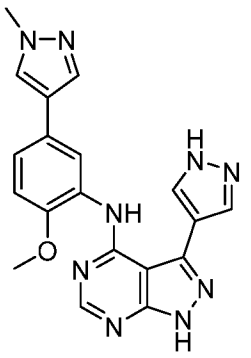
152

[0647] In embodiments, the compound has the formula: .



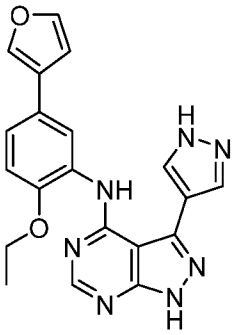
154B

[0648] In embodiments, the compound has the formula: .



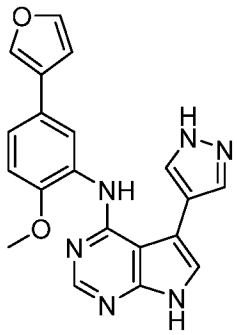
154C

[0649] In embodiments, the compound has the formula: .

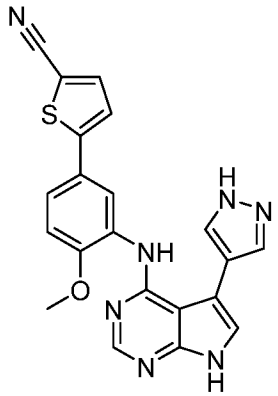


153

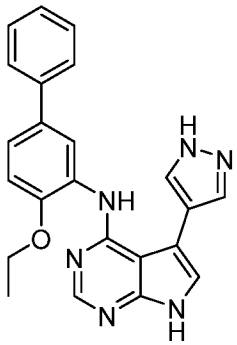
[0650] In embodiments, the compound has the formula: .



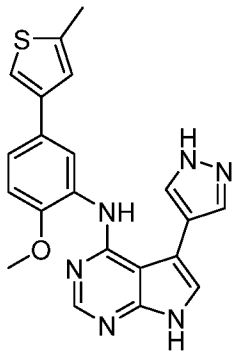
[0651] In embodiments, the compound has the formula: 155 .



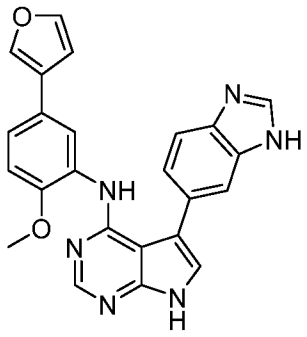
[0652] In embodiments, the compound has the formula: 170 .



[0653] In embodiments, the compound has the formula: 171 .

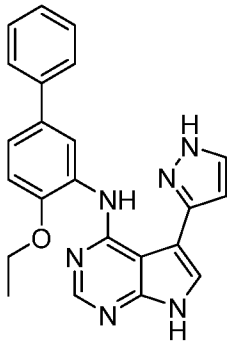


[0654] In embodiments, the compound has the formula: 172 .



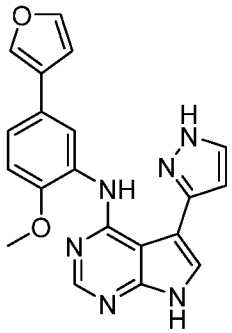
173B

[0655] In embodiments, the compound has the formula: .



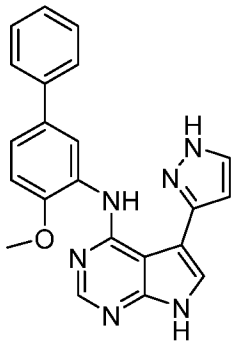
176

[0656] In embodiments, the compound has the formula: .



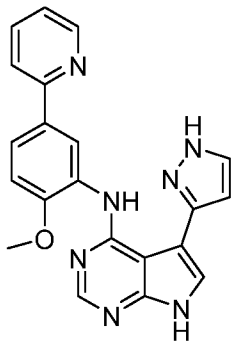
178

[0657] In embodiments, the compound has the formula: .



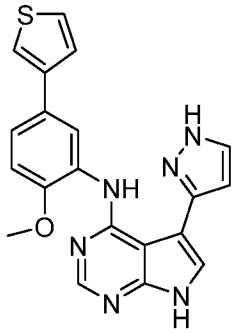
8-089

[0658] In embodiments, the compound has the formula: , also referred to as CJN-08-089 in FIG. 31A.



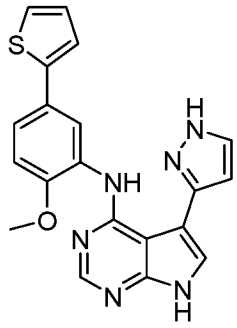
8-090

[0659] In embodiments, the compound has the formula: , also referred to herein as CJN-08-090 as in FIG. 31B.



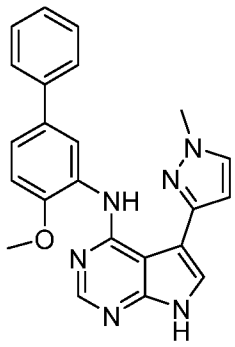
8-091

[0660] In embodiments, the compound has the formula: , also referred to herein as CJN-08-091 as in FIG. 31C.



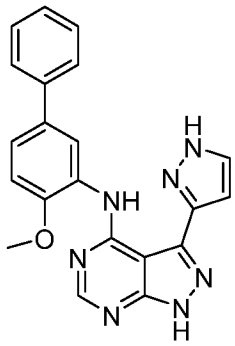
8-092

[0661] In embodiments, the compound has the formula: , also referred to herein as CJN-08-092 as in FIG. 31D.



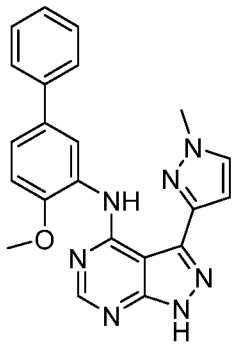
8-095

[0662] In embodiments, the compound has the formula: , also referred to herein as CJN-08-0985 as in FIG. 33A.



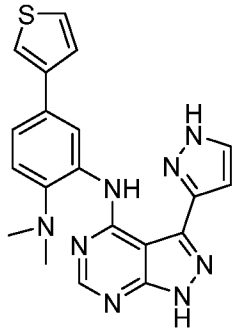
8-096

[0663] In embodiments, the compound has the formula: , also referred to herein as CJN-08-096 as in FIG. 33B.



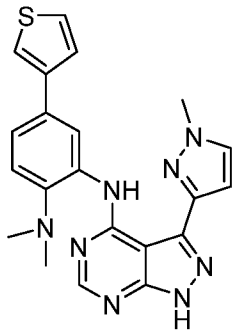
8-097

[0664] In embodiments, the compound has the formula: , also referred to herein as CJN-08-097 as in FIG. 33C.



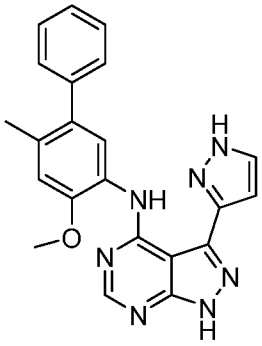
104A

[0665] In embodiments, the compound has the formula: .



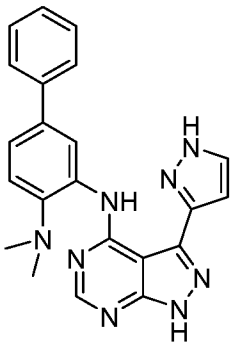
104B

[0666] In embodiments, the compound has the formula: .



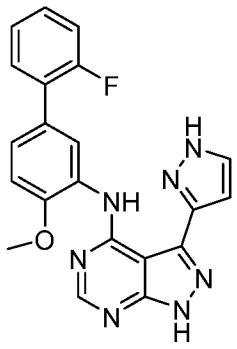
8134

[0667] In embodiments, the compound has the formula: .

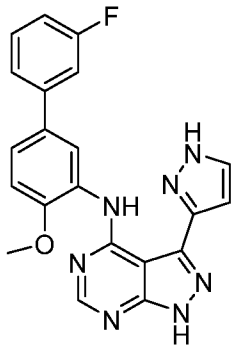


8164

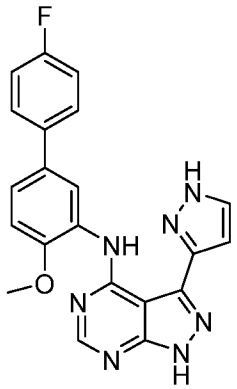
[0668] In embodiments, the compound has the formula: .



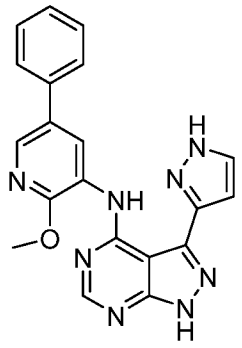
[0669] In embodiments, the compound has the formula: 8168A .



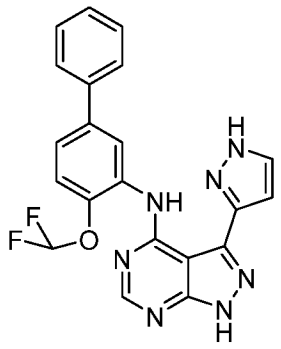
[0670] In embodiments, the compound has the formula: 8168B .



[0671] In embodiments, the compound has the formula: 8168C .

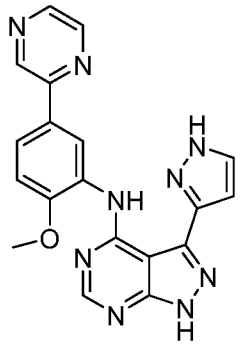


[0672] In embodiments, the compound has the formula: 8177 .



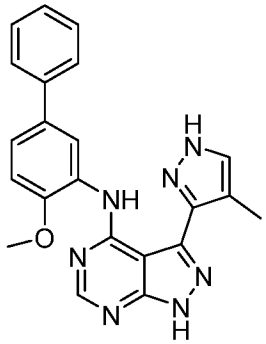
8179

[0673] In embodiments, the compound has the formula: .



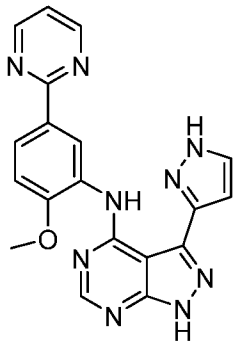
8184

[0674] In embodiments, the compound has the formula: .



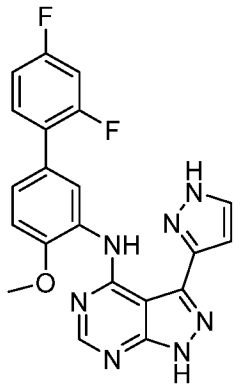
8186

[0675] In embodiments, the compound has the formula: .



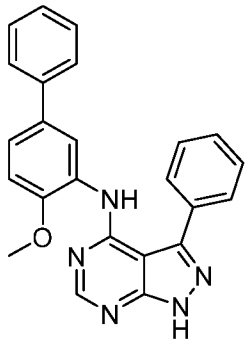
8185

[0676] In embodiments, the compound has the formula: .



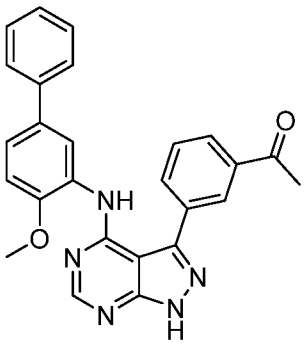
8168A8168C .

[0677] In embodiments, the compound has the formula:

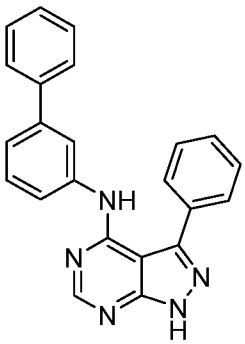


184 ,

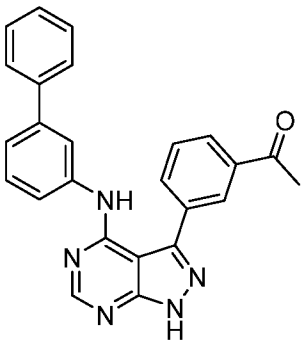
[0678] In embodiments, the compound has the formula:



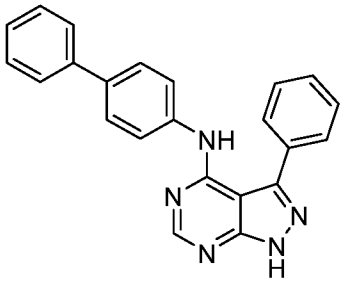
185 ,



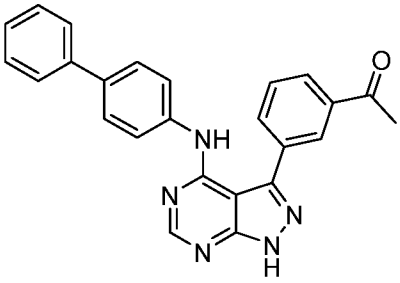
186A ,



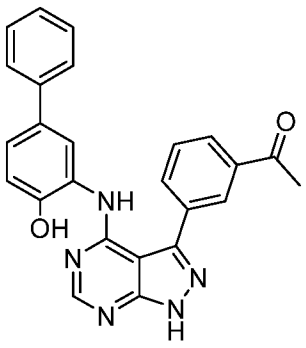
186B ,



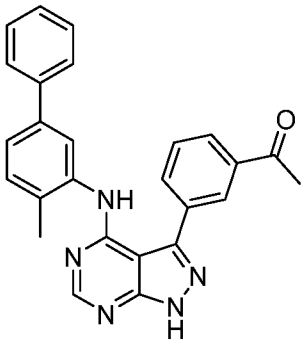
188A ,



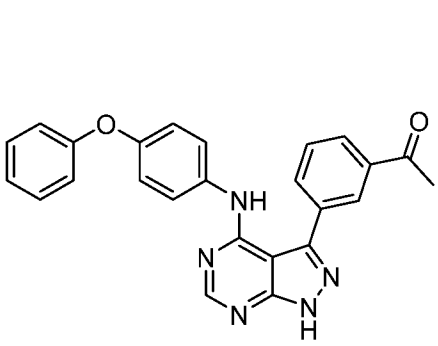
188B ,



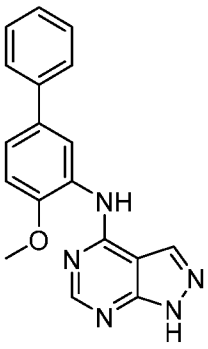
191A ,



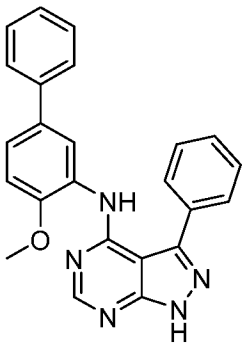
5-001A ,



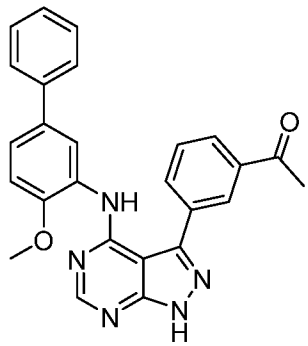
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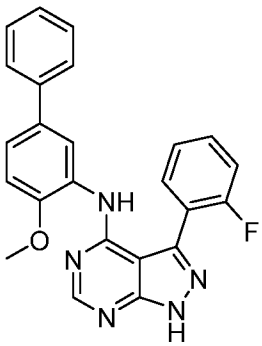
5-004 ,



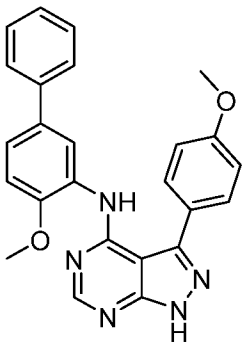
184 ,



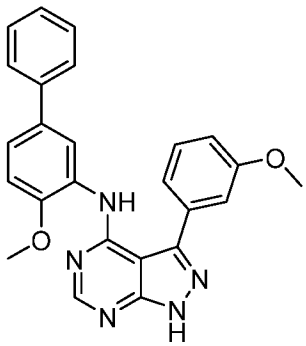
185 ,



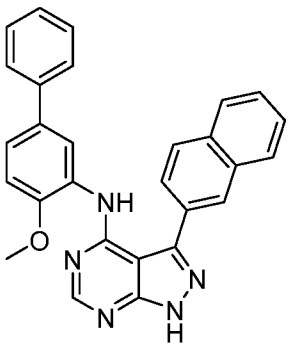
189A ,



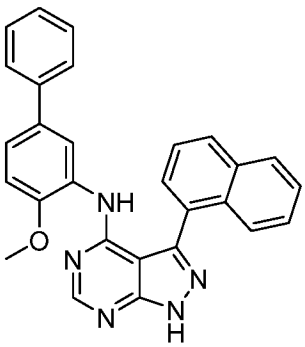
189B ,



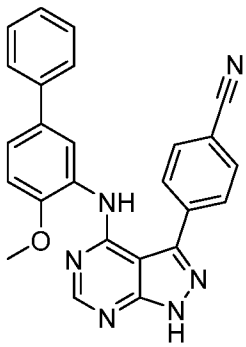
190A ,



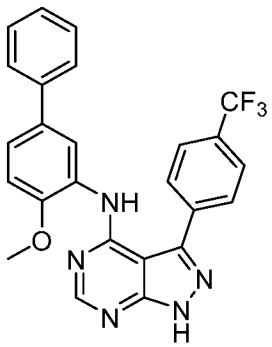
190C ,



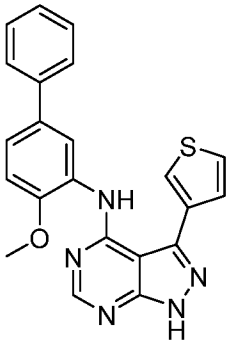
191B ,



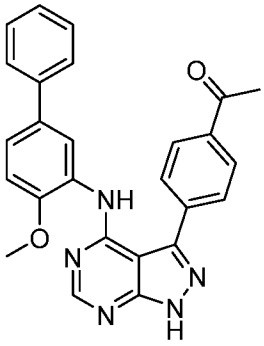
191D ,



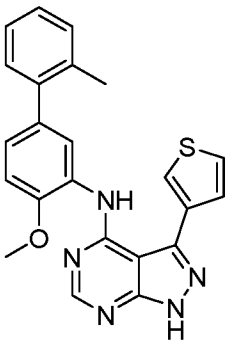
191E ,



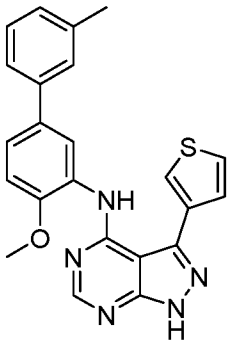
191F ,



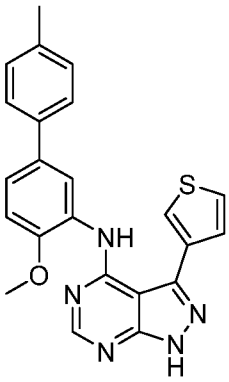
191H ,



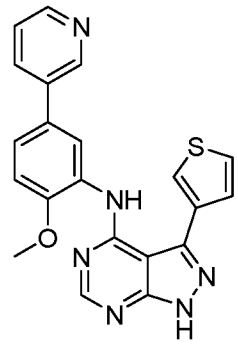
39A ,

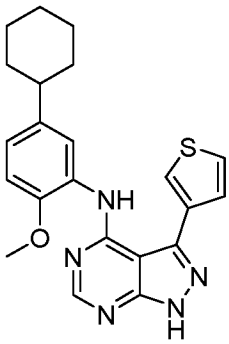


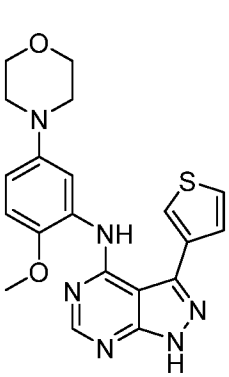
39B ,

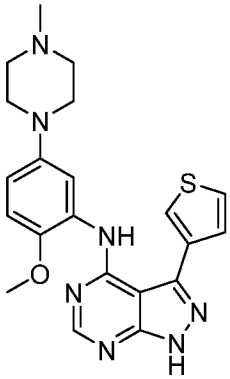


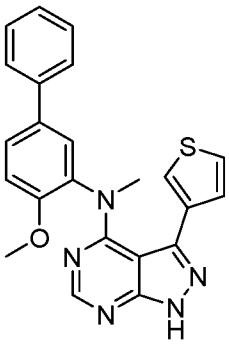
39C ,

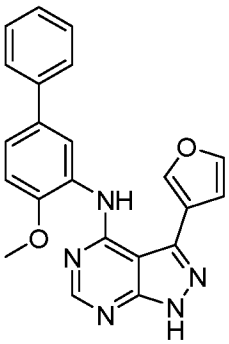

39D ,

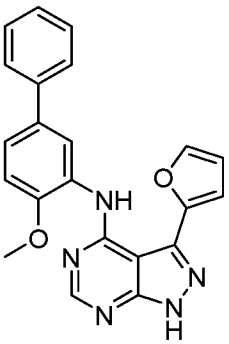

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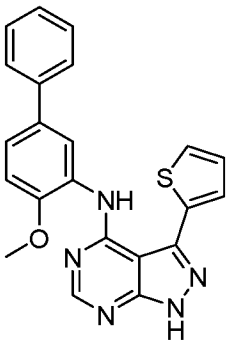

41A ,

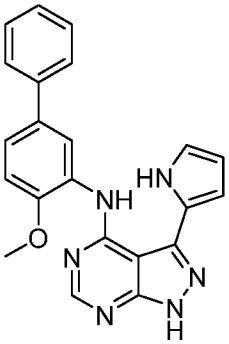

41B ,

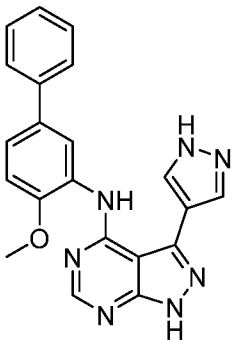

43 ,

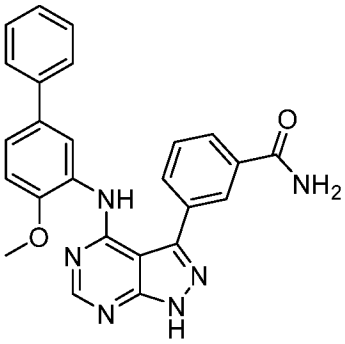

13 ,

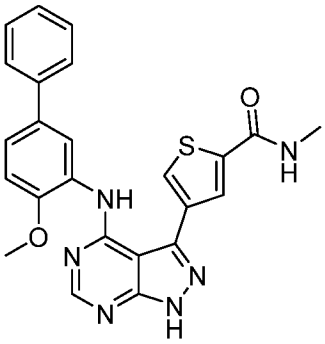

45A ,

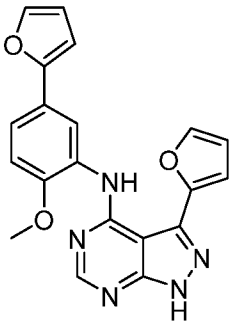

45B ,

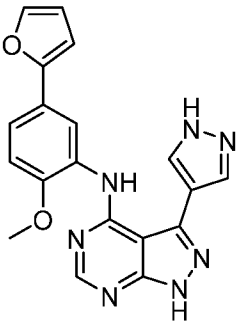

45C ,

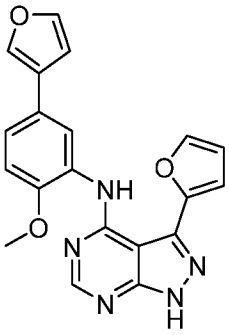

45E ,

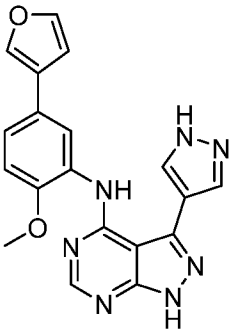

45D ,

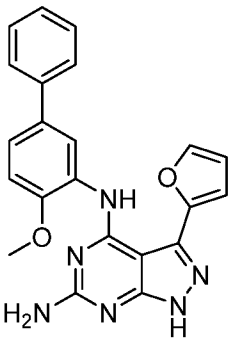

45F ,

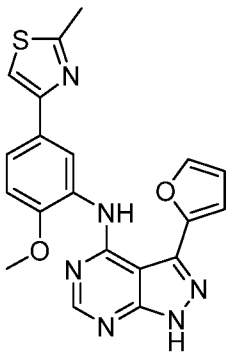

55A ,

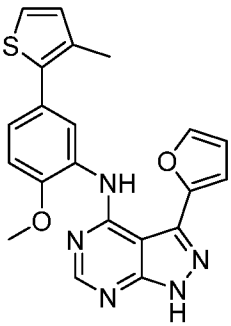

53B ,

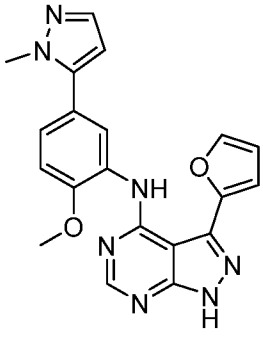

57A ,


57B ,

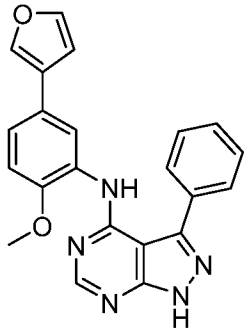

65 ,


66A ,

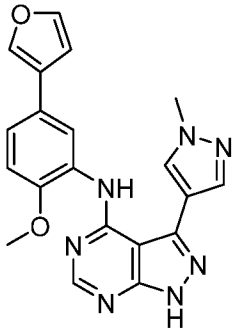

66B ,



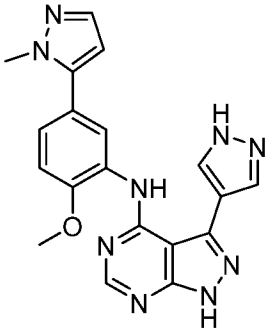
66C ,



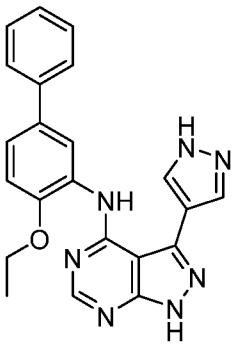
144A ,



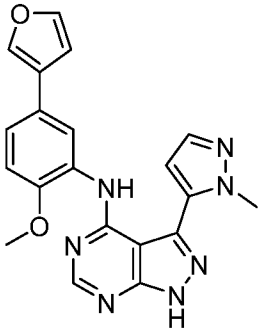
144B ,



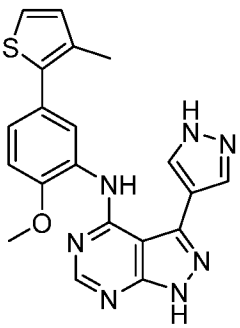
154A ,



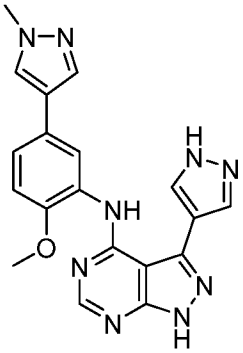
147 ,



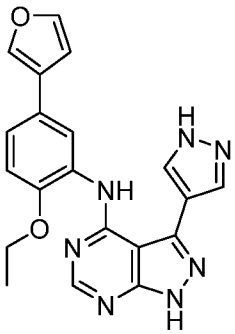
152 ,



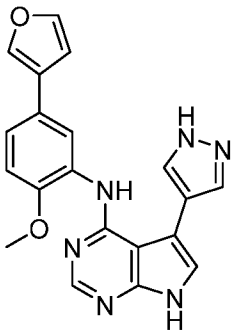
154B ,



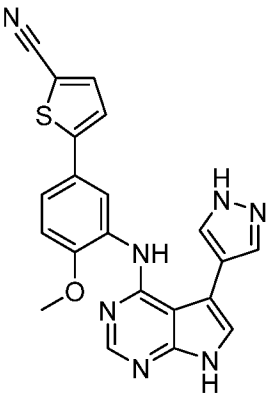
154C ,



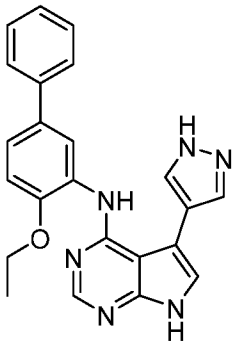
153 ,



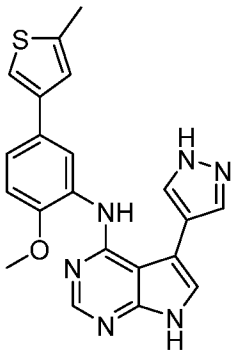
155 ,



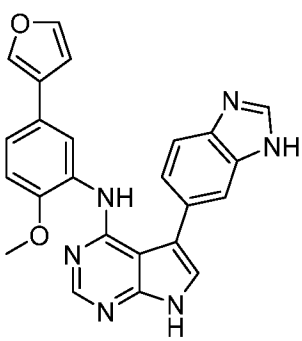
170 ,



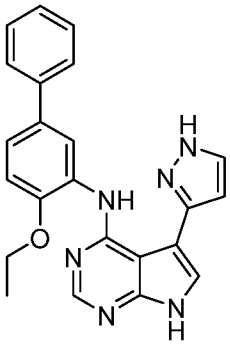
171 ,



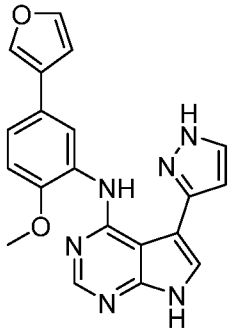
172 ,



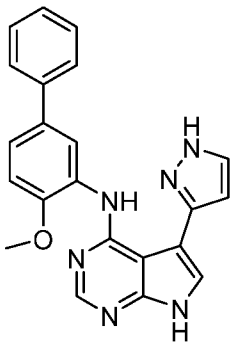
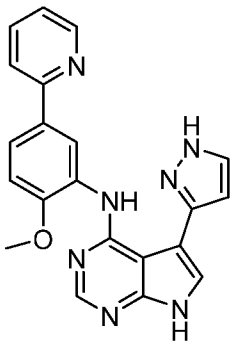
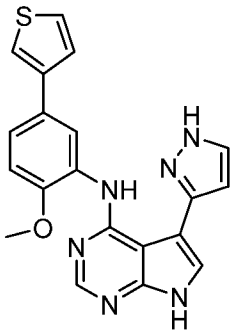
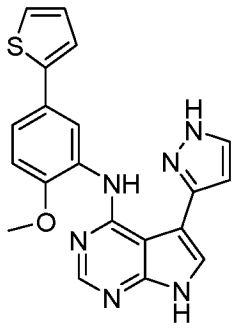
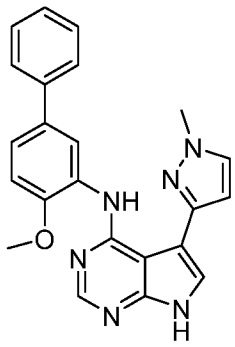
173B ,

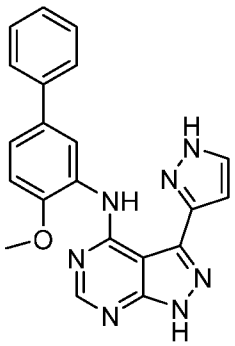
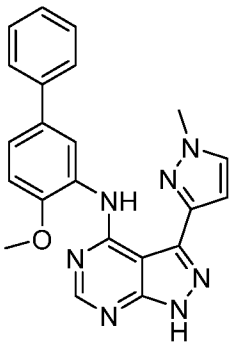
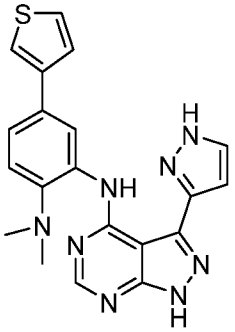
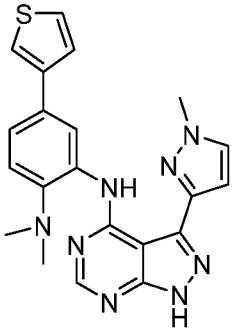


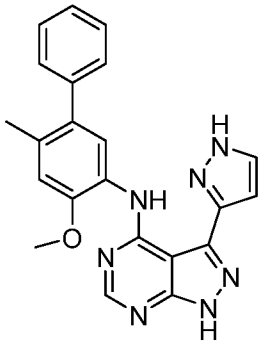
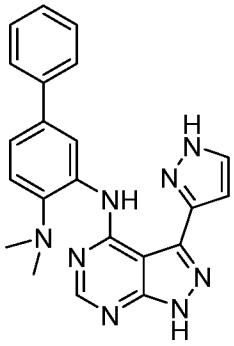
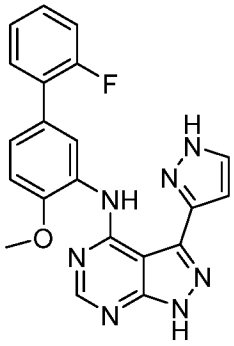
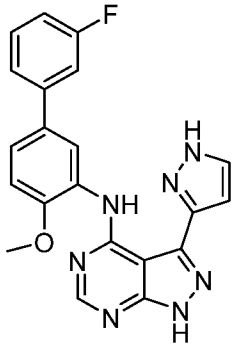
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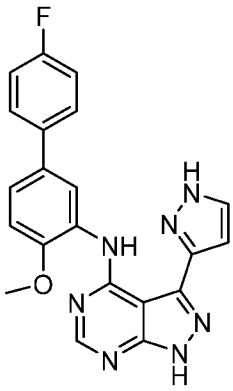
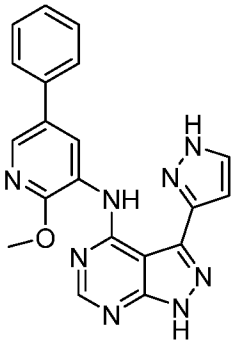
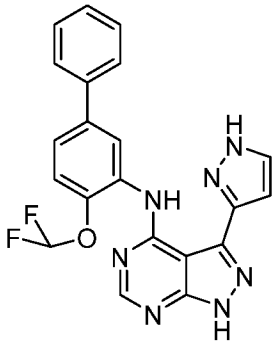
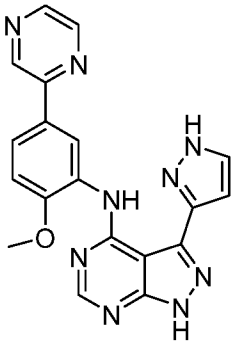


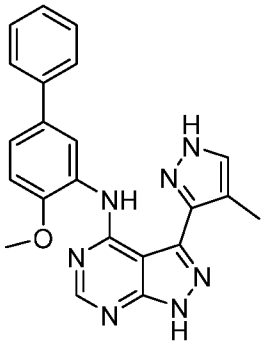
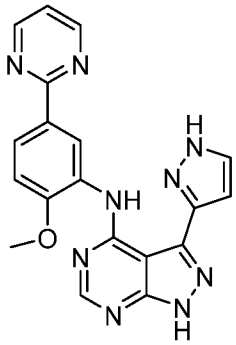
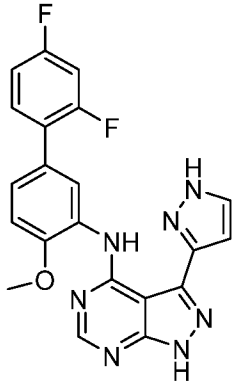
178 ,

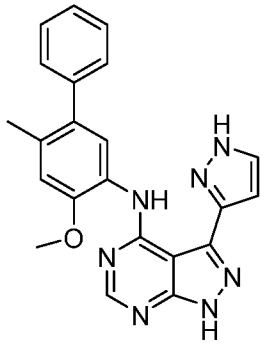

8-089,

8-090,

8-091,

8-092,

8-095,


8-096,

8-097,

104A,

104B,

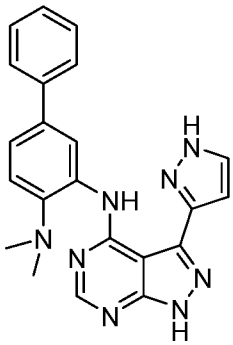
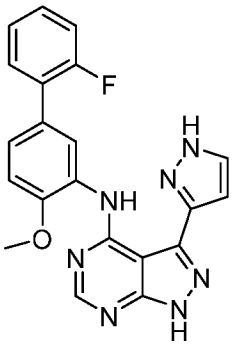
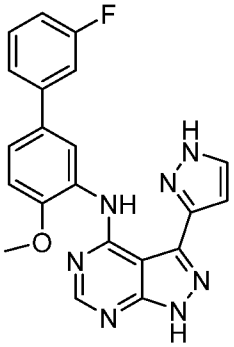
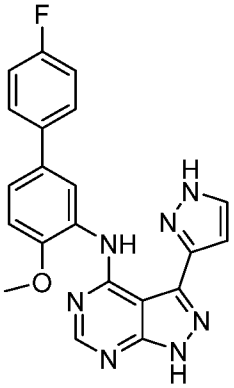
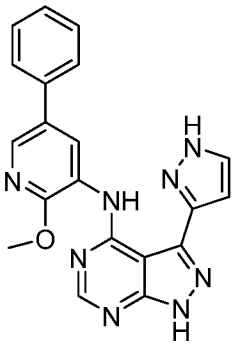

8134,

8164,

8168A,

8168B,

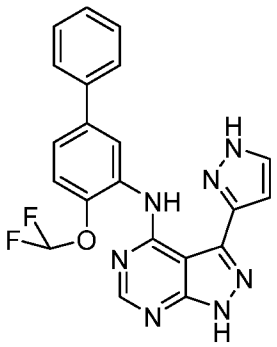
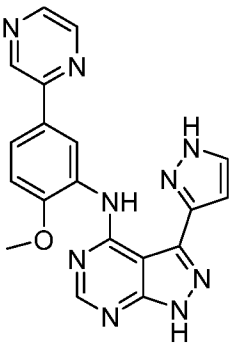
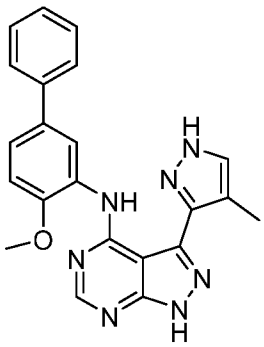
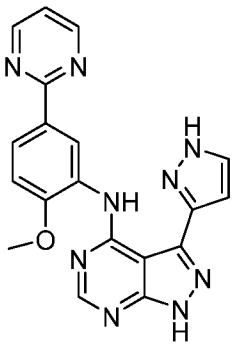

8168C ,

8177 ,

8179 ,

8184 ,

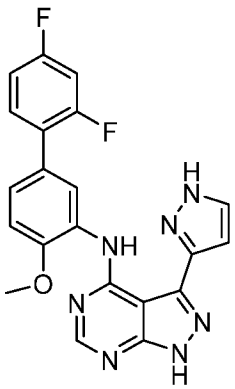

8186 ,

8185 , or

8168A8168C .

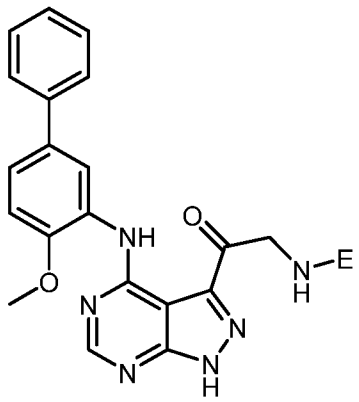

8134 ,

[0679] In embodiments, the compound has the formula:

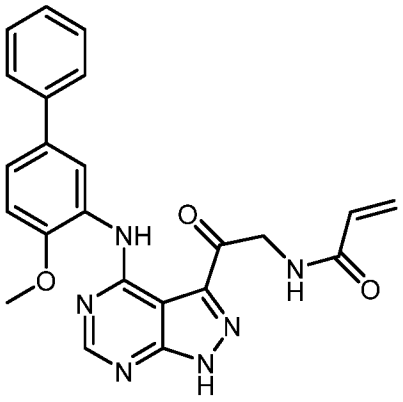

8164 ,

8168A ,

8168B ,

8168C ,

8177 ,


8179 ,

8184 ,

8186 ,

8185 , or

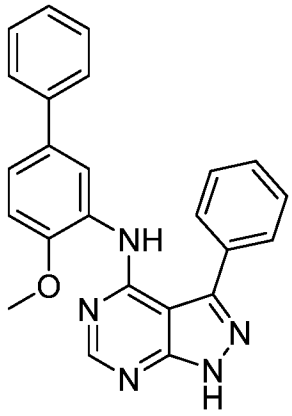

8168A8168C .

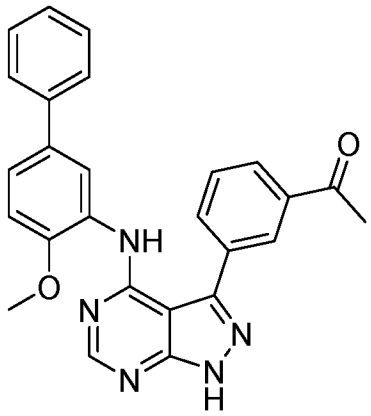


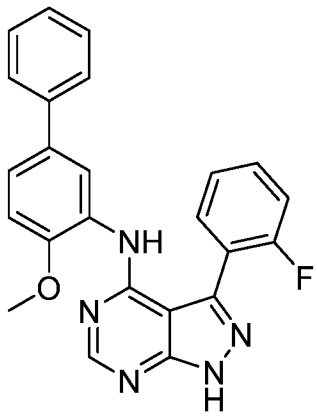
[0680] In embodiments, the compound has the formula: , wherein E is as described herein. In embodiments, the compound has the formula:

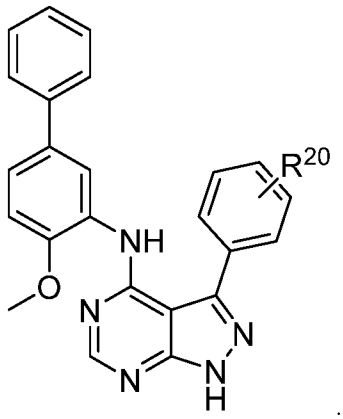

8156 .

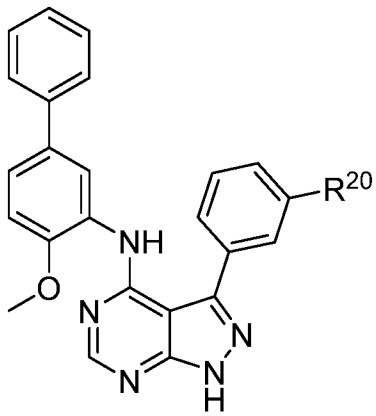
[0681] In embodiments, a compound is a compound described herein, including in an aspect, embodiment, table, figure, example, scheme, or claim.

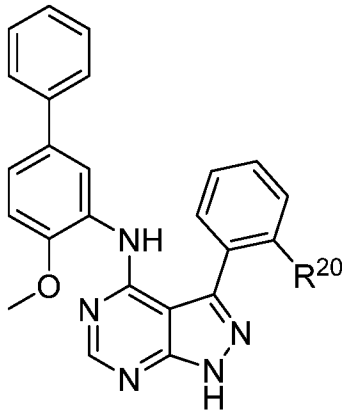
[0682] In embodiments, the compound is not  .

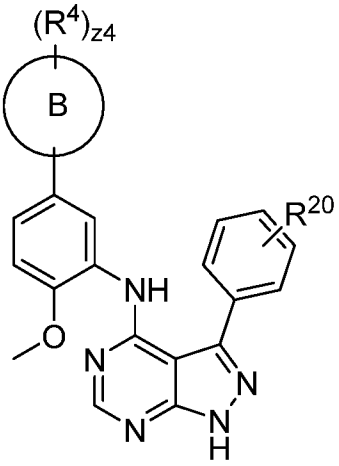
[0683] In embodiments, the compound is not  .

[0684] In embodiments, the compound is not  .

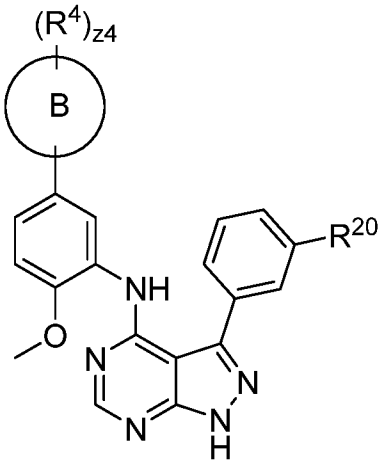
[0685] In embodiments, the compound is not  .

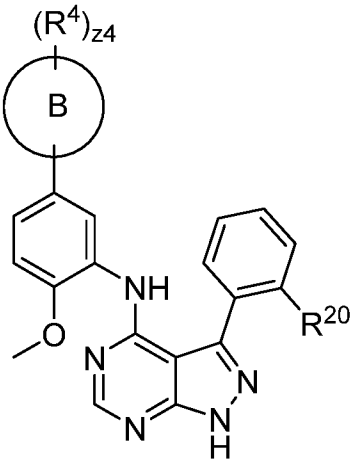
[0686] In embodiments, the compound is not  .

[0687] In embodiments, the compound is not  .

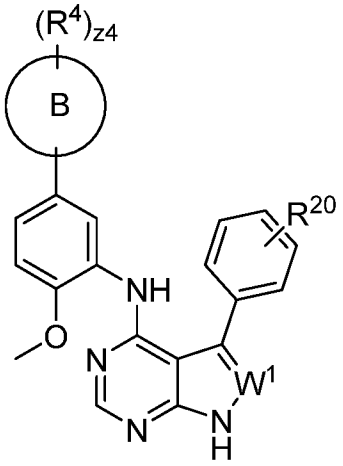


[0688] In embodiments, the compound is not . In embodiments, the compound is not .

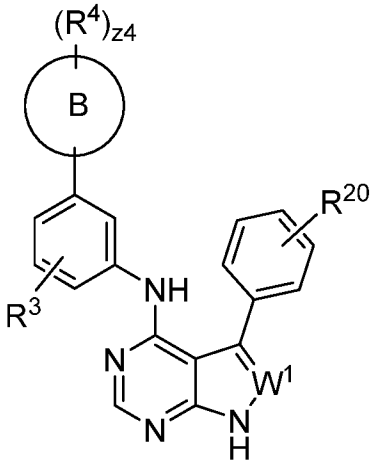




[0689] In embodiments, the compound is not .

[0690] In embodiments, the compound is not 

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[0691] In embodiments, the compound is not 

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[0692] In embodiments, the compound is not a compound described in WO 2011/149827. In embodiments, the compound is not a compound described in Lawhorn et al. (J. Med Chem. 2915, 58, 7431-7448). In embodiments, the compound is not a compound described in an example, table, or figure herein. In embodiments, the compound is not compound 184. In embodiments, the compound is not compound 185. In embodiments, the compound is not compound 187A. In embodiments, the compound is not compound 187B. In embodiments, the compound is not compound 186A. In embodiments, the compound is not compound 186B. In embodiments, the compound is not compound 188A. In embodiments, the compound is not compound 188B. In embodiments, the compound is not compound 190D. In embodiments, the compound is not compound 191A. In embodiments, the compound is not compound 5-001A. In embodiments, the compound is not compound 5-001B. In embodiments, the compound is not compound 5-004. In embodiments, the compound is not compound 184. In embodiments, the compound is not compound 185. In embodiments, the compound is not compound 189A. In embodiments, the compound is not compound 189B. In embodiments, the compound is not compound 190A. In embodiments, the compound is not compound 190C. In embodiments, the

compound is not compound191B. In embodiments, the compound is not compound 191D. In embodiments, the compound is not compound 191E. In embodiments, the compound is not compound 191F. In embodiments, the compound is not compound 191H. In embodiments, the compound is not compound 39A. In embodiments, the compound is not compound 39B. In embodiments, the compound is not compound 39C. In embodiments, the compound is not compound 39D. In embodiments, the compound is not compound 6. In embodiments, the compound is not compound 41A. In embodiments, the compound is not compound 41B. In embodiments, the compound is not compound 42. In embodiments, the compound is not compound 43. In embodiments, the compound is not compound 13. In embodiments, the compound is not compound 45A. In embodiments, the compound is not compound 45B. In embodiments, the compound is not compound 45C. In embodiments, the compound is not compound 45E. In embodiments, the compound is not compound 45D. In embodiments, the compound is not compound 45F. In embodiments, the compound is not compound 55A. In embodiments, the compound is not compound 53B. In embodiments, the compound is not compound 57A. In embodiments, the compound is not compound 57B. In embodiments, the compound is not compound 45A. In embodiments, the compound is not compound 45E. In embodiments, the compound is not compound 53B. In embodiments, the compound is not compound 55A. In embodiments, the compound is not compound 57A. In embodiments, the compound is not compound 57B. In embodiments, the compound is not compound 65. In embodiments, the compound is not compound 66A. In embodiments, the compound is not compound 66B. In embodiments, the compound is not compound 66C. In embodiments, the compound is not compound 57B. In embodiments, the compound is not compound 144A. In embodiments, the compound is not compound 144B. In embodiments, the compound is not compound 154A. In embodiments, the compound is not compound 45E. In embodiments, the compound is not compound 147. In embodiments, the compound is not compound 152. In embodiments, the compound is not compound 57A. In embodiments, the compound is not compound 154B. In embodiments, the compound is not compound 154C. In embodiments, the compound is not compound 153. In embodiments, the compound is not compound 155. In embodiments, the compound is not compound 170. In embodiments, the compound is not compound 171. In embodiments, the compound is not compound 172. In embodiments, the compound is not compound 173B. In embodiments, the compound is not compound 176. In embodiments, the compound is not compound 178. In embodiments, the compound is not compound 8-0089. In embodiments, the compound is not compound 8-090. In embodiments, the compound is not compound 8-091. In embodiments, the compound is not compound 8-092.

In embodiments, the compound is not compound 8-095. In embodiments, the compound is not compound 8-096. In embodiments, the compound is not compound 8-097. In embodiments, the compound is not compound 8-091. In embodiments, the compound is not compound 104A. In embodiments, the compound is not compound 104B.

[0693] In embodiments, W^1 is not N. In embodiments, W^1 is not CH.

[0694] In embodiments, R^1 is not hydrogen. In embodiments, R^1 is not substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is not substituted or unsubstituted phenyl. In embodiments, R^1 is not unsubstituted phenyl. In embodiments, R^1 is not substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is not unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is not substituted phenyl. In embodiments, R^1 is not substituted pyridyl. In embodiments, R^1 is not substituted cyclohexyl. In embodiments, R^1 is not substituted morpholinyl. In embodiments, R^1 is not substituted piperazinyl. In embodiments, R^1 is not substituted furanyl. In embodiments, R^1 is not substituted thiazolyl. In embodiments, R^1 is not substituted pyrazolyl. In embodiments, R^1 is not substituted thienyl. In embodiments, R^1 is not substituted pyrazinyl. In embodiments, R^1 is not substituted pyrimidinyl. In embodiments, R^1 is not substituted pyridazinyl. In embodiments, R^1 is not substituted triazinyl. In embodiments, R^1 is not substituted tetrazinyl. In embodiments, R^1 is not substituted tetrazolyl. In embodiments, R^1 is not substituted triazolyl. In embodiments, R^1 is not substituted quinolinyl. In embodiments, R^1 is not substituted isoquinolinyl. In embodiments, R^1 is not substituted quinazolinyl. In embodiments, R^1 is not substituted quinoxalinyl. In embodiments, R^1 is not substituted imidazolyl. In embodiments, R^1 is not substituted oxazolyl. In embodiments, R^1 is not substituted isoxazolyl. In embodiments, R^1 is not substituted thiazolyl. In embodiments, R^1 is not substituted piperidinyl. In embodiments, R^1 is not substituted thiomorpholinyl. In embodiments, R^1 is not substituted thianyl. In embodiments, R^1 is not substituted oxanyl. In embodiments, R^1 is not substituted tetrahydropuranyl. In embodiments, R^1 is not substituted dihydropuranyl. In embodiments, R^1 is not substituted dioxanyl. In embodiments, R^1 is not substituted pyrazolyl. In embodiments, R^1 is not substituted pyrrolyl. In embodiments, R^1 is not substituted thienyl. In embodiments, R^1 is not substituted benzofuranyl. In embodiments, R^1 is not substituted indolyl. In embodiments, R^1 is not substituted benzothienyl. In embodiments, R^1 is not substituted benzimidazolyl. In embodiments, R^1 is not substituted isobenzofuranyl. In embodiments, R^1 is not substituted isoindolyl. In embodiments, R^1 is not substituted benzo[c]thienyl. In embodiments, R^1 is not substituted purinyl. In embodiments, R^1 is not

substituted indazolyl. In embodiments, R^1 is not substituted benzoxazolyl. In embodiments, R^1 is not substituted benzisoxazolyl. In embodiments, R^1 is not substituted benzothiazolyl. In embodiments, R^1 is not substituted cyclopentyl. In embodiments, R^1 is not substituted cyclobutyl. In embodiments, R^1 is not substituted naphthyl. In embodiments, R^1 is not substituted 1-naphthyl. In embodiments, R^1 is not substituted 2-naphthyl. In embodiments, R^1 is not hydrogen. In embodiments, R^1 is not substituted 2-thienyl. In embodiments, R^1 is not substituted 3-thienyl. In embodiments, R^1 is not substituted 2-furanyl. In embodiments, R^1 is not substituted 3-furanyl. In embodiments, R^1 is not substituted 2-pyridyl. In embodiments, R^1 is not substituted 3-pyridyl. In embodiments, R^1 is not substituted 4-pyridyl. In embodiments, R^1 is not substituted 3-pyrazolyl. In embodiments, R^1 is not substituted 4-pyrazolyl. In embodiments, R^1 is not substituted 5- pyrazolyl. In embodiments, R^1 is not substituted 2-pyrrolyl. In embodiments, R^1 is not substituted 3-pyrrolyl.

[0695] In embodiments, R^1 is not R^{20}-substituted phenyl. In embodiments, R^1 is not R^{20}-substituted pyridyl. In embodiments, R^1 is not R^{20}-substituted cyclohexyl. In embodiments, R^1 is not R^{20}-substituted morpholinyl. In embodiments, R^1 is not R^{20}-substituted piperazinyl. In embodiments, R^1 is not R^{20}-substituted furanyl. In embodiments, R^1 is not R^{20}-substituted thiazolyl. In embodiments, R^1 is not R^{20}-substituted pyrazolyl. In embodiments, R^1 is not R^{20}-substituted thienyl. In embodiments, R^1 is not R^{20}-substituted pyrazinyl. In embodiments, R^1 is not R^{20}-substituted pyrimidinyl. In embodiments, R^1 is not R^{20}-substituted pyridazinyl. In embodiments, R^1 is not R^{20}-substituted triazinyl. In embodiments, R^1 is not R^{20}-substituted tetrazinyl. In embodiments, R^1 is not R^{20}-substituted tetrazolyl. In embodiments, R^1 is not R^{20}-substituted triazolyl. In embodiments, R^1 is not R^{20}-substituted quinolinyl. In embodiments, R^1 is not R^{20}-substituted isoquinolinyl. In embodiments, R^1 is not R^{20}-substituted quinazolinyl. In embodiments, R^1 is not R^{20}-substituted quinoxalinyl. In embodiments, R^1 is not R^{20}-substituted imidazolyl. In embodiments, R^1 is not R^{20}-substituted oxazolyl. In embodiments, R^1 is not R^{20}-substituted isoxazolyl. In embodiments, R^1 is not R^{20}-substituted thiazolyl. In embodiments, R^1 is not R^{20}-substituted piperidinyl. In embodiments, R^1 is not R^{20}-substituted thiomorpholinyl. In embodiments, R^1 is not R^{20}-substituted thianyl. In embodiments, R^1 is not R^{20}-substituted oxanyl. In embodiments, R^1 is not R^{20}-substituted tetrahydropuranyl. In embodiments, R^1 is not R^{20}-substituted dihydropuranyl. In embodiments, R^1 is not R^{20}-substituted dioxanyl. In embodiments, R^1 is not R^{20}-substituted pyrazolyl. In embodiments, R^1 is not R^{20}-substituted pyrrolyl. In embodiments, R^1 is not R^{20}-substituted thienyl. In embodiments, R^1 is not R^{20}-substituted benzofuranyl. In embodiments, R^1 is not R^{20}-substituted indolyl. In embodiments, R^1

is not R^{20}-substituted benzothienyl. In embodiments, R^1 is not R^{20}-substituted benzimidazolyl. In embodiments, R^1 is not R^{20}-substituted isobenzofuranyl. In embodiments, R^1 is not R^{20}-substituted isoindolyl. In embodiments, R^1 is not R^{20}-substituted benzo[c]thienyl. In embodiments, R^1 is not R^{20}-substituted purinyl. In embodiments, R^1 is not R^{20}-substituted indazolyl. In embodiments, R^1 is not R^{20}-substituted benzoxazolyl. In embodiments, R^1 is not R^{20}-substituted benzisoxazolyl. In embodiments, R^1 is not R^{20}-substituted benzothiazolyl. In embodiments, R^1 is not R^{20}-substituted cyclopentyl. In embodiments, R^1 is not R^{20}-substituted cyclobutyl. In embodiments, R^1 is not R^{20}-substituted naphthyl. In embodiments, R^1 is not R^{20}-substituted 1-naphthyl. In embodiments, R^1 is not R^{20}-substituted 2-naphthyl. In embodiments, R^1 is not R^{20}-substituted 2-thienyl. In embodiments, R^1 is not R^{20}-substituted 3-thienyl. In embodiments, R^1 is not R^{20}-substituted 2-furanyl. In embodiments, R^1 is not R^{20}-substituted 3-furanyl. In embodiments, R^1 is not R^{20}-substituted 2-pyridyl. In embodiments, R^1 is not R^{20}-substituted 3-pyridyl. In embodiments, R^1 is not R^{20}-substituted 4-pyridyl. In embodiments, R^1 is not R^{20}-substituted 3-pyrazolyl. In embodiments, R^1 is not R^{20}-substituted 4-pyrazolyl. In embodiments, R^1 is not R^{20}-substituted 5- pyrazolyl. In embodiments, R^1 is not R^{20}-substituted 2-pyrrolyl. In embodiments, R^1 is not R^{20}-substituted 3-pyrrolyl.

[0696] In embodiments, R^1 is not unsubstituted phenyl. In embodiments, R^1 is not unsubstituted pyridyl. In embodiments, R^1 is not unsubstituted cyclohexyl. In embodiments, R^1 is not unsubstituted morpholinyl. In embodiments, R^1 is not unsubstituted piperazinyl. In embodiments, R^1 is not unsubstituted furanyl. In embodiments, R^1 is not unsubstituted thiazolyl. In embodiments, R^1 is not unsubstituted pyrazolyl. In embodiments, R^1 is not unsubstituted thienyl. In embodiments, R^1 is not unsubstituted pyrazinyl. In embodiments, R^1 is not unsubstituted pyrimidinyl. In embodiments, R^1 is not unsubstituted pyridazinyl. In embodiments, R^1 is not unsubstituted triazinyl. In embodiments, R^1 is not unsubstituted tetrazinyl. In embodiments, R^1 is not unsubstituted tetrazolyl. In embodiments, R^1 is not unsubstituted triazolyl. In embodiments, R^1 is not unsubstituted quinolinyl. In embodiments, R^1 is not unsubstituted isoquinolinyl. In embodiments, R^1 is not unsubstituted quinazolinyl. In embodiments, R^1 is not unsubstituted quinoxalinyl. In embodiments, R^1 is not unsubstituted imidazolyl. In embodiments, R^1 is not unsubstituted oxazolyl. In embodiments, R^1 is not unsubstituted isoxazolyl. In embodiments, R^1 is not unsubstituted thiazolyl. In embodiments, R^1 is not unsubstituted piperidinyl. In embodiments, R^1 is not unsubstituted thiomorpholinyl. In embodiments, R^1 is not unsubstituted thianyl. In embodiments, R^1 is not unsubstituted oxanyl. In embodiments, R^1 is not unsubstituted tetrahydropuranyl. In embodiments, R^1 is not

unsubstituted dihydropuranyl. In embodiments, R^1 is not unsubstituted dioxanyl. In embodiments, R^1 is not unsubstituted pyrazolyl. In embodiments, R^1 is not unsubstituted pyrrolyl. In embodiments, R^1 is not unsubstituted thienyl. In embodiments, R^1 is not unsubstituted benzofuranyl. In embodiments, R^1 is not unsubstituted indolyl. In embodiments, R^1 is not unsubstituted benzothienyl. In embodiments, R^1 is not unsubstituted benzimidazolyl. In embodiments, R^1 is not unsubstituted isobenzofuranyl. In embodiments, R^1 is not unsubstituted isoindolyl. In embodiments, R^1 is not unsubstituted benzo[c]thienyl. In embodiments, R^1 is not unsubstituted purinyl. In embodiments, R^1 is not unsubstituted indazolyl. In embodiments, R^1 is not unsubstituted benzoxazolyl. In embodiments, R^1 is not unsubstituted benzisoxazolyl. In embodiments, R^1 is not unsubstituted benzothiazolyl. In embodiments, R^1 is not unsubstituted cyclopentyl. In embodiments, R^1 is not unsubstituted cyclobutyl. In embodiments, R^1 is not unsubstituted naphthyl. In embodiments, R^1 is not unsubstituted 1-naphthyl. In embodiments, R^1 is not unsubstituted 2-naphthyl. In embodiments, R^1 is not unsubstituted 2-thienyl. In embodiments, R^1 is not unsubstituted 3-thienyl. In embodiments, R^1 is not unsubstituted 2-furanyl. In embodiments, R^1 is not unsubstituted 3-furanyl. In embodiments, R^1 is not unsubstituted 2-pyridyl. In embodiments, R^1 is not unsubstituted 3-pyridyl. In embodiments, R^1 is not unsubstituted 4-pyridyl. In embodiments, R^1 is not unsubstituted 3-pyrazolyl. In embodiments, R^1 is not unsubstituted 4-pyrazolyl. In embodiments, R^1 is not unsubstituted 5- pyrazolyl. In embodiments, R^1 is not unsubstituted 2-pyrrolyl. In embodiments, R^1 is not unsubstituted 3-pyrrolyl.

[0697] In embodiments, R^1 is not substituted aryl. In embodiments, R^1 is not unsubstituted aryl. In embodiments, R^1 is not substituted C_6-C_{10} aryl. In embodiments, R^1 is not unsubstituted C_6-C_{10} aryl. In embodiments, R^1 is not substituted phenyl. In embodiments, R^1 is not unsubstituted phenyl. In embodiments, R^1 is not substituted heteroaryl. In embodiments, R^1 is not unsubstituted heteroaryl. In embodiments, R^1 is not substituted 5 to 10 membered heteroaryl. In embodiments, R^1 is not substituted 5 to 9 membered heteroaryl. In embodiments, R^1 is not unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^1 is not unsubstituted 5 to 9 membered heteroaryl. In embodiments, R^1 is not substituted 5 to 6 membered heteroaryl. In embodiments, R^1 is not unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is not substituted 9 membered heteroaryl. In embodiments, R^1 is not substituted 10 membered heteroaryl. In embodiments, R^1 is not unsubstituted 9 membered heteroaryl. In embodiments, R^1 is not unsubstituted 10 membered heteroaryl. In embodiments, R^1 is not substituted 5 membered heteroaryl. In embodiments, R^1 is not substituted 6 membered heteroaryl. In

embodiments, R^1 is not unsubstituted 5 membered heteroaryl. In embodiments, R^1 is not unsubstituted 6 membered heteroaryl.

[0698] In embodiments, R^1 is not substituted or unsubstituted pyrazolyl. In embodiments, R^1 is not substituted or unsubstituted pyridyl. In embodiments, R^1 is not substituted or unsubstituted imidazolyl. In embodiments, R^1 is not substituted or unsubstituted oxazolyl. In embodiments, R^1 is not substituted or unsubstituted isoxazolyl. In embodiments, R^1 is not substituted or unsubstituted thiazolyl. In embodiments, R^1 is not substituted or unsubstituted furanyl. In embodiments, R^1 is not substituted or unsubstituted pyrrolyl. In embodiments, R^1 is not substituted or unsubstituted thienyl. In embodiments, R^1 is not substituted pyrazolyl. In embodiments, R^1 is not substituted pyridyl. In embodiments, R^1 is not substituted imidazolyl. In embodiments, R^1 is not substituted oxazolyl. In embodiments, R^1 is not substituted isoxazolyl. In embodiments, R^1 is not substituted thiazolyl. In embodiments, R^1 is not substituted furanyl. In embodiments, R^1 is not substituted pyrrolyl. In embodiments, R^1 is not substituted thienyl.

[0699] In embodiments, R^1 is not unsubstituted pyrazolyl. In embodiments, R^1 is not unsubstituted pyridyl. In embodiments, R^1 is not unsubstituted imidazolyl. In embodiments, R^1 is not unsubstituted oxazolyl. In embodiments, R^1 is not unsubstituted isoxazolyl. In embodiments, R^1 is not unsubstituted thiazolyl. In embodiments, R^1 is not unsubstituted furanyl. In embodiments, R^1 is not unsubstituted pyrrolyl. In embodiments, R^1 is not unsubstituted thienyl.

[0700] In embodiments, R^1 is not methyl-substituted pyrazolyl. In embodiments, R^1 is not methyl-substituted pyridyl. In embodiments, R^1 is not methyl-substituted imidazolyl. In embodiments, R^1 is not methyl-substituted oxazolyl. In embodiments, R^1 is not methyl-substituted isoxazolyl. In embodiments, R^1 is not methyl-substituted thiazolyl. In embodiments, R^1 is not methyl-substituted furanyl. In embodiments, R^1 is not methyl-substituted pyrrolyl. In embodiments, R^1 is not methyl-substituted thienyl.

[0701] In embodiments, R^1 is not independently R^{20}-substituted or unsubstituted aryl or R^{20}-substituted or unsubstituted heteroaryl. In embodiments, R^1 is not independently R^{20}-substituted or unsubstituted phenyl or R^{20}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, X^1 is not –F,-Cl, -Br, or –I.

[0702] In embodiments, R^{20} is not $-C(O)CH_3$. In embodiments, R^{20} is not $-C(O)CH_2CH_3$. In embodiments, R^{20} is not $-C(O)CH(CH_3)_2$. In embodiments, R^{20} is not unsubstituted methyl. In embodiments, R^{20} is not $-C(O)N(CH_3)_2$. In embodiments, R^{20} is not –CN. In embodiments, R^{20}

is not unsubstituted methoxy. In embodiments, R^{20} is not unsubstituted tert-butyl. In embodiments, R^{20} is not –OH. In embodiments, R^{20} is not unsubstituted ethoxy. In embodiments, R^{20} is not $-N(CH_3)_2$. In embodiments, R^{20} is not –SH. In embodiments, R^{20} is not $-SCH_3$. In embodiments, R^{20} is not $–SCH_2CH_3$. In embodiments, R^{20} is not unsubstituted ethyl. In embodiments, R^{20} is not unsubstituted propyl. In embodiments, R^{20} is not unsubstituted isopropyl. In embodiments, R^{20} is not unsubstituted butyl. In embodiments, R^{20} is not unsubstituted isobutyl. In embodiments, R^{20} is not $–NH_2$. In embodiments, R^{20} is not $-NHCH_3$. In embodiments, R^{20} is not $–NHCH_2CH_3$. In embodiments, R^{20} is not $-N(CH_2CH_3)_2$. In embodiments, R^{20} is not $-N(CH_3)(CH_2CH_3)$. In embodiments, R^{20} is not halogen. In embodiments, R^{20} is not –F. In embodiments, R^{20} is not –Cl. In embodiments, R^{20} is not –I. In embodiments, R^{20} is not –Br. In embodiments, R^{20} is not $–C(O)NH_2$. In embodiments, R^{20} is not $-C(O)NHCH_3$. In embodiments, R^{20} is not $–C(O)NHCH_2CH_3$. In embodiments, R^{20} is not $-C(O)N(CH_2CH_3)_2$. In embodiments, R^{20} is not $-C(O)N(CH_3)(CH_2CH_3)$.

[0703] In embodiments, R^{20} is not independently oxo, halogen, $-CX^{20}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $–NHNH_2$, $–ONH_2$, $–NHC(O)NHNH_2$, $–NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{20}_3$, $-OCHX^{20}_2$, R^{21}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{21}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{21}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{21}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{21}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{21}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{20}

[0704] In embodiments, R^{21} is not independently oxo, halogen, $-CX^{21}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $–NHNH_2$, $–ONH_2$, $–NHC(O)NHNH_2$, $–NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{21}_3$, $-OCHX^{21}_2$, R^{22}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{22}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{22}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{22}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{22}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{22}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{21} is not –F, -Cl, -Br, or –I.

[0705] In embodiments, R^{22} is not independently oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0706] In embodiments, R^1 is not R^{20}-substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R^1 is not R^{20}-substituted aryl. In embodiments, R^1 is not unsubstituted aryl. In embodiments, R^1 is not R^{20}-substituted C_6-C_{10} aryl. In embodiments, R^1 is not unsubstituted C_6-C_{10} aryl. In embodiments, R^1 is not R^{20}-substituted phenyl. In embodiments, R^1 is not unsubstituted phenyl. In embodiments, R^1 is not R^{20}-substituted heteroaryl. In embodiments, R^1 is not unsubstituted heteroaryl. In embodiments, R^1 is not R^{20}-substituted 5 to 10 membered heteroaryl. In embodiments, R^1 is not R^{20}-substituted 5 to 9 membered heteroaryl. In embodiments, R^1 is not unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^1 is not unsubstituted 5 to 9 membered heteroaryl. In embodiments, R^1 is not R^{20}-substituted 5 to 6 membered heteroaryl. In embodiments, R^1 is not unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is not R^{20}-substituted 9 membered heteroaryl. In embodiments, R^1 is not R^{20}-substituted 10 membered heteroaryl. In embodiments, R^1 is not unsubstituted 9 membered heteroaryl. In embodiments, R^1 is not unsubstituted 10 membered heteroaryl. In embodiments, R^1 is not R^{20}-substituted 5 membered heteroaryl. In embodiments, R^1 is not R^{20}-substituted 6 membered heteroaryl. In embodiments, R^1 is not unsubstituted 5 membered heteroaryl. In embodiments, R^1 is not unsubstituted 6 membered heteroaryl.

[0707] In embodiments, R^1 is not R^{20}-substituted or unsubstituted pyrazolyl. In embodiments, R^1 is not R^{20}-substituted or unsubstituted pyridyl. In embodiments, R^1 is not R^{20}-substituted or unsubstituted imidazolyl. In embodiments, R^1 is not R^{20}-substituted or unsubstituted oxazolyl. In embodiments, R^1 is not R^{20}-substituted or unsubstituted isoxazolyl. In embodiments, R^1 is not R^{20}-substituted or unsubstituted thiazolyl. In embodiments, R^1 is not R^{20}-substituted or unsubstituted furanyl. In embodiments, R^1 is not R^{20}-substituted or unsubstituted pyrrolyl. In embodiments, R^1 is not R^{20}-substituted or unsubstituted thienyl. In embodiments, R^1 is not ortho-R^{20}-substituted phenyl. In embodiments, R^1 is not meta-R^{20}-substituted phenyl. In embodiments, R^1 is not para-R^{20}-substituted phenyl. In embodiments, R^1 is not ortho-halo-

substituted phenyl. In embodiments, R^1 is not ortho-F-substituted phenyl. In embodiments, R^1 is not meta-$C(O)CH_3$-substituted phenyl.

[0708] In embodiments, R^1 is not R^{20}-substituted pyrazolyl. In embodiments, R^1 is not R^{20}-substituted pyridyl. In embodiments, R^1 is not R^{20}-substituted imidazolyl. In embodiments, R^1 is not R^{20}-substituted oxazolyl. In embodiments, R^1 is not R^{20}-substituted isoxazolyl. In embodiments, R^1 is not R^{20}-substituted thiazolyl. In embodiments, R^1 is not R^{20}-substituted furanyl. In embodiments, R^1 is not R^{20}-substituted pyrrolyl. In embodiments, R^1 is not R^{20}-substituted thienyl. In embodiments, R^1 is not unsubstituted pyrazolyl. In embodiments, R^1 is not unsubstituted pyridyl. In embodiments, R^1 is not unsubstituted imidazolyl. In embodiments, R^1 is not unsubstituted oxazolyl. In embodiments, R^1 is not unsubstituted isoxazolyl. In embodiments, R^1 is not unsubstituted thiazolyl. In embodiments, R^1 is not unsubstituted furanyl. In embodiments, R^1 is not unsubstituted pyrrolyl. In embodiments, R^1 is not unsubstituted thienyl.

[0709] In embodiments, R^2 is not hydrogen.

[0710] In embodiments, R^3 is independently not halogen. In embodiments, R^3 is independently not $-CX^3_3$. In embodiments, R^3 is independently not $-CHX^3_2$. In embodiments, R^3 is independently not $-CH_2X^3$. In embodiments, R^3 is independently not $-OCX^3_3$. In embodiments, R^3 is independently not $-OCH_2X^3$. In embodiments, R^3 is independently not $-OCHX^3_2$. In embodiments, R^3 is independently not -CN. In embodiments, R^3 is independently not $-SO_{n3}R^{3D}$. In embodiments, R^3 is independently not $-SO_{v3}NR^{3A}R^{3B}$. In embodiments, R^3 is independently not $-NHC(O)NR^{3A}R^{3B}$. In embodiments, R^3 is independently not $-N(O)_{m3}$. In embodiments, R^3 is independently not $-NR^{3A}R^{3B}$. In embodiments, R^3 is independently not $-C(O)R^{3C}$. In embodiments, R^3 is independently not $-C(O)-OR^{3C}$. In embodiments, R^3 is independently not $-C(O)NR^{3A}R^{3B}$. In embodiments, R^3 is independently not $-OR^{3D}$. In embodiments, R^3 is independently not $-NR^{3A}SO_2R^{3D}$. In embodiments, R^3 is independently not $-NR^{3A}C(O)R^{3C}$. In embodiments, R^3 is independently not $-NR^{3A}C(O)OR^{3C}$. In embodiments, R^3 is independently not $-NR^{3A}OR^{3C}$. In embodiments, R^3 is independently not -OH. In embodiments, R^3 is independently not $-NH_2$. In embodiments, R^3 is independently not -COOH. In embodiments, R^3 is independently not $-CONH_2$. In embodiments, R^3 is independently not $-NO_2$. In embodiments, R^3 is independently not –SH. In embodiments, R^3 is independently not $–SO_2NR^{3A}R^{3B}$. In embodiments, R^3 is independently not meta-OCH_3 (relative to the bond to the remainder to the amine bonded to the pyrazolopyrimidine or

pyrrolopyrimidine). In embodiments, R^3 is independently not ortho unsubstituted phenyl (relative to the bond to the remainder to the amine bonded to the pyrazolopyrimidine or pyrrolopyrimidine).

[0711] In embodiments, R^3 is independently not substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^3 is independently not substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^3 is independently not unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^3 is independently not substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^3 is independently not substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^3 is independently not unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^3 is independently not substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^3 is independently not substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^3 is independently not unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^3 is independently not substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^3 is independently not substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^3 is independently not unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^3 is independently not substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^3 is independently not substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^3 is independently not unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^3 is independently not substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^3 is independently not substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^3 is independently not unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0712] In embodiments, R^{3A} is independently not hydrogen. In embodiments, R^{3A} is independently not $-CX^{3A}_3$. In embodiments, R^{3A} is independently not $-CHX^{3A}_2$. In embodiments, R^{3A} is independently not $-CH_2X^{3A}$. In embodiments, R^{3A} is independently not -CN. In embodiments, R^{3A} is independently not -COOH. In embodiments, R^{3A} is independently not $-CONH_2$.

[0713] In embodiments, R^{3A} is independently not substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3A} is independently not substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3A} is independently not unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3A} is independently not substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3A} is independently not substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3A} is independently not unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3A} is independently not substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3A} is independently not substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3A} is independently not unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3A} is independently not substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently not substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently not unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently not substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3A} is independently not substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3A} is independently not unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3A} is independently not substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently not substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently not unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3A} is independently not unsubstituted methyl. In embodiments, R^{3A} is independently not unsubstituted ethyl. In embodiments, R^{3A} is independently not unsubstituted propyl. In embodiments, R^{3A} is independently not unsubstituted isopropyl. In embodiments, R^{3A} is independently not unsubstituted tert-butyl.

[0714] In embodiments, R^{3B} is independently not hydrogen. In embodiments, R^{3B} is independently not $-CX^{3B}_3$. In embodiments, R^{3B} is independently not $-CHX^{3B}_2$. In embodiments, R^{3B} is independently not $-CH_2X^{3B}$. In embodiments, R^{3B} is independently not -CN. In embodiments, R^{3B} is independently not -COOH. In embodiments, R^{3B} is independently not $-CONH_2$.

[0715] In embodiments, R^{3B} is independently not substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3B} is independently not substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3B} is independently not unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3B} is independently not substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3B} is independently not substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3B} is independently not unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3B} is independently not substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3B} is independently not substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3B} is independently not unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3B} is independently not substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently not substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently not unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently not substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3B} is independently not substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3B} is independently not unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3B} is independently not substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently not substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently not unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently not unsubstituted methyl. In embodiments, R^{3B} is independently not unsubstituted ethyl. In embodiments, R^{3B} is independently not unsubstituted propyl. In embodiments, R^{3B} is independently not unsubstituted isopropyl. In embodiments, R^{3B} is independently not unsubstituted tert-butyl.

[0716] In embodiments, R^{3C} is independently not hydrogen. In embodiments, R^{3C} is independently not $-CX^{3C}_3$. In embodiments, R^{3C} is independently not $-CHX^{3C}_2$. In embodiments, R^{3C} is independently not $-CH_2X^{3C}$. In embodiments, R^{3C} is independently not -CN. In embodiments, R^{3C} is independently not -COOH. In embodiments, R^{3C} is independently not $-CONH_2$.

[0717] In embodiments, R^{3C} is independently not substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3C} is independently not substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3C} is independently not unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3C} is independently not substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3C} is independently not substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3C} is independently not unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3C} is independently not substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3C} is independently not substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3C} is independently not unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3C} is independently not substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently not substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently not unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently not substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3C} is independently not substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3C} is independently not unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3C} is independently not substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently not substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently not unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3C} is independently not unsubstituted methyl. In embodiments, R^{3C} is independently not unsubstituted ethyl. In embodiments, R^{3C} is independently not unsubstituted propyl. In embodiments, R^{3C} is independently not unsubstituted isopropyl. In embodiments, R^{3C} is independently not unsubstituted tert-butyl.

[0718] In embodiments, R^{3D} is independently not hydrogen. In embodiments, R^{3D} is independently not $-CX^{3D}_3$. In embodiments, R^{3D} is independently not $-CHX^{3D}_2$. In embodiments, R^{3D} is independently not $-CH_2X^{3D}$. In embodiments, R^{3D} is independently not -CN. In embodiments, R^{3D} is independently not -COOH. In embodiments, R^{3D} is independently not $-CONH_2$.

[0719] In embodiments, R^{3D} is independently not substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3D} is independently not substituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3D} is independently not unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4). In embodiments, R^{3D} is independently not substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3D} is independently not substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3D} is independently not unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{3D} is independently not substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3D} is independently not substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3D} is independently not unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6). In embodiments, R^{3D} is independently not substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently not substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently not unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently not substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3D} is independently not substituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3D} is independently not unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl). In embodiments, R^{3D} is independently not substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently not substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently not unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3D} is independently not unsubstituted methyl. In embodiments, R^{3D} is independently not unsubstituted ethyl. In embodiments, R^{3D} is independently not unsubstituted propyl. In embodiments, R^{3D} is independently not unsubstituted isopropyl. In embodiments, R^{3D} is independently not unsubstituted tert-butyl.

[0720] In embodiments, R^3 is independently not hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, R^{26}-substituted or unsubstituted alkyl, R^{26}-substituted or unsubstituted heteroalkyl, R^{26}-substituted or unsubstituted cycloalkyl, R^{26}-substituted or unsubstituted heterocycloalkyl, R^{26}-substituted or unsubstituted aryl, or R^{26}-

substituted or unsubstituted heteroaryl. In embodiments, R^3 is independently not halogen, $-CX^3_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^3_3$, $-OCHX^3_2$, R^{26}-substituted or unsubstituted alkyl, R^{26}-substituted or unsubstituted heteroalkyl, R^{26}-substituted or unsubstituted cycloalkyl, R^{26}-substituted or unsubstituted heterocycloalkyl, R^{26}-substituted or unsubstituted aryl, or R^{26}-substituted or unsubstituted heteroaryl. In embodiments, R^3 is independently not halogen, $-CX^3_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^3_3$, $-OCHX^3_2$, R^{26}-substituted or unsubstituted C_1-C_8 alkyl, R^{26}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26}-substituted or unsubstituted phenyl, or R^{26}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, X^3 is not –F,-Cl, -Br, or –I. In embodiments, R^3 is independently not hydrogen. In embodiments, R^3 is independently not methyl. In embodiments, R^3 is independently not ethyl.

[0721] In embodiments, R^{26} is independently not oxo, halogen, $-CX^{26}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{26}_3$, $-OCHX^{26}_2$, R^{27}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{26} is not –F, -Cl, -Br, or –I.

[0722] In embodiments, R^{27} is independently not oxo, halogen, $-CX^{27}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{27}_3$, $-OCHX^{27}_2$, R^{28}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{28}-substituted

or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{27} is not –F, -Cl, -Br, or –I.

[0723] In embodiments, R^{3A} is independently not hydrogen, $-CX^{3A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{3A}_2$, $-CH_2X^{3A}$, R^{26A}-substituted or unsubstituted alkyl, R^{26A}-substituted or unsubstituted heteroalkyl, R^{26A}-substituted or unsubstituted cycloalkyl, R^{26A}-substituted or unsubstituted heterocycloalkyl, R^{26A}-substituted or unsubstituted aryl, or R^{26A}-substituted or unsubstituted heteroaryl. In embodiments, R^{3A} is independently not hydrogen, $-CX^{3A}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{3A}_2$, $-CH_2X^{3A}$, R^{26A}-substituted or unsubstituted C_1-C_8 alkyl, R^{26A}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26A}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26A}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26A}-substituted or unsubstituted phenyl, or R^{26A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, X^{3A} is not –F, -Cl, -Br, or –I. In embodiments, R^{3A} is independently not hydrogen. In embodiments, R^{3A} is independently not methyl. In embodiments, R^{3A} is independently not ethyl.

[0724] In embodiments, R^{26A} is independently not oxo, halogen, $-CX^{26A}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{26A}_3$, $-OCHX^{26A}_2$, R^{27A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{26A} is not –F, -Cl, -Br, or –I.

[0725] In embodiments, R^{27A} is independently not oxo, halogen, $-CX^{27A}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{27A}_3$, $-OCHX^{27A}_2$, R^{28A}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28A}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28A}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{28A}-

substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{27A} is not –F, -Cl, -Br, or –I.

[0726] In embodiments, R^{3B} is independently not hydrogen, $-CX^{3B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{3B}_2$, $-CH_2X^{3B}$, R^{26B}-substituted or unsubstituted alkyl, R^{26B}-substituted or unsubstituted heteroalkyl, R^{26B}-substituted or unsubstituted cycloalkyl, R^{26B}-substituted or unsubstituted heterocycloalkyl, R^{26B}-substituted or unsubstituted aryl, or R^{26B}-substituted or unsubstituted heteroaryl. In embodiments, R^{3B} is independently not hydrogen, $-CX^{3B}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{3B}_2$, $-CH_2X^{3B}$, R^{26B}-substituted or unsubstituted C_1-C_8 alkyl, R^{26B}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26B}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26B}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26B}-substituted or unsubstituted phenyl, or R^{26B}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, X^{3B} is not –F, -Cl, -Br, or –I. In embodiments, R^{3B} is independently not hydrogen. In embodiments, R^{3B} is independently not methyl. In embodiments, R^{3B} is independently not ethyl.

[0727] In embodiments, R^{26B} is independently not oxo, halogen, $-CX^{26B}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{26B}_3$, $-OCHX^{26B}_2$, R^{27B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{26B} is not –F, -Cl, -Br, or –I.

[0728] In embodiments, R^{27B} is independently not oxo, halogen, $-CX^{27B}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{27B}_3$, $-OCHX^{27B}_2$, R^{28B}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28B}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{28B}-

substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{27B} is not –F, -Cl, -Br, or –I.

[0729] In embodiments, R^{3C} is independently not hydrogen, $-CX^{3C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{3C}_2$, $-CH_2X^{3C}$, R^{26C}-substituted or unsubstituted alkyl, R^{26C}-substituted or unsubstituted heteroalkyl, R^{26C}-substituted or unsubstituted cycloalkyl, R^{26C}-substituted or unsubstituted heterocycloalkyl, R^{26C}-substituted or unsubstituted aryl, or R^{26C}-substituted or unsubstituted heteroaryl. In embodiments, R^{3C} is independently not hydrogen, $-CX^{3C}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{3C}_2$, $-CH_2X^{3C}$, R^{26C}-substituted or unsubstituted C_1-C_8 alkyl, R^{26C}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26C}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26C}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26C}-substituted or unsubstituted phenyl, or R^{26C}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, X^{3C} is not –F, -Cl, -Br, or –I. In embodiments, R^{3C} is independently not hydrogen. In embodiments, R^{3C} is independently not methyl. In embodiments, R^{3C} is independently not ethyl.

[0730] In embodiments, R^{26C} is independently not oxo, halogen, $-CX^{26C}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{26C}_3$, $-OCHX^{26C}_2$, R^{27C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{26C} is not –F, -Cl, -Br, or –I.

[0731] In embodiments, R^{27C} is independently not oxo, halogen, $-CX^{27C}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{27C}_3$, $-OCHX^{27C}_2$, R^{28C}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28C}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28C}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{28C}-

substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{27C} is not –F, -Cl, -Br, or –I.

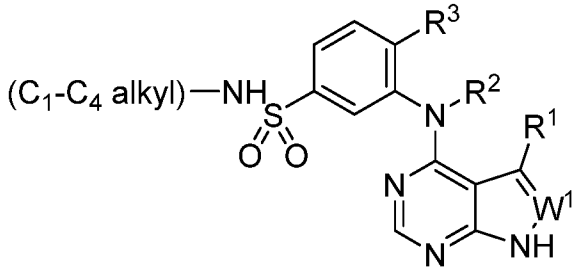
[0732] In embodiments, R^{3D} is independently not hydrogen, $-CX^{3D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{3D}_2$, $-CH_2X^{3D}$, R^{26D}-substituted or unsubstituted alkyl, R^{26D}-substituted or unsubstituted heteroalkyl, R^{26D}-substituted or unsubstituted cycloalkyl, R^{26D}-substituted or unsubstituted heterocycloalkyl, R^{26D}-substituted or unsubstituted aryl, or R^{26D}-substituted or unsubstituted heteroaryl. In embodiments, R^{3D} is independently not hydrogen, $-CX^{3D}_3$, -CN, -COOH, $-CONH_2$, $-CHX^{3D}_2$, $-CH_2X^{3D}$, R^{26D}-substituted or unsubstituted C_1-C_8 alkyl, R^{26D}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{26D}-substituted or unsubstituted C_3-C_8 cycloalkyl, R^{26D}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{26D}-substituted or unsubstituted phenyl, or R^{26D}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, X^{3D} is not –F, -Cl, -Br, or –I. In embodiments, R^{3D} is independently not hydrogen. In embodiments, R^{3D} is independently not methyl. In embodiments, R^{3D} is independently not ethyl.

[0733] In embodiments, R^{26D} is independently not oxo, halogen, $-CX^{26D}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{26D}_3$, $-OCHX^{26D}_2$, R^{27D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{27D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{27D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{27D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{27D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{27D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{26D} is not –F, -Cl, -Br, or –I.

[0734] In embodiments, R^{27D} is independently not oxo, halogen, $-CX^{27D}_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCX^{27D}_3$, $-OCHX^{27D}_2$, R^{28D}-substituted or unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), R^{28D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{28D}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), R^{28D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{28D}-substituted or unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or R^{28D}-

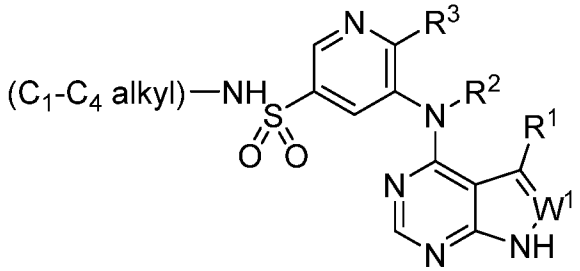
substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, X^{27D} is not –F, -Cl, -Br, or –I.

[0735] In embodiments, R^{28}, R^{28A}, R^{28B}, R^{28C}, and R^{28D} are independently not oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl (e.g., C_1-C_8, C_1-C_6, or C_1-C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10}, C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).



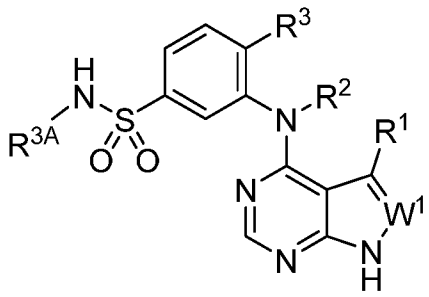
[0736] In embodiments, the compound is not

wherein R^1, R^2, R^3, and W^1 are as described herein, including in an embodiment.

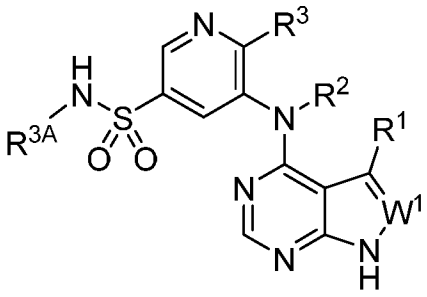


[0737] In embodiments, the compound is not

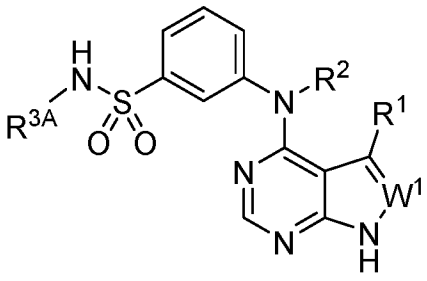
wherein R^1, R^2, R^3, and W^1 are as described herein, including in an embodiment.



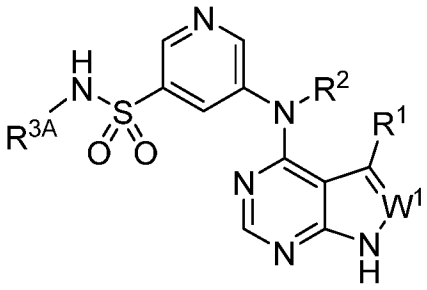
[0738] In embodiments, the compound is not wherein R^1, R^2, R^3, R^{3A}, and W^1 are as described herein, including in an embodiment.



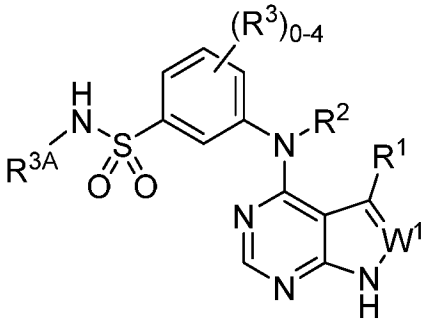
[0739] In embodiments, the compound is not wherein R^1, R^2, R^3, R^{3A}, and W^1 are as described herein, including in an embodiment.



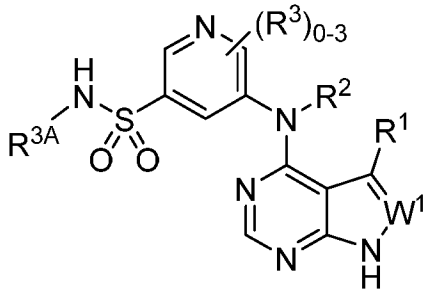
[0740] In embodiments, the compound is not wherein R^1, R^2, R^3, R^{3A}, and W^1 are as described herein, including in an embodiment.



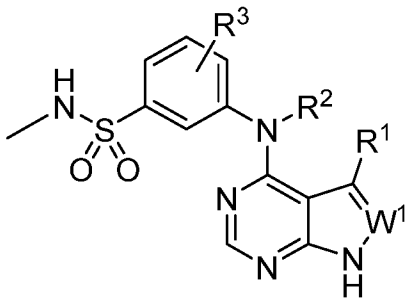
[0741] In embodiments, the compound is not wherein R^1, R^2, R^3, R^{3A}, and W^1 are as described herein, including in an embodiment.



[0742] In embodiments, the compound is not wherein R^1, R^2, R^3, R^{3A}, and W^1 are as described herein, including in an embodiment.



[0743] In embodiments, the compound is not wherein R^1, R^2, R^3, R^{3A}, and W^1 are as described herein, including in an embodiment.



[0744] In embodiments, the compound is not wherein R^1, R^2, R^3, R^{3A}, and W^1 are as described herein, including in an embodiment.

C. Pharmaceutical Compositions

[0745] In another aspect is provided a pharmaceutical composition including a pharmaceutically acceptable excipient and a compound, or pharmaceutically acceptable salt thereof, as described herein, including embodiments.

[0746] In embodiments, the pharmaceutical composition includes the active ingredient (e.g., compound described herein or pharmaceutically acceptable salt thereof) in a therapeutically effective amount, *i.e.*, in an amount effective to achieve its intended purpose. In embodiments, the therapeutically effective amount is administered in one dose. In embodiments, the therapeutically effective amount is administered in divided doses that combine to provide a therapeutically effective amount. In embodiments, the therapeutically effective amount is administered in a single dose that is administered multiple times over the course of a treatment. The actual amount effective for a particular application will depend, *inter alia,* on the condition being treated. When administered in methods to treat a disease, such compositions will contain an amount of active ingredient effective to achieve the desired result, e.g., inhibiting cell proliferation. In embodiments, the pharmaceutical composition includes an anti-cancer agent (i.e., an anti-cancer agent in addition to the compound described herein that is included in the pharmaceutical composition). In embodiments, the pharmaceutical composition includes an anti-cancer agent in an effective amount. In embodiments, the anti-cancer agent is an EGFR

modulator, HER2 modulator, HER3 modulator, HER4 modulator, c-MET modulator, PI3K modulator, MEK modulator, MAPK modulator, RAF modulator, BRAF modulator, AKT modulator, RAS modulator, KRAS modulator, heregulin modulator, neuregulin modulator, or mTOR modulator. In embodiments, the anti-cancer agent is lapatinib, vemurafenib, or selumetinib. In embodiments, the anti-cancer agent is trastuzumab, trastuzumab emtansine, pertuzumab, tamoxifen, gefitinib, erlotinib, afatinib, brigatinib, icotinib, cetuximab, panitumumab, zalutumumab, nimotuzumab, matuzumab, or lapatinib.

D. Methods of Treatment

[0747] In an aspect is provided a method of treating cancer in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein.

[0748] In embodiments, the cancer is lung cancer, non-small cell lung cancer, ovarian cancer, breast cancer, triple negative breast cancer, melanoma, head and neck cancer, colon cancer, gatric cancer, glioma, anal cancer, stomach cancer, uterine cancer, uterine serous endometrial carcinoma, salivary duct carcinoma, testicular cancer, esophageal cancer, or glioblastoma multiforme. In embodiments, the cancer is lung cancer, breast cancer, colorectal carcinoma, head and neck cancer, uveal melanoma, gastric cancer, ovarian cancer, prostate cancer, or bladder cancer. In embodiments, the cancer is lung cancer. In embodiments, the cancer is breast cancer. In embodiments, the cancer is colorectal carcinoma. In embodiments, the cancer is head and neck cancer. In embodiments, the cancer is uveal melanoma. In embodiments, the cancer is gastric cancer. In embodiments, the cancer is ovarian cancer. In embodiments, the cancer is prostate cancer. In embodiments, the cancer is bladder cancer. In embodiments, the cancer possesses an activating mutation in EGFR. In embodiments, the cancer possesses an activating mutation in HER2. In embodiments, the cancer possesses an activating mutation in HER3. In embodiments, the cancer possesses an activating mutation in HER4. The cancer is dependent on neuregulin signaling through HER2/HER3. In embodiments, the cancer overexpresses neuregulin. In embodiments, the cancer possesses a drug resistance mutation in EGFR. In embodiments, the cancer possesses a drug resistance mutation in HER2. In embodiments, the cancer possesses a drug resistance mutation in HER3. In embodiments, the cancer possesses a drug resistance mutation in HER4. In embodiments, the cancer is dependent on neuregulin signaling through HER2/HER3.

[0749] In embodiments, the cancer is resistant to a HER2 inhibitor. In embodiments, the cancer is resistant to an EGFR inhibitor. In embodiments, the cancer is a HER2 overexpressing cancer. In embodiments, the cancer is a HER2 positive cancer. In embodiments, the cancer is HER2-positive metastatic breast cancer. In embodiments, the cancer is a HER3 overexpressing cancer. In embodiments, the cancer is a HER2/HER3 overexpressing cancer. In embodiments, the cancer is a HER2 overexpressing breast cancer. In embodiments, the cancer is resistant to treatment with lapatinib. In embodiments, the cancer is resistant to treatment with vemurafenib. In embodiments, the cancer is resistant to treatment with selumetinib. In embodiments, the cancer is resistant to treatment with trastuzumab. In embodiments, the cancer is resistant to treatment with trastuzumab emtansine. In embodiments, the cancer is resistant to treatment with pertuzumab. In embodiments, the cancer is resistant to treatment with tamoxifen. In embodiments, the cancer is resistant to treatment with gefitinib. In embodiments, the cancer is resistant to treatment with erlotinib. In embodiments, the cancer is resistant to treatment with afatinib. In embodiments, the cancer is resistant to treatment with brigatinib. In embodiments, the cancer is resistant to treatment with icotinib. In embodiments, the cancer is resistant to treatment with cetuximab. In embodiments, the cancer is resistant to treatment with panitumumab. In embodiments, the cancer is resistant to treatment with zalutumumab. In embodiments, the cancer is resistant to treatment with nimotuzumab. In embodiments, the cancer is resistant to treatment with matuzumab. In embodiments, the cancer is resistant to treatment with lapatinib. In embodiments, the cancer is resistant to treatment with trastuzumab emtansine. In embodiments, a cancer that is resistant to treatment with a drug is less inhibited than after the first dose of the drug to the same cancer, less inhibited than a treatment-naïve form of the cancer, less inhibited than treatment with a therapeutically effective amount of a compound described herein, less inhibited than the average cancer of the same type, or not inhibited by the drug. In embodiments, inhibition of a cancer is inhibition of cell growth. In embodiments, inhibition of a cancer is inhibition of cell proliferation.

[0750] In embodiments, the therapeutically effective amount is administered in one dose. In embodiments, the therapeutically effective amount is administered in divided doses that combine to provide a therapeutically effective amount. In embodiments, the therapeutically effective amount is administered in a single dose that is administered multiple times over the course of a treatment.

[0751] In another aspect is provided, a method of treating a disease associated with HER2 activity, wherein the method includes administering a compound described herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0752] In another aspect is provided, a method of treating a disease associated with EGFR activity, wherein the method includes administering a compound described herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0753] In embodiments, the method includes administering a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, described herein.

[0754] In embodiments, the method includes administering a second agent (e.g., therapeutic agent). In embodiments, the second agent is an anti-cancer agent. In embodiments, the anti-cancer agent is an EGFR modulator, HER2 modulator, HER3 modulator, HER4 modulator, c-MET modulator, PI3K modulator, MEK modulator, MAPK modulator, RAF modulator, BRAF modulator, AKT modulator, RAS modulator, KRAS modulator, heregulin modulator, neuregulin modulator, or mTOR modulator. In embodiments, the anti-cancer agent is lapatinib, vemurafenib, or selumetinib. In embodiments, the anti-cancer agent is lapatinib, vemurafenib, or selumetinib. In embodiments, the anti-cancer agent is trastuzumab, trastuzumab emtansine, pertuzumab, tamoxifen, gefitinib, erlotinib, afatinib, brigatinib, icotinib, cetuximab, panitumumab, zalutumumab, nimotuzumab, matuzumab, or lapatinib. In embodiments, the proteins described above are human proteins.

[0755] In an aspect is provided a method of treating a disease associated with EGFR activity, HER2 activity, HER3 activity, HER4 activity, c-MET activity, PI3K activity, MEK activity, MAPK activity, RAF activity, BRAF activity, AKT activity, RAS activity, KRAS activity, heregulin activity, or neuregulin activity in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof. In embodiments, the proteins described above are human proteins.

[0756] In an aspect is provided a method of treating psoriasis, eczema, or atherosclerosis, in a patient in need of such treatment, the method including administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, described herein.

[0757] In another aspect a compound described herein is provided for use as a medicament.

E. **Methods of Inhibiting ERBB**

[0758] In an aspect is provided a method of inhibiting an ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) activity, the method including contacting ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) with an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0759] In embodiments, the ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) is a human ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4). In embodiments, ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) is in an active conformation. In embodiments, ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) is in an ERRB heterodimer. In embodiments the compound contacts ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) and is covalently bound to ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4). In embodiments the compound contacts ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) and is not covalently bound to ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4). In embodiments the compound irreversibly inhibits ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4). In embodiments the compound reversibly inhibits ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4).

F. **Methods of Inhibiting HER2**

[0760] In an aspect is provided a method of inhibiting HER2 activity, the method including contacting HER2 with an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0761] In embodiments, the HER2 is a human HER2. In embodiments, HER2 is in an active conformation. In embodiments, HER2 is in a HER2-HER3 heterodimer. In embodiments the compound contacts HER2 and is covalently bound to HER2. In embodiments the compound contacts HER2 and is not covalently bound to HER2. In embodiments the compound irreversibly inhibits HER2. In embodiments the compound reversibly inhibits HER2.

G. **Methods of Inhibiting EGFR**

[0762] In an aspect is provided a method of inhibiting EGFR activity, the method including contacting EGFR with an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

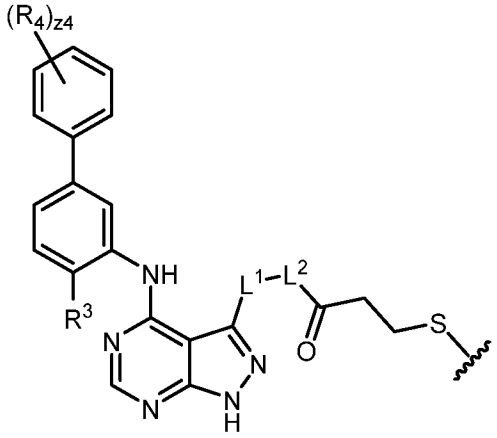
[0763] In embodiments, the EGFR is a human EGFR. In embodiments, EGFR is in an active conformation. In embodiments the compound contacts EGFR and is covalently bound to EGFR.

In embodiments the compound contacts EGFR and is not covalently bound to EGFR. In embodiments the compound irreversibly inhibits EGFR. In embodiments the compound irreversibly inhibits EGFR. In embodiments the compound reversibly inhibits EGFR.

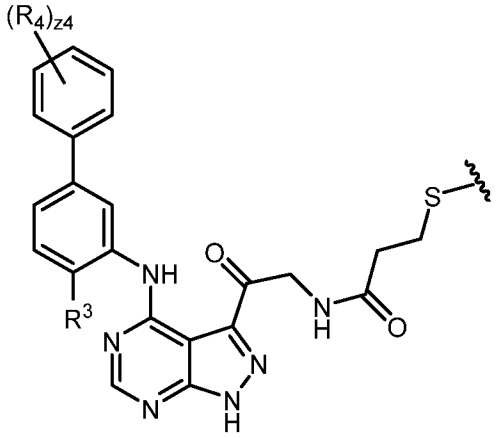
H. Modified proteins

[0764] In an aspect is provided an EGFR protein covalently bonded to a compound (e.g., a compound described herein, an EGFR inhibitor). In embodiments, the compound (or a fragment thereof) is covalently bonded to a cysteine of the protein. In embodiments the EGFR includes a mutation corresponding to L858R of human EGFR. In embodiments the EGFR includes a mutation corresponding to T790M of human EGFR. In embodiments, the compound (or a fragment thereof) is covalently bonded to C797 of human EGFR. In embodiments, the compound (or a fragment thereof) is covalently bonded to a residue corresponding to C797 of human EGFR.

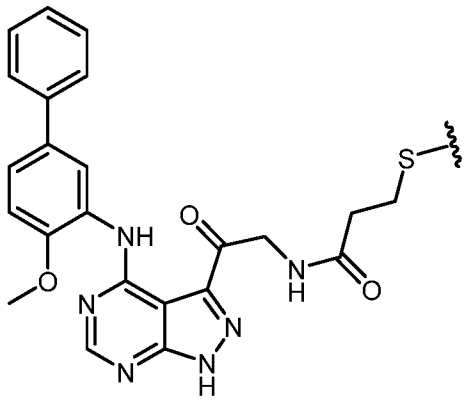
[0765] In embodiments, the EGFR protein covalently bonded to a compound described herein is the product of a reaction between the EGFR protein and compound described herein. It will be understood that the covalently bonded EGFR protein and compound described herein are the remnants of the reactant EGFR protein and compound, wherein each reactant now participates in the covalent bond between the EGFR protein and compound. In embodiments of the covalently bonded EGFR protein and compound described herein, the remnant of the substituted formula I is a linker including a covalent bond between the EGFR protein and the remainder of the compound described herein. It will be understood by a person of ordinary skill in the art that when a EGFR protein is covalently bonded to a compound described herein, the compound described herein forms a remnant of the pre-reacted compound wherein a bond connects the remnant of the compound to the remnant of the EGFR protein (e.g., amino acid corresponding to C797 of human EGFR). As a non-limiting example, the EGFR protein covalently bonded to a compound (e.g., a compound described herein) may have the formula:



, wherein S is the sulfur of a EGFR protein cysteine (e.g., corresponding to C797 of human EGFR), which is bonded to the remainder of the EGFR protein, "〰" is the attachment point to the EGFR protein, and wherein R^3, R^4, L^1, L^2, and z4 are as described herein. As a non-limiting example, the EGFR protein covalently bonded to a compound (e.g., a compound described herein) may have the formula:



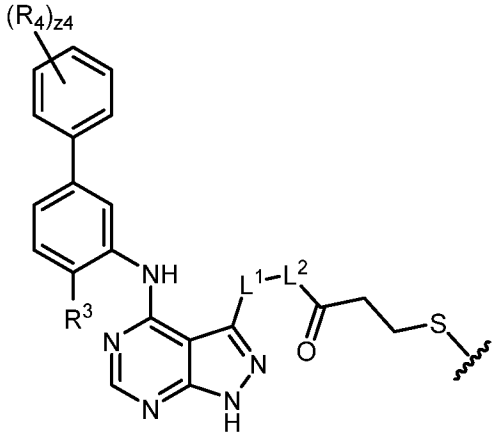
, wherein S is the sulfur of a EGFR protein cysteine (e.g., corresponding to C797 of human EGFR), which is bonded to the remainder of the EGFR protein, "〰" is the attachment point to the EGFR protein, and wherein R^3, R^4, and z4 are as described herein. As a non-limiting example, the EGFR protein covalently bonded to a compound (e.g., a compound described herein) may have the formula:



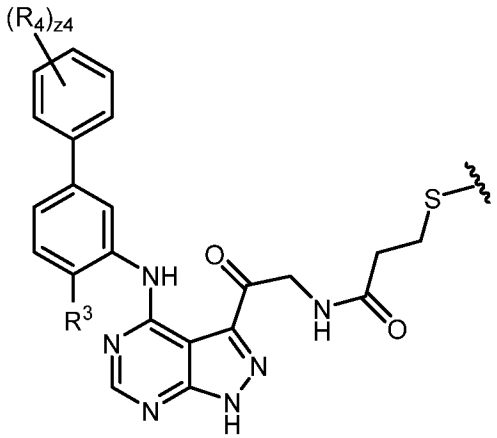
, wherein S is the sulfur of a EGFR protein cysteine (e.g., corresponding to C797 of human EGFR), which is bonded to the remainder of the EGFR protein, and "〰" is the attachment point to the EGFR protein.

[0766] In an aspect is provided a HER2 protein covalently bonded to a compound (e.g., a compound described herein, a HER2 inhibitor). In embodiments, the compound (or a fragment thereof) is covalently bonded to a cysteine of the protein. In embodiments, the compound (or a fragment thereof) is covalently bonded to C805 of human HER2. In embodiments, the compound (or a fragment thereof) is covalently bonded to a residue corresponding to C805 of human HER2.

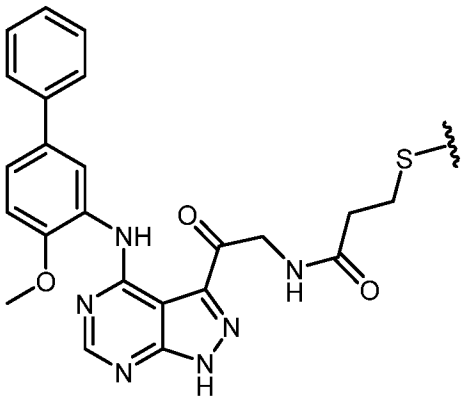
[0767] In embodiments, the HER2 protein covalently bonded to a compound described herein is the product of a reaction between the HER2 protein and compound described herein. It will be understood that the covalently bonded HER2 protein and compound described herein are the remnants of the reactant HER2 protein and compound, wherein each reactant now participates in the covalent bond between the HER2 protein and compound. In embodiments of the covalently bonded HER2 protein and compound described herein, the remnant of the substituted formula I is a linker including a covalent bond between the HER2 protein and the remainder of the compound described herein. It will be understood by a person of ordinary skill in the art that when a HER2 protein is covalently bonded to a compound described herein, the compound forms a remnant of the pre-reacted compound wherein a bond connects the remnant of the compound to the remnant of the HER2 protein (e.g., amino acid corresponding to C805 of human HER2. As a non-limiting example, the HER2 protein covalently bonded to a compound (e.g., a compound described herein) may have the formula:



, wherein S is the sulfur of a HER2 protein cysteine (e.g., corresponding to C805 of human HER2), which is bonded to the remainder of the HER2 protein, "〰" is the attachment point to the HER2 protein, and wherein R^3, R^4, L^1, L^2, and z4 are as described herein. As a non-limiting example, the HER2 protein covalently bonded to a compound (e.g., a compound described herein) may have the formula:



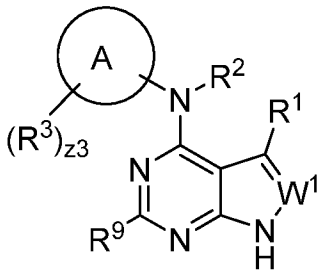
, wherein S is the sulfur of a HER2 protein cysteine (e.g., corresponding to C805 of human HER2), which is bonded to the remainder of the HER2 protein, "〰" is the attachment point to the HER2 protein, and wherein R^3, R^4, and z4 are as described herein. As a non-limiting example, the HER2 protein covalently bonded to a compound (e.g., a compound described herein) may have the formula:



, wherein S is the sulfur of a HER2 protein cysteine (e.g., corresponding to C805 of human HER2), which is bonded to the remainder of the HER2 protein and " ~~~~ " is the attachment point to the HER2 protein.

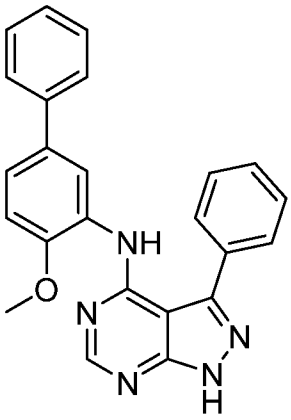
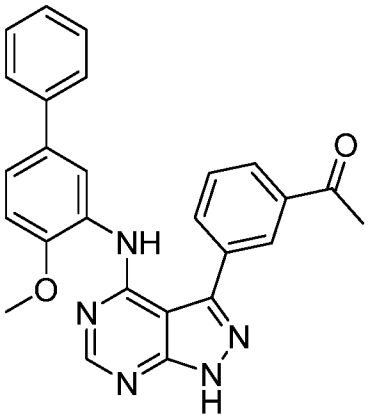
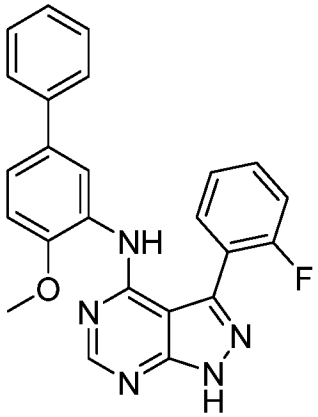
[0768] In an aspect is provided an ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) protein covalently bonded to a compound (e.g., a compound described herein, an ERBB (e.g., ERBB1, ERBB2, ERBB3, or ERBB4) inhibitor). In embodiments, the compound (or a fragment thereof) is covalently bonded to a cysteine of the protein. In embodiments, the ERBB protein covalently bonded to a compound described herein is the product of a reaction between the ERBB protein and compound described herein. It will be understood that the covalently bonded ERBB protein and compound described herein are the remnants of the reactant ERBB protein and compound, wherein each reactant now participates in the covalent bond between the ERBB protein and compound. In embodiments of the covalently bonded ERBB protein and compound described herein, the remnant of the substituted formula I is a linker including a covalent bond between the ERBB protein and the remainder of the compound described herein. It will be understood by a person of ordinary skill in the art that when a ERBB protein is covalently bonded to a compound described herein, the compound described herein forms a remnant of the pre-reacted compound wherein a bond connects the remnant of the compound to the remnant of the ERBB protein (e.g., amino acid corresponding to a cysteine amino acid of human ERBB).

EMBODIMENTS

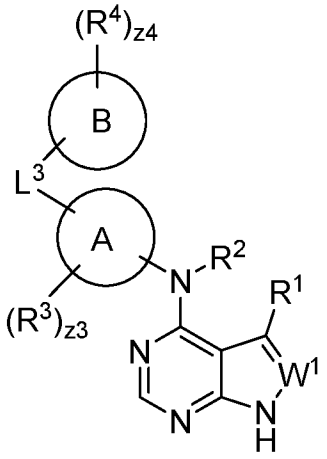


[0769] Embodiment P1. A compound having the formula: (I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $-L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, –

CH_2X^2, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently

hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2; wherein the compound is not  ,  , or  .

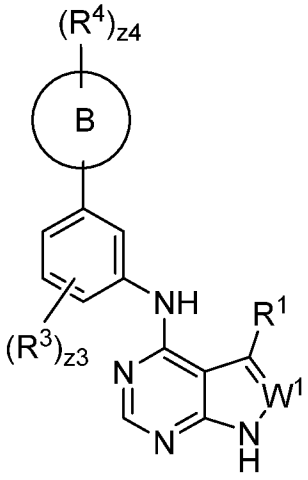
[0770] Embodiment P2. A compound of embodiment P1, having the formula:



(II) wherein Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; L^3 is a bond, $-S(O)_2-$, $-NR^8-$, -O-, -S-, -C(O)-, $-C(O)NR^8-$, $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-NHC(O)NR^8-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, 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^8 is independently halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, -CN, $-SO_{n8}R^{8D}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-C(O)R^{8C}$, $-C(O)-OR^{8C}$, $-C(O)NR^{8A}R^{8B}$, $-OR^{8D}$, $-NR^{8A}SO_2R^{8D}$, $-NR^{8A}C(O)R^{8C}$, $-NR^{8A}C(O)OR^{8C}$, $-NR^{8A}OR^{8C}$, 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; z4 is an integer from 0 to 5; Each R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{8A}, R^{8B}, R^{8C}, and R^{8D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} 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^4

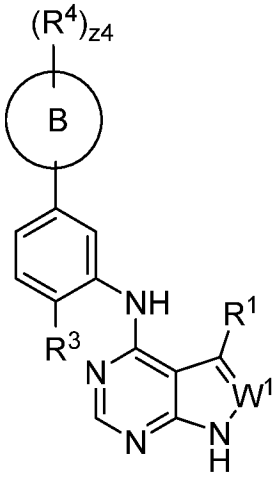
and X^8 are independently –F, -Cl, -Br, or –I; n4 and n8 are independently an integer from 0 to 4; and m4, m8, v4, and v8, are independently an integer from 1 to 2.

[0771] Embodiment P3. A compound of embodiment P2, having the formula:



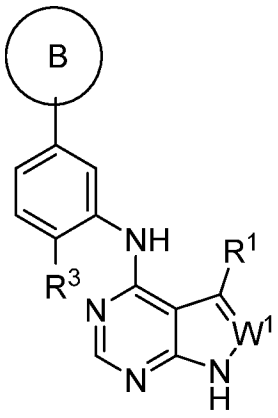
(III).

[0772] Embodiment P4. The compound of embodiment P2, having the formula:



(IV).

[0773] Embodiment P5. The compound of embodiment P2, having the formula:



(V).

[0774] Embodiment P6. The compound of one of embodiments P1 or P5, wherein W^1 is C(H).

[0775] Embodiment P7. The compound of one of embodiments P1 or P5, wherein W^1 is N.

[0776] Embodiment P8. The compound of one of embodiments P1 or P7, wherein R^3 is unsubstituted heteroalkyl.

[0777] Embodiment P9. The compound of one of embodiments P1 or P7, wherein R^3 is unsubstituted 2 to 5 membered heteroalkyl.

[0778] Embodiment P10. The compound of one of embodiments P1 or P7, wherein R^3 is –OCH_3, -OCH_2CH_3, -$N(CH_3)_2$, -NH_2, -$NH(CH_3)$, -$N(CH_2CH_3)_2$, -$NH(CH_2CH_3)$, or -SH.

[0779] Embodiment P11. The compound of one of embodiments P2 or P10, wherein Ring B is aryl or heteroaryl.

[0780] Embodiment P12. The compound of one of embodiments P2 or P10, wherein Ring B is phenyl or 5 to 6 membered heteroaryl.

[0781] Embodiment P13. The compound of one of embodiments P2 or P10, wherein Ring B is phenyl.

[0782] Embodiment P 14. The compound of one of embodiments P2 or P10, wherein Ring B is 5 to 6 membered heteroaryl.

[0783] Embodiment P15. The compound of one of embodiments P2 or P10, wherein Ring B is furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0784] Embodiment P16. The compound of one of embodiments P1 or P15, wherein R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0785] Embodiment P17. The compound of one of embodiments P1 or P15, wherein R^1 is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0786] Embodiment P18. The compound of one of embodiments P1 or P15, wherein R^1 is substituted or unsubstituted phenyl.

[0787] Embodiment P19. The compound of one of embodiments P1 or P15, wherein R^1 is unsubstituted phenyl.

[0788] Embodiment P20. The compound of one of embodiments P1 or P15, wherein R^1 is substituted or unsubstituted 5 to 6 membered heteroaryl.

[0789] Embodiment P21. The compound of one of embodiments P1 or P15, wherein R^1 is unsubstituted 5 to 6 membered heteroaryl.

[0790] Embodiment P22. The compound of one of embodiments P1 or P15, wherein R^1 is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, or substituted or unsubstituted thiazolyl.

[0791] Embodiment P23. The compound of one of embodiments P1 or P15, wherein R^1 is unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl.

[0792] Embodiment P24. The compound of one of embodiments P1 or P23, wherein R^1 is –L^1-L^2-E.

[0793] Embodiment P25. The compound of one of embodiments P1 to P24, wherein L^1 is a bond, -C(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0794] Embodiment P26. The compound of one of embodiments P1 to P24, wherein L^1 is a substituted or unsubstituted C_1-C_4 alkylene.

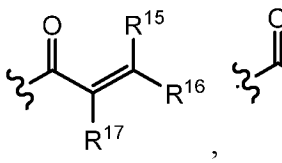
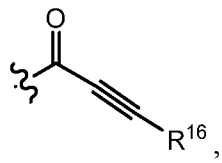
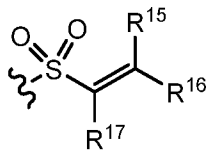
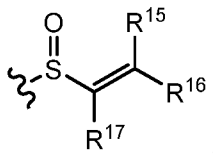
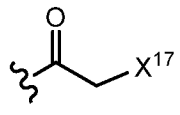
[0795] Embodiment P27. The compound of one of embodiments P1 to P24, wherein L^1 is –$C(O)CH_2CH_2CH_2$-, –$C(O)CH_2CH_2$-, or –$C(O)CH_2$-.

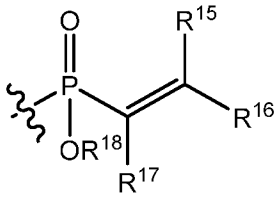
[0796] Embodiment P28. The compound of one of embodiments P1 to P27, wherein L^2 is -NR^7-, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heterocycloalkylene.

[0797] Embodiment P29. The compound of one of embodiments P1 to P27, wherein L^2 is -NH-.

[0798] Embodiment P30. The compound of one of embodiments P1 to P29, wherein E is a covalent cysteine modifier moiety.

[0799] Embodiment P31. The compound of one of embodiments P1 to P29, wherein E is:






, or



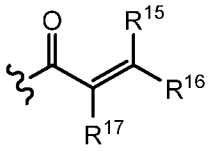
; R^{15} is independently hydrogen, halogen, CX^{15}_3, $-CHX^{15}_2$, $-CH_2X^{15}$, -CN, $-SO_{n15}R^{15D}$, $-SO_{v15}NR^{15A}R^{15B}$, $-NHNR^{15A}R^{15B}$, $-ONR^{15A}R^{15B}$, $-NHC(=O)NHNR^{15A}R^{15B}$, $-NHC(O)NR^{15A}R^{15B}$, $-N(O)_{m15}$, $-NR^{15A}R^{15B}$, $-C(O)R^{15C}$, $-C(O)-OR^{15C}$, $-C(O)NR^{15A}R^{15B}$, $-OR^{15D}$, $-NR^{15A}SO_2R^{15D}$, $-NR^{15A}C(O)R^{15C}$, $-NR^{15A}C(O)OR^{15C}$, $-NR^{15A}OR^{15C}$, $-OCX^{15}_3$, $-OCHX^{15}_2$, 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^{16} is independently hydrogen, halogen, CX^{16}_3, $-CHX^{16}_2$, $-CH_2X^{16}$, -CN, $-SO_{n16}R^{16D}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHNR^{16A}R^{16B}$, $-ONR^{16A}R^{16B}$, $-NHC(=O)NHNR^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16C}$, $-C(O)-OR^{16C}$, $-C(O)NR^{16A}R^{16B}$, $-OR^{16D}$, $-NR^{16A}SO_2R^{16D}$, $-NR^{16A}C(O)R^{16C}$, $-NR^{16A}C(O)OR^{16C}$, $-NR^{16A}OR^{16C}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, 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^{17} is independently hydrogen, halogen, CX^{17}_3, $-CHX^{17}_2$, $-CH_2X^{17}$, -CN, $-SO_{n17}R^{17D}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC(=O)NHNR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17C}$, $-C(O)-OR^{17C}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17D}$, $-NR^{17A}SO_2R^{17D}$, $-NR^{17A}C(O)R^{17C}$, $-NR^{17A}C(O)OR^{17C}$, $-NR^{17A}OR^{17C}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{18} is independently hydrogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-C(O)R^{18C}$, $-C(O)OR^{18C}$, $-C(O)NR^{18A}R^{18B}$, 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^{15A}, R^{15B}, R^{15C}, R^{15D}, R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B},

R^{17C}, R^{17D}, R^{18A}, R^{18B}, R^{18C}, R^{18D}, are independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{15A} and R^{15B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; each X, X^{15}, X^{16}, X^{17} and X^{18} is independently –F, -Cl, -Br, or –I; n15, n16, n17, v15, v16, and v17, are independently an integer from 0 to 4; and

m15, m16, and m17 are independently and integer from 1 to 2.

[0800] Embodiment P32. The compound of embodiment P31, wherein R^{15}, R^{16}, R^{17}, and R^{18} are hydrogen.

[0801] Embodiment P33. The compound of one of embodiments P31 to P32, wherein E is:



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[0802] Embodiment P34. The compound of embodiment P33, wherein R^{15} is hydrogen; R^{16} is hydrogen, $-CH_3$, or $-CH_2NR^{16A}R^{16B}$; R^{17} is hydrogen; and R^{16A} and R^{16B} are independently hydrogen or unsubstituted alkyl.

[0803] Embodiment P35. The compound of embodiment P34, wherein R^{16A} and R^{16B} are independently unsubstituted methyl.

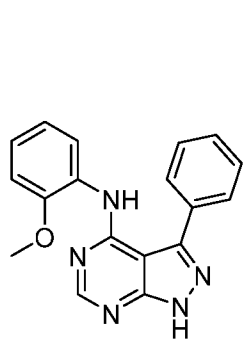
[0804] Embodiment P36. The compound of embodiment P33, wherein R^{15} is hydrogen; R^{16} is hydrogen; R^{17} is hydrogen, $-CH_3$, or $-CH_2NR^{17A}R^{17B}$; and R^{17A} and R^{17B} are independently hydrogen or unsubstituted alkyl.

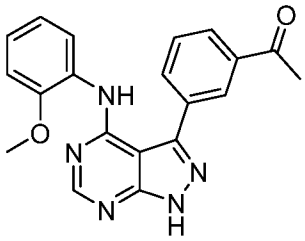
[0805] Embodiment P37. The compound of embodiment P36, wherein R^{17A} and R^{17B} are independently unsubstituted methyl.

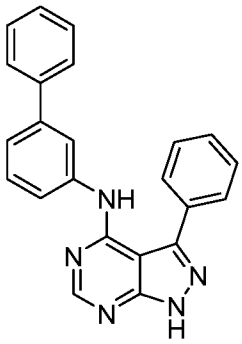
[0806] Embodiment P 38. The compound of embodiment P33, wherein R^{15} is hydrogen, -CH_3, or $-CH_2NR^{15A}R^{15B}$; R^{16} is hydrogen; R^{17} is hydrogen; and R^{15A} and R^{15B} are independently hydrogen or unsubstituted alkyl.

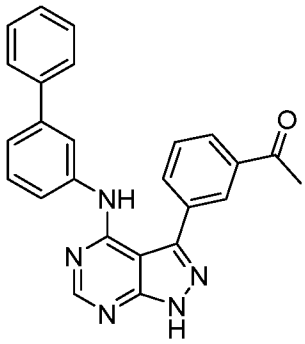
[0807] Embodiment P39. The compound of embodiment P38, wherein R^{15A} and R^{15B} are independently unsubstituted methyl.

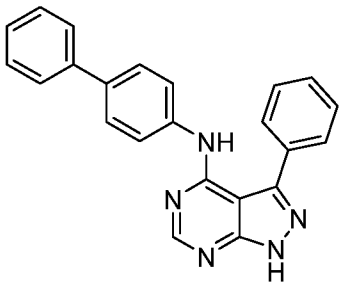
[0808] Embodiment P40. The compound of embodiment P1,wherein the compound has the formula:

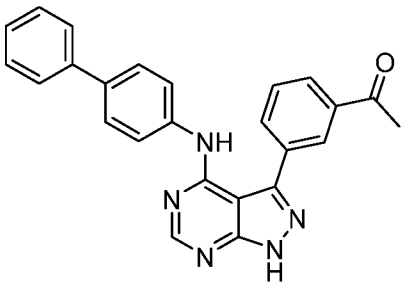

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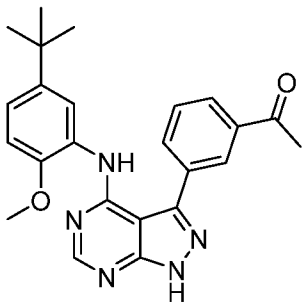

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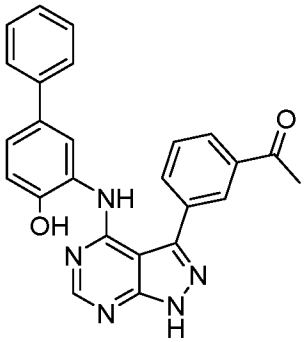

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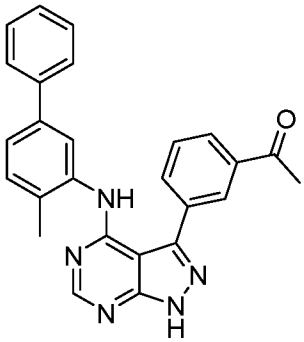

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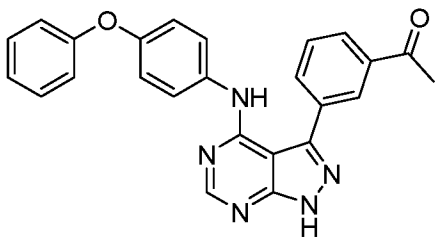

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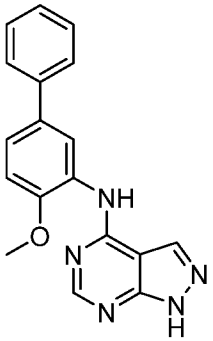

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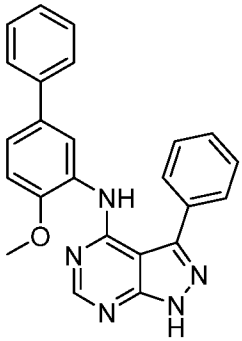

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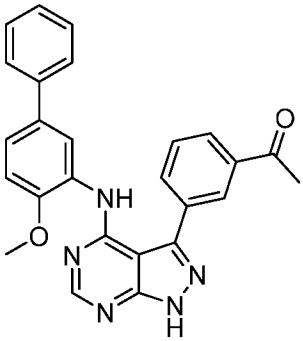

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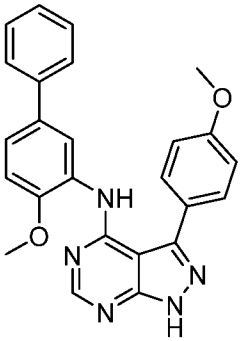

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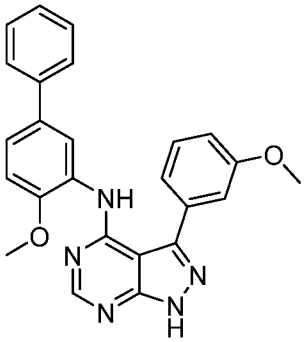

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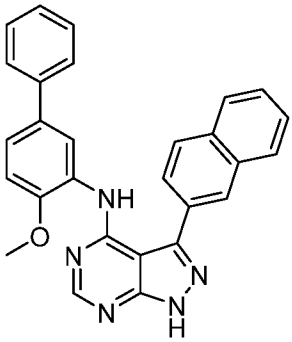

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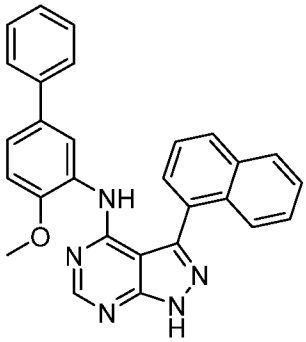

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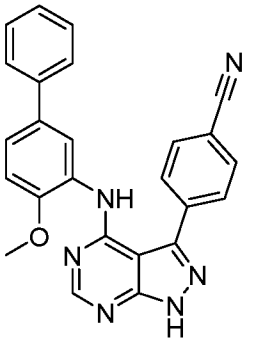

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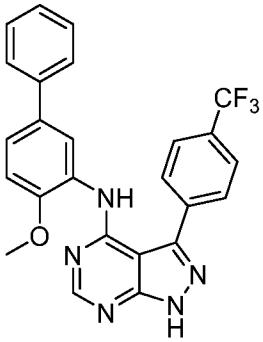

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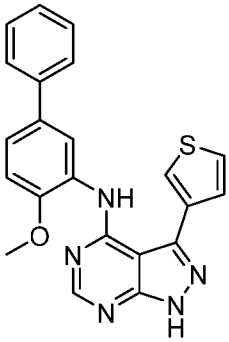

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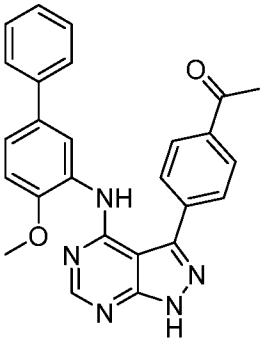

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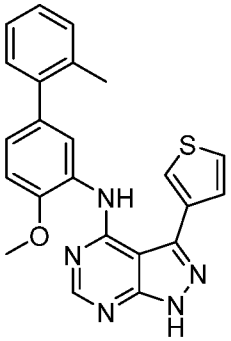

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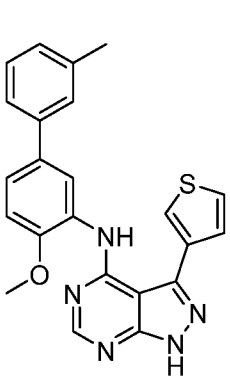

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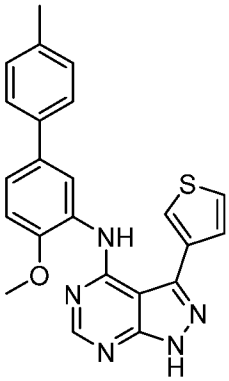

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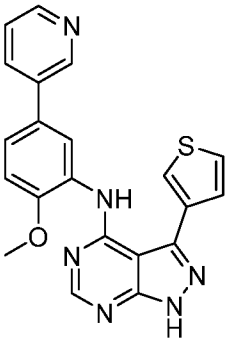

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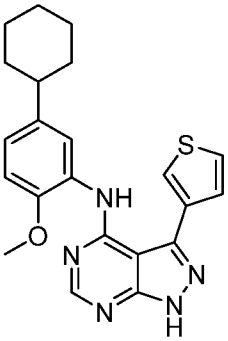

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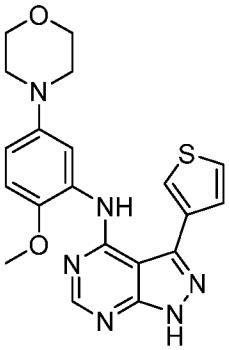

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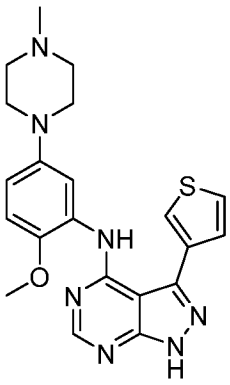

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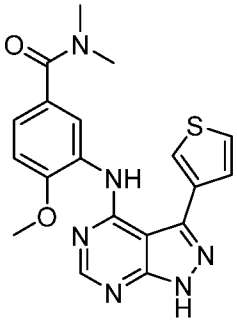

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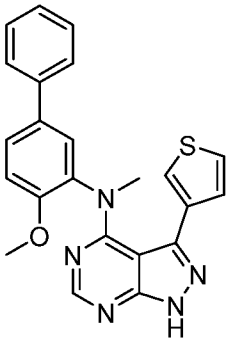

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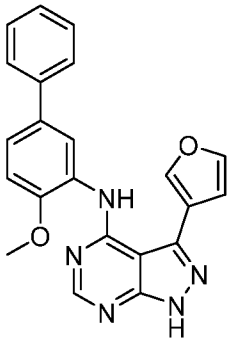
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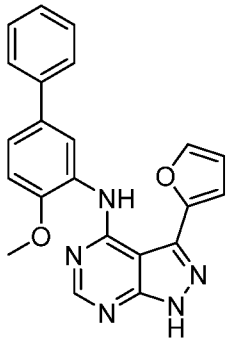
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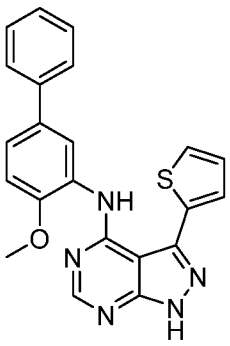
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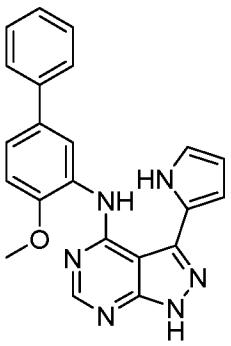
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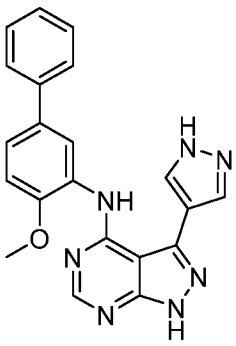
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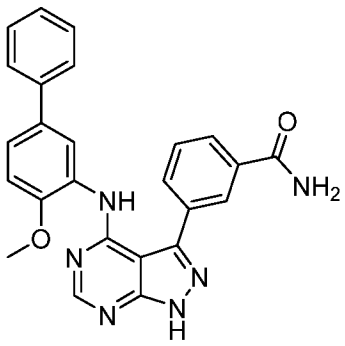
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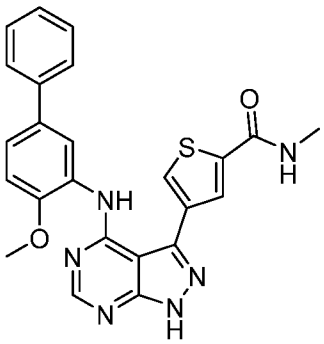
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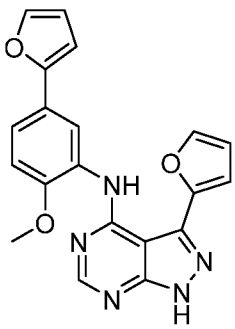
45E ,



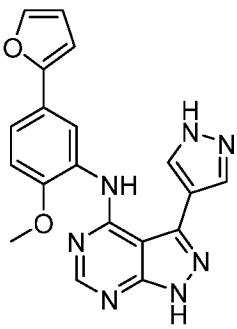
45D ,



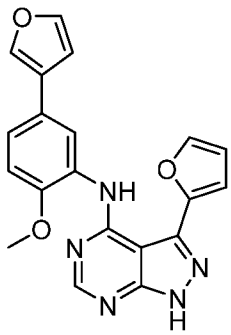
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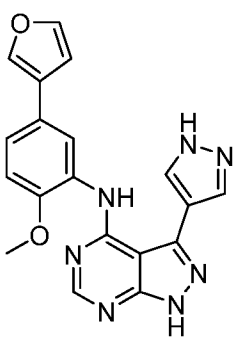
55A ,



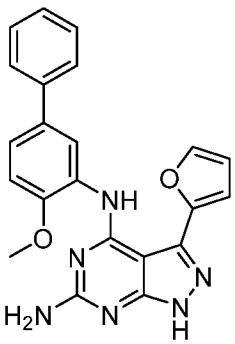
53B ,



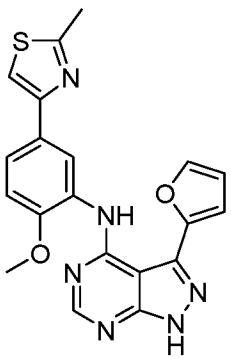
57A ,



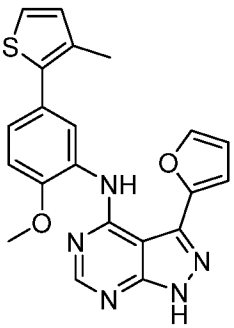
57B ,



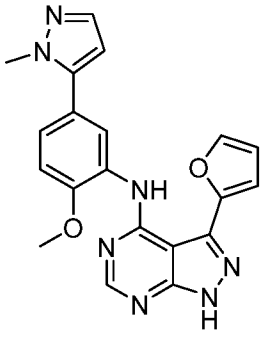
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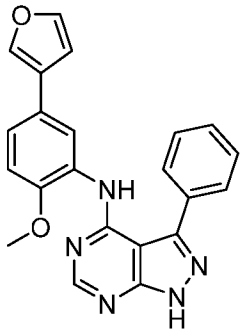
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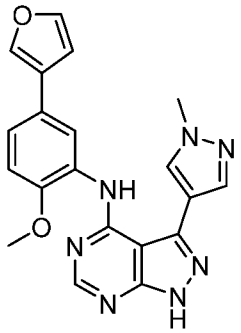
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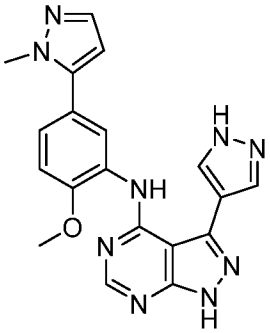
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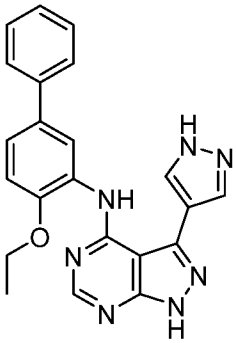
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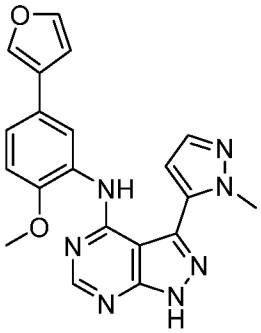
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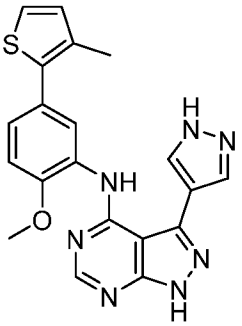
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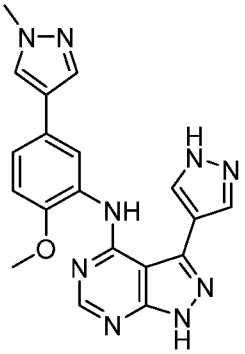
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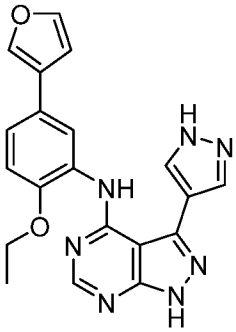
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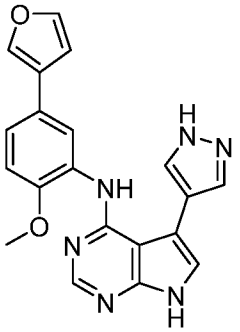
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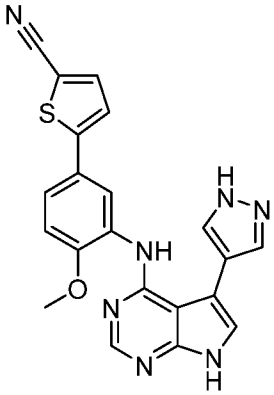
154C ,



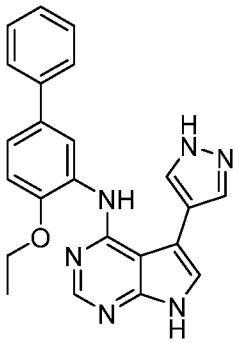
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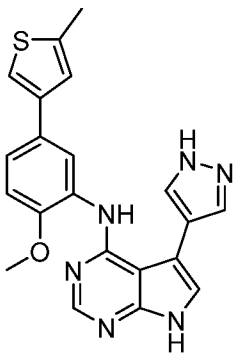
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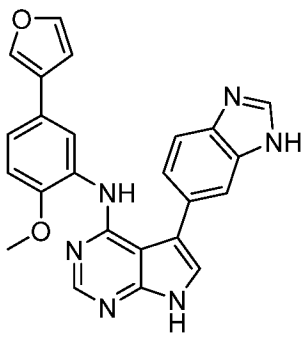
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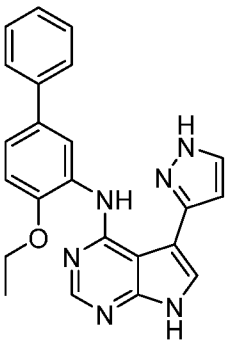
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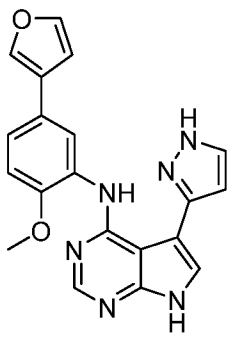
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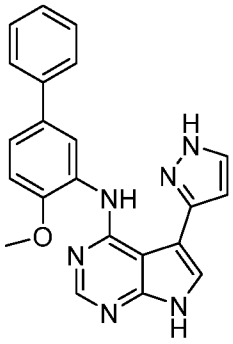
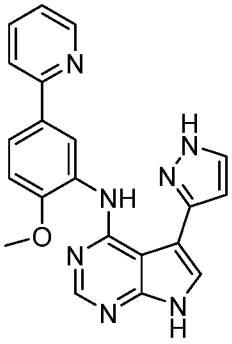
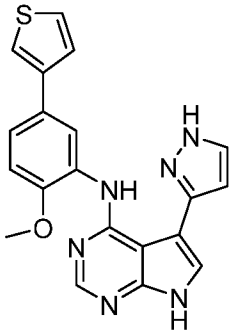
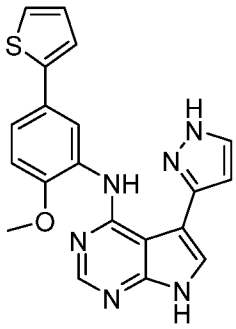
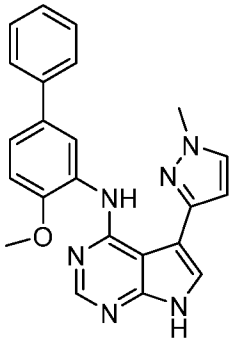
173B ,

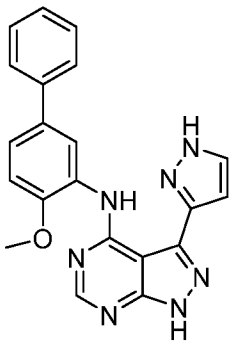
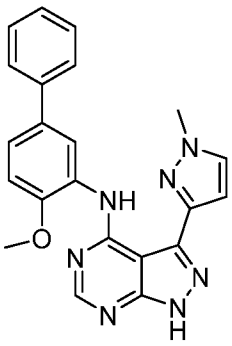
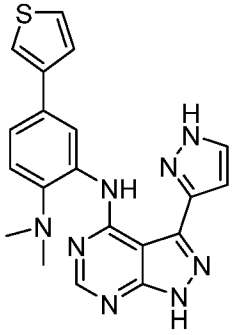
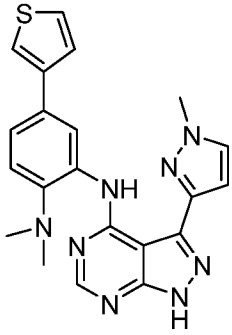


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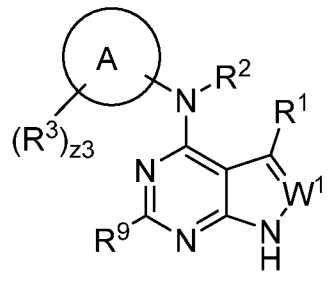
178 ,


8-089 ,

8-090 ,

8-091 ,

8-092 ,

8-095 ,


8-096 ,

8-097 ,

104A , or

104B .

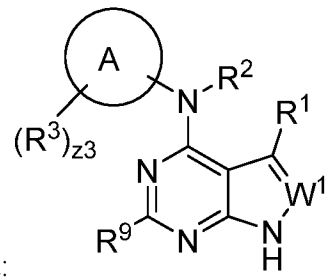
[0809] Embodiment P41. A pharmaceutical composition comprising a compound of one of embodiments P1 to P39 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0810] Embodiment P42. The pharmaceutical composition of embodiment P41, further comprising an anti-cancer agent.

[0811] Embodiment P43. A method of treating a disease associated with HER2 activity in a patient in need of such treatment, said method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:  (I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, -

OCH_2X^3, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; $z3$ is an integer from 0 to 4; L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or

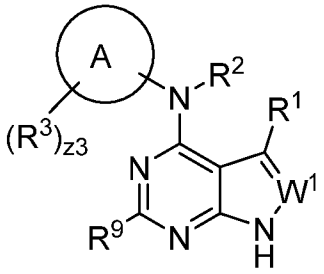
unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0812] Embodiment P44. A method of treating a disease associated with EGFR activity in a patient in need of such treatment, said method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:  (I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $–L^1-L^2-E$, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, -

OCH_2X^6, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and

X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0813] Embodiment P45. A method of treating cancer in a patient in need of such treatment, said method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:



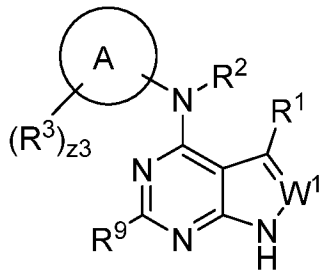
(I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $–L^1-L^2-E$, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, -C(O)-OR^{3C}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, -C(O)-OR^{6C}, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, -

OCH_2X^7, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0814] Embodiment P46. The method of embodiment P45, wherein the cancer is resistant to a HER2 inhibitor.

[0815] Embodiment P47. The method of embodiment P45, wherein the cancer is resistant to an EGFR inhibitor.

[0816] Embodiment P48. A method of inhibiting HER2 activity, said method comprising contacting HER2 with an effective amount of a compound, or a pharmaceutically acceptable salt



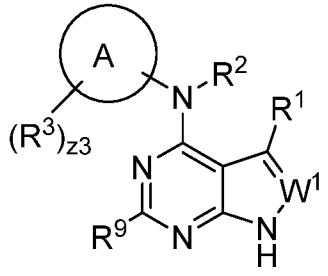
thereof, having the formula: (I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, -C(O)-OR^{3C}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^6$-, -O-, -S-, -C(O)-, $-C(O)NR^6$-, $-NR^6C(O)$-, $-NR^6C(O)NH$-, $-NHC(O)NR^6$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, -C(O)-OR^{6C}, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^7$-, -O-, -S-, -C(O)-, $-C(O)NR^7$-, $-NR^7C(O)$-, $-NR^7C(O)NH$-, $-NHC(O)NR^7$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, -C(O)-OR^{7C}, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0817] Embodiment P49. The method of embodiment P48, wherein HER2 is in an active conformation.

[0818] Embodiment P50. The method of embodiment P49, wherein HER2 is in a HER2-HER3 heterodimer.

[0819] Embodiment P51. A method of inhibiting EGFR activity, said method comprising contacting EGFR with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:



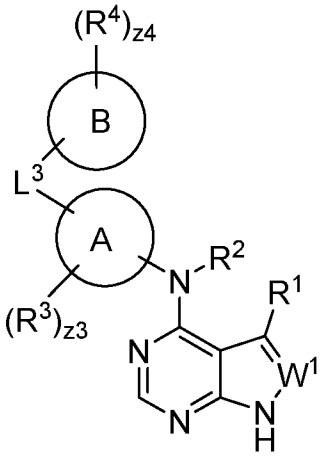
(I) wherein Ring A is aryl or heteroaryl;

W^1 is N or C(H); R^1 is hydrogen, $-L^1-L^2-E$, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0820] Embodiment P52. The method of embodiment P51, wherein EGFR is in an active conformation.

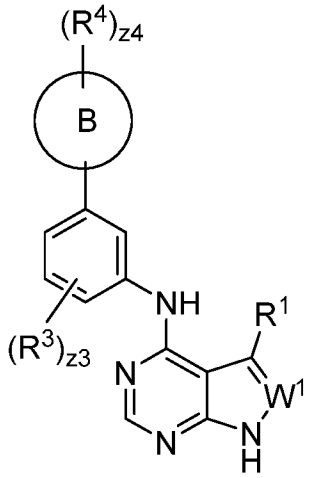
[0821] Embodiment P53. A method of one of embodiments P43 to P52, wherein the compound has the formula:



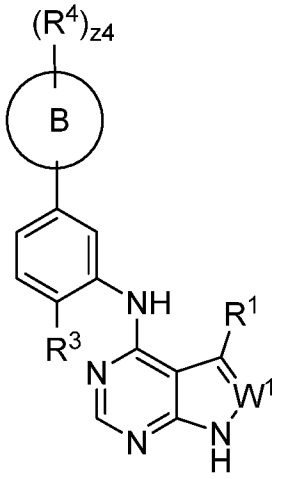
(II) wherein Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; L^3 is a bond, $-S(O)_2-$, $-NR^8-$, -O-, -S-, -C(O)-, $-C(O)NR^8-$, $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-NHC(O)NR^8-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, -N

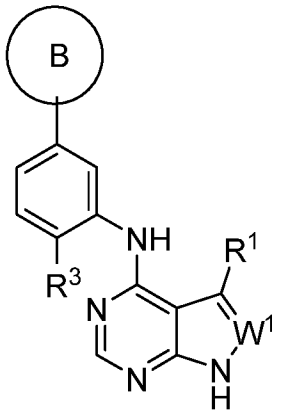
$R^{4A}OR^{4C}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^8 is independently halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, -CN, $-SO_{n8}R^{8D}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-C(O)R^{8C}$, $-C(O)-OR^{8C}$, $-C(O)NR^{8A}R^{8B}$, $-OR^{8D}$, $-NR^{8A}SO_2R^{8D}$, $-NR^{8A}C(O)R^{8C}$, $-NR^{8A}C(O)OR^{8C}$, $-NR^{8A}OR^{8C}$, 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; z4 is an integer from 0 to 5; Each R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{8A}, R^{8B}, R^{8C}, and R^{8D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} 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^4 and X^8 are independently –F, -Cl, -Br, or –I; n4 and n8 are independently an integer from 0 to 4; and m4, m8, v4, and v8, are independently an integer from 1 to 2.

[0822] Embodiment P54. A method of one of embodiments P43 to P52, wherein the compound has the formula:



(III).

[0823] Embodiment P55. A method of one of embodiments P43 to P52, wherein the compound has the formula:  (IV).

[0824] Embodiment P56. A method of one of embodiments P43 to P52, wherein the compound has the formula:  (V).

[0825] Embodiment P57. The method of one of embodiments P43 to P56, wherein W^1 is C(H).

[0826] Embodiment P58. The method of one of embodiments P43 to P56, wherein W^1 is N.

[0827] Embodiment P59. The method of one of embodiments P43 to P58, wherein R^3 is unsubstituted heteroalkyl.

[0828] Embodiment P60. The method of one of embodiments P43 to P58, wherein R^3 is unsubstituted 2 to 5 membered heteroalkyl.

[0829] Embodiment P61. The method of one of embodiments P43 to P58, wherein R^3 is –OCH_3, -OCH_2CH_3, -$N(CH_3)_2$, -NH_2, -$NH(CH_3)$, -$N(CH_2CH_3)_2$, -$NH(CH_2CH_3)$, or -SH.

[0830] Embodiment P62. The method of one of embodiments P44 to P61, wherein Ring B is aryl or heteroaryl.

[0831] Embodiment P63. The method of one of embodiments P44 to P61, wherein Ring B is phenyl or 5 to 6 membered heteroaryl.

[0832] Embodiment P64. The method of one of embodiments P44 to P61, wherein Ring B is phenyl.

[0833] Embodiment P65. The method of one of embodiments P44 to P61, wherein Ring B is 5 to 6 membered heteroaryl.

[0834] Embodiment P66. The method of one of embodiments P44 to P61, wherein Ring B is furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0835] Embodiment P67. The method of one of embodiments P43 to P66, wherein R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0836] Embodiment P68. The method of one of embodiments P43 to P66, wherein R^1 is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0837] Embodiment P69. The method of one of embodiments P43 to P66, wherein R^1 is substituted or unsubstituted phenyl.

[0838] Embodiment P70. The method of one of embodiments P43 to P66, wherein R^1 is unsubstituted phenyl.

[0839] Embodiment P71. The method of one of embodiments P43 to P66, wherein R^1 is substituted or unsubstituted 5 to 6 membered heteroaryl.

[0840] Embodiment P72. The method of one of embodiments P43 to P66, wherein R^1 is unsubstituted 5 to 6 membered heteroaryl.

[0841] Embodiment P73. The method of one of embodiments P43 to P66, wherein R^1 is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, or substituted or unsubstituted thiazolyl.

[0842] Embodiment P74. The method of one of embodiments P43 to P66, wherein R^1 is unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl.

[0843] Embodiment P75. The method of one of embodiments P43 to P74, wherein R^1 is –L^1-L^2-E.

[0844] Embodiment P76. The method of one of embodiments P43 to P75, wherein L^1 is a bond, -C(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0845] Embodiment P77. The method of one of embodiments P43 to P75, wherein L^1 is a substituted or unsubstituted C_1-C_4 alkylene.

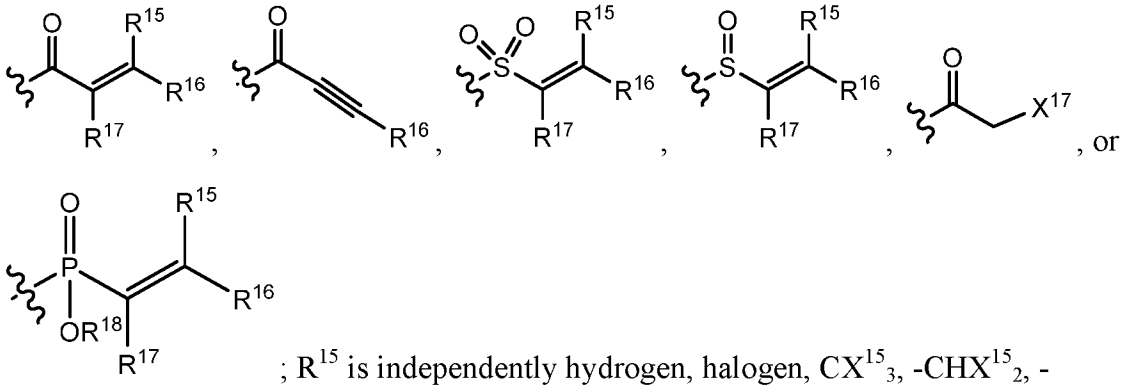
[0846] Embodiment P78. The method of one of embodiments P43 to P75, wherein L^1 is –$C(O)CH_2CH_2CH_2$-, –$C(O)CH_2CH_2$-, or –$C(O)CH_2$-.

[0847] Embodiment P79. The method of one of embodiments P43 to P78, wherein L^2 is -NR^7-, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heterocycloalkylene.

[0848] Embodiment P80. The method of one of embodiments P43 to P78, wherein L^2 is -NH-.

[0849] Embodiment P81. The method of one of embodiments P43 to P80, wherein E is a covalent cysteine modifier moiety.

[0850] Embodiment P82. The method of one of embodiments P43 to P80, wherein E is:



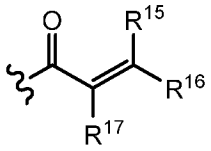
; R^{15} is independently hydrogen, halogen, CX^{15}_3, -CHX^{15}_2, -CH_2X^{15}, -CN, -$SO_{n15}R^{15D}$, -$SO_{v15}NR^{15A}R^{15B}$, –$NHNR^{15A}R^{15B}$, –$ONR^{15A}R^{15B}$, –$NHC{=}(O)NHNR^{15A}R^{15B}$, –$NHC(O)NR^{15A}R^{15B}$, -$N(O)_{m15}$, -$NR^{15A}R^{15B}$, -$C(O)R^{15C}$, -C(O)-$OR^{15C}$, -$C(O)NR^{15A}R^{15B}$, -$OR^{15D}$, -$NR^{15A}SO_2R^{15D}$, -$NR^{15A}C(O)R^{15C}$, -$NR^{15A}C(O)OR^{15C}$, -$NR^{15A}OR^{15C}$, -$OCX^{15}_3$, -$OCHX^{15}_2$, 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^{16} is independently hydrogen, halogen, CX^{16}_3, $-CHX^{16}_2$, $-CH_2X^{16}$, -CN, $-SO_{n16}R^{16D}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHNR^{16A}R^{16B}$, $-ONR^{16A}R^{16B}$, $-NHC=(O)NHNR^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16C}$, $-C(O)-OR^{16C}$, $-C(O)NR^{16A}R^{16B}$, $-OR^{16D}$, $-NR^{16A}SO_2R^{16D}$, $-NR^{16A}C(O)R^{16C}$, $-NR^{16A}C(O)OR^{16C}$, $-NR^{16A}OR^{16C}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, 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^{17} is independently hydrogen, halogen, CX^{17}_3, $-CHX^{17}_2$, $-CH_2X^{17}$, -CN, $-SO_{n17}R^{17D}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC=(O)NHNR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17C}$, $-C(O)-OR^{17C}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17D}$, $-NR^{17A}SO_2R^{17D}$, $-NR^{17A}C(O)R^{17C}$, $-NR^{17A}C(O)OR^{17C}$, $-NR^{17A}OR^{17C}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{18} is independently hydrogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-C(O)R^{18C}$, $-C(O)OR^{18C}$, $-C(O)NR^{18A}R^{18B}$, 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^{15A}, R^{15B}, R^{15C}, R^{15D}, R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B}, R^{17C}, R^{17D}, R^{18A}, R^{18B}, R^{18C}, R^{18D}, are independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{15A} and R^{15B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; each X, X^{15}, X^{16}, X^{17} and X^{18} is independently –F, -Cl, -Br, or –I; n15, n16, n17,

v15, v16, and v17, are independently an integer from 0 to 4; and m15, m16, and m17 are independently and integer from 1 to 2.

[0851] Embodiment P83. The method of embodiment P82, wherein R^{15}, R^{16}, R^{17}, and R^{18} are hydrogen.

[0852] Embodiment P84. The method of one of embodiments P82 to P83, wherein E is:



[0853] Embodiment P85. The method of embodiment P84, wherein R^{15} is hydrogen;R^{16} is hydrogen, -CH_3, or –$CH_2NR^{16A}R^{16B}$; R^{17} is hydrogen; and R^{16A} and R^{16B} are independently hydrogen or unsubstituted alkyl.

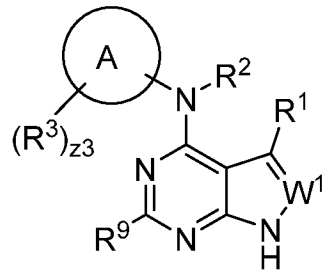
[0854] Embodiment P86. The method of embodiment P85, wherein R^{16A} and R^{16B} are independently unsubstituted methyl.

[0855] Embodiment P87. The method of embodiment P84, wherein R^{15} is hydrogen; R^{16} is hydrogen; R^{17} is hydrogen, -CH_3, or –$CH_2NR^{17A}R^{17B}$; and R^{17A} and R^{17B} are independently hydrogen or unsubstituted alkyl.

[0856] Embodiment P88. The method of embodiment P87, wherein R^{17A} and R^{17B} are independently unsubstituted methyl.

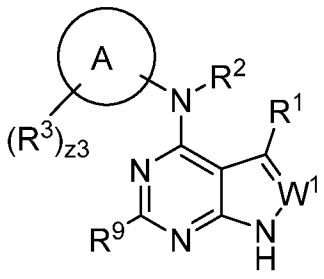
[0857] Embodiment P89. The compound of embodiment P84, wherein R^{15} is hydrogen, -CH_3, or –$CH_2NR^{15A}R^{15B}$; R^{16} is hydrogen; R^{17} is hydrogen; and R^{15A} and R^{15B} are independently hydrogen or unsubstituted alkyl.

[0858] Embodiment P90. The method of embodiment P89, wherein R^{15A} and R^{15B} are independently unsubstituted methyl.

[0859] Embodiment P91. An EGFR protein covalently bonded to a compound having the formula:  (I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1

is $-L^1-L^2-E$; R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B},

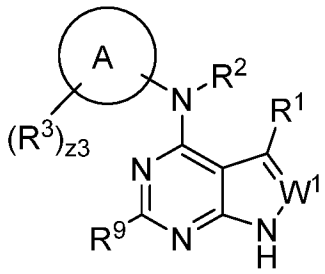
R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0860] Embodiment P92. A HER2 protein covalently bonded to a compound having the formula:  (I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is $–L^1$-L^2-E; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)$-OR^{3C}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^6$-, -O-, -S-, -C(O)-, $-C(O)NR^6$-, $-NR^6C(O)$-, $-NR^6C(O)NH$-, $-NHC(O)NR^6$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, -

OCH_2X^6, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; Each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and

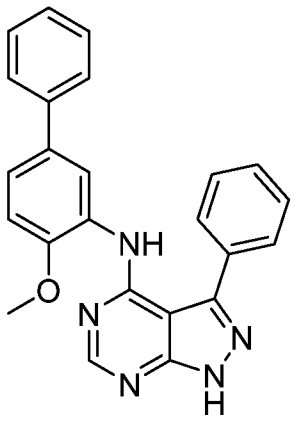
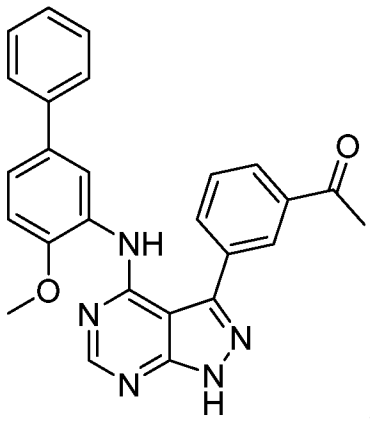
X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

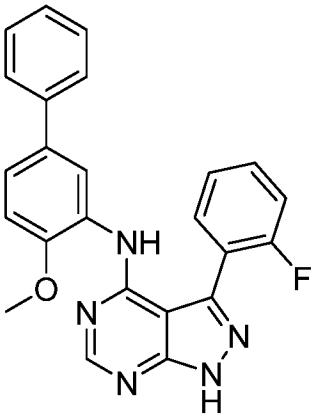
ADDITIONAL EMBODIMENTS



[0861] Embodiment 1. A compound having the formula: (I); wherein Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)$-OR^{3C}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^6$-, -O-, -S-, -C(O)-, $-C(O)NR^6$-, $-NR^6C(O)$-, $-NR^6C(O)NH$-, $-NHC(O)NR^6$-, $-C(O)O$-, $-OC(O)$-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)$-OR^{6C}, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^7$-, -O-, -S-, -C(O)-, $-C(O)NR^7$-, $-NR^7C(O)$-, $-NR^7C(O)NH$-, $-NHC(O)NR^7$-, $-C(O)O$-, $-OC(O)$-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C($

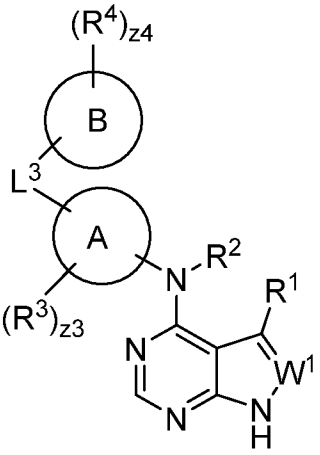
O)R^{7C}, -C(O)-OR^{7C}, -C(O)N$R^{7A}R^{7B}$, -OR^{7D}, -N$R^{7A}SO_2R^{7D}$, -NR^{7A}C(O)R^{7C}, -NR^{7A}C(O)OR^{7C}, -NR^{7A}OR^{7C}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^9 is hydrogen, halogen, -CX^9_3, -CHX^9_2, -CH_2X^9, -OCX^9_3, -OCH_2X^9, -OCHX^9_2, -CN, -$SO_{n9}R^{9D}$, -$SO_{v9}NR^{9A}R^{9B}$, -NHC(O)N$R^{9A}R^{9B}$, -N$(O)_{m9}$, -N$R^{9A}R^{9B}$, -C(O)R^{9C}, -C(O)-OR^{9C}, -C(O)N$R^{9A}R^{9B}$, -OR^{9D}, -N$R^{9A}SO_2R^{9D}$, -NR^{9A}C(O)R^{9C}, -NR^{9A}C(O)OR^{9C}, -NR^{9A}OR^{9C}, 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; E is an electrophilic moiety; each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, -CX_3, -CN, -COOH, -$CONH_2$, -CHX_2, -CH_2X, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2; wherein

the compound is not  ,  , or



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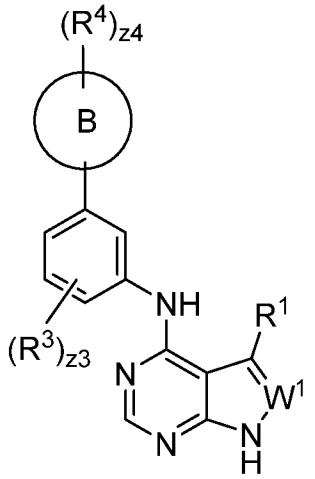
[0862] Embodiment 2. A compound of embodiment 1, having the formula:



(II); wherein Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; L^3 is a bond, $-S(O)_2-$, $-NR^8-$, -O-, -S-, -C(O)-, $-C(O)NR^8-$, $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-NHC(O)NR^8-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted

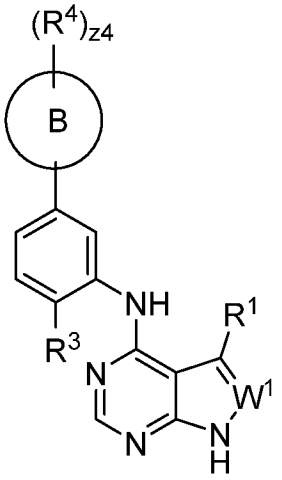
or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^8 is independently halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, -CN, $-SO_{n8}R^{8D}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-C(O)R^{8C}$, $-C(O)-OR^{8C}$, $-C(O)NR^{8A}R^{8B}$, $-OR^{8D}$, $-NR^{8A}SO_2R^{8D}$, $-NR^{8A}C(O)R^{8C}$, $-NR^{8A}C(O)OR^{8C}$, $-NR^{8A}OR^{8C}$, 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; z4 is an integer from 0 to 5; each R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{8A}, R^{8B}, R^{8C}, and R^{8D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} 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^4 and X^8 are independently –F, -Cl, -Br, or –I; n4 and n8 are independently an integer from 0 to 4; and m4, m8, v4, and v8, are independently an integer from 1 to 2.

[0863] Embodiment 3. A compound of embodiment 2, having the formula:



(III).

[0864] Embodiment 4. The compound of embodiment 2, having the formula:



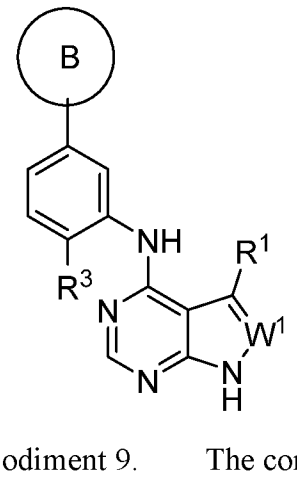
(IV).

[0865] Embodiment 5. The compound of one of embodiments 2 to 4, wherein R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, or –CN.

[0866] Embodiment 6. The compound of one of embodiments 2 to 4, wherein R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, or $-CH_2X^4$.

[0867] Embodiment 7. The compound of one of embodiments 2 to 4, wherein R^4 is independently halogen.

[0868] Embodiment 8. The compound of embodiment 2, having the formula:



(V).

[0869] Embodiment 9. The compound of one of embodiments 1 to 8, wherein W^1 is C(H).

[0870] Embodiment 10. The compound of one of embodiments 1 to 8, wherein W^1 is N.

[0871] Embodiment 11. The compound of one of embodiments 1 to 10, wherein R^3 is an unsubstituted heteroalkyl.

[0872] Embodiment 12. The compound of one of embodiments 1 to 10, wherein R^3 is an unsubstituted 2 to 5 membered heteroalkyl.

[0873] Embodiment 13. The compound of one of embodiments 1 to 10, wherein R^3 is –OCH_3, -OCH_2CH_3, -$N(CH_3)_2$, -NH_2, -$NH(CH_3)$, -$N(CH_2CH_3)_2$, -$NH(CH_2CH_3)$, -OCX^3_3, -OCH_2X^3, -$OCHX^3_2$, or -SH.

[0874] Embodiment 14. The compound of one of embodiments 1 to 10, wherein R^3 is –OCH_3, -OCH_2CH_3, -$N(CH_3)_2$, -OCX^3_3, -OCH_2X^3, or -$OCHX^3_2$.

[0875] Embodiment 15. The compound of one of embodiments 2 to 13, wherein Ring B is substituted or unsubstituted aryl or heteroaryl.

[0876] Embodiment 16. The compound of one of embodiments 2 to 13, wherein Ring B is substituted or unsubstituted phenyl or 5 to 6 membered heteroaryl.

[0877] Embodiment 17. The compound of one of embodiments 2 to 13, wherein Ring B is substituted or unsubstituted phenyl.

[0878] Embodiment 18. The compound of one of embodiments 2 to 13, wherein Ring B is substituted or unsubstituted 5 to 6 membered heteroaryl.

[0879] Embodiment 19. The compound of one of embodiments 2 to 13, wherein Ring B is substituted or unsubstituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0880] Embodiment 20. The compound of one of embodiments 1 to 19, wherein R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0881] Embodiment 21. The compound of one of embodiments 1 to 19, wherein R^1 is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0882] Embodiment 22. The compound of one of embodiments 1 to 19, wherein R^1 is substituted or unsubstituted phenyl.

[0883] Embodiment 23. The compound of one of embodiments 1 to 19, wherein R^1 is an unsubstituted phenyl.

[0884] Embodiment 24. The compound of one of embodiments 1 to 19, wherein R^1 is substituted or unsubstituted 5 to 6 membered heteroaryl.

[0885] Embodiment 25. The compound of one of embodiments 1 to 19, wherein R^1 is an unsubstituted 5 to 6 membered heteroaryl.

[0886] Embodiment 26. The compound of one of embodiments 1 to 19, wherein R^1 is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, or substituted or unsubstituted thiazolyl.

[0887] Embodiment 27. The compound of one of embodiments 1 to 19, wherein R^1 is an unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl.

[0888] Embodiment 28. The compound of one of embodiments 1 to 27, wherein R^1 is –L^1-L^2-E.

[0889] Embodiment 29. The compound of one of embodiments 1 to 28, wherein L^1 is a bond, -C(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0890] Embodiment 30. The compound of one of embodiments 1 to 28, wherein L^1 is a substituted or unsubstituted C_1-C_4 alkylene.

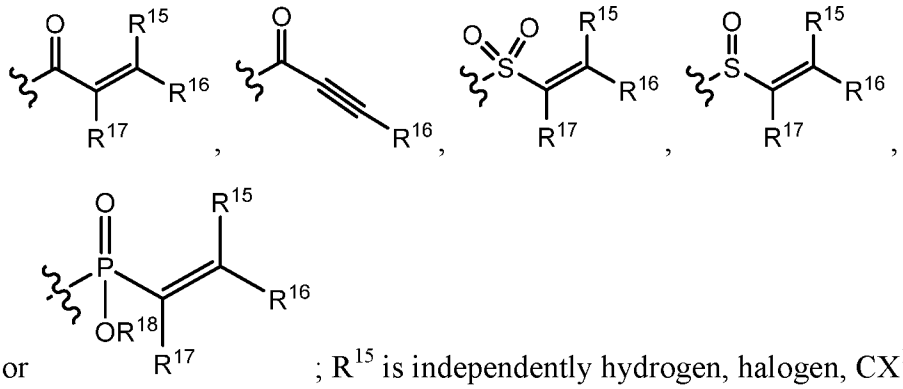
[0891] Embodiment 31. The compound of one of embodiments 1 to 28, wherein L^1 is –$C(O)CH_2CH_2CH_2$-, –$C(O)CH_2CH_2$-, or –$C(O)CH_2$-.

[0892] Embodiment 32. The compound of one of embodiments 1 to 31, wherein L^2 is -NR^7-, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heterocycloalkylene.

[0893] Embodiment 33. The compound of one of embodiments 1 to 31, wherein L^2 is -NH-.

[0894] Embodiment 34. The compound of one of embodiments 1 to 33, wherein E is a covalent cysteine modifier moiety.

[0895] Embodiment 35. The compound of one of embodiments 1 to 33, wherein E is:

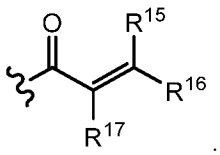


; R^{15} is independently hydrogen, halogen, CX^{15}_3, -CHX^{15}_2, -CH_2X^{15}, -CN, -$SO_{n15}R^{15D}$, -$SO_{v15}NR^{15A}R^{15B}$, –$NHNR^{15A}R^{15B}$, –$ONR^{15A}R^{15B}$, –$NHC{=}(O)NHNR^{15A}R^{15B}$, –$NHC(O)NR^{15A}R^{15B}$, -$N(O)_{m15}$, -$NR^{15A}R^{15B}$, -$C(O)R^{15C}$, -$C(O)$-$OR^{15C}$, -$C(O)NR^{15A}R^{15B}$, -$OR^{15D}$, -$NR^{15A}SO_2R^{15D}$, -$NR^{15A}C(O)R^{15C}$, -$NR^{15A}C(O)OR^{15C}$, -$NR^{15A}OR^{15C}$, -$OCX^{15}_3$, -$OCHX^{15}_2$, 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^{16} is independently hydrogen, halogen, CX^{16}_3, -CHX^{16}_2, -CH_2X^{16}, -CN, -$SO_{n16}R^{16D}$, -$SO_{v16}NR^{16A}R^{16B}$, –$NHNR^{16A}R^{16B}$, –$ONR^{16A}R^{16B}$, –$NHC{=}(O)NHNR^{16A}R^{16B}$, –$NHC(O)NR^{16A}R^{16B}$, -$N(O)_{m16}$, -$NR^{16A}R^{16B}$, -$C(O)R^{16C}$, -$C(O)$-$OR^{16C}$, -$C(O)NR^{16A}R^{16B}$, -$OR^{16D}$, -$NR^{16A}SO_2R^{16D}$, -$NR^{16A}C(O)R^{16C}$, -$NR^{16A}C(O)OR^{16C}$, -$NR^{16A}OR^{16C}$, -$OCX^{16}_3$, -$OCHX^{16}_2$, 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^{17} is independently hydrogen, halogen, CX^{17}_3, -CHX^{17}_2, -CH_2X^{17}, -CN, -$SO_{n17}R^{17D}$, -$SO_{v17}NR^{17A}R^{17B}$, –$NHNR^{17A}R^{17B}$, –$ONR^{17A}R^{17B}$, –$NHC{=}(O)NHNR^{17A}R^{17B}$, –$NHC(O)NR^{17A}R^{17B}$, -$N(O)_{m17}$, -$NR^{17A}R^{17B}$, -$C(O)R^{17C}$, -$C(O)$-$OR^{17C}$, -$C(O)NR^{17A}R^{17B}$, -$OR^{17D}$, -$NR^{17A}SO_2R^{17D}$, -$NR^{17A}C(O)R^{17C}$, -$NR^{17A}C(O)OR^{17C}$, -$NR^{17A}OR^{17C}$, -$OCX^{17}_3$, -$OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{18} is independently hydrogen, -CX^{18}_3, -CHX^{18}_2, -CH_2X^{18}, -$C(O)R^{18C}$, -$C(O)OR^{18C}$, -$C(O)NR^{18A}R^{18B}$, 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^{15A}, R^{15B}, R^{15C}, R^{15D}, R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B}, R^{17C}, R^{17D}, R^{18A}, R^{18B}, R^{18C}, R^{18D}, are independently

hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{15A} and R^{15B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; each X, X^{15}, X^{16}, X^{17} and X^{18} is independently –F, -Cl, -Br, or –I; n15, n16, n17, v15, v16, and v17, are independently an integer from 0 to 4; and m15, m16, and m17 are independently and integer from 1 to 2.

[0896] Embodiment 36. The compound of embodiment 35, wherein R^{15}, R^{16}, R^{17}, and R^{18} are hydrogen.

[0897] Embodiment 37. The compound of one of embodiments 35 to 36, wherein E is:



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[0898] Embodiment 38. The compound of embodiment 37, wherein R^{15} is hydrogen; R^{16} is hydrogen, $-CH_3$, or $-CH_2NR^{16A}R^{16B}$; R^{17} is hydrogen; and R^{16A} and R^{16B} are independently hydrogen or unsubstituted alkyl.

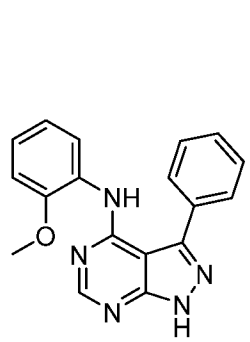
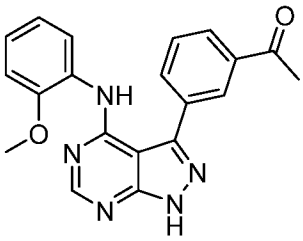
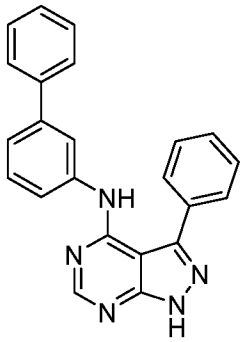
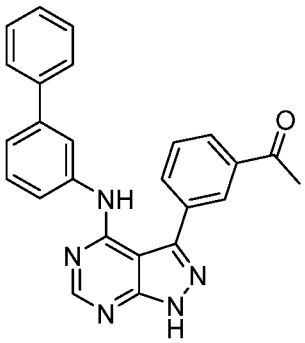
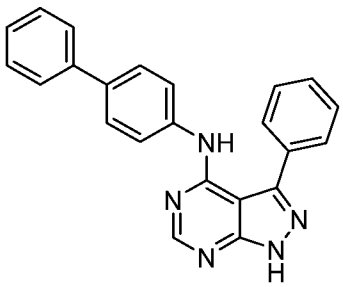
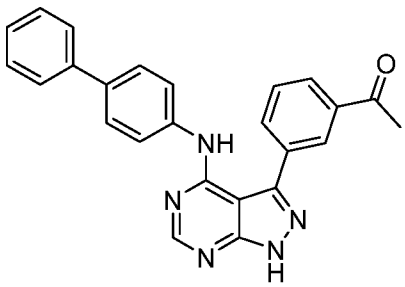
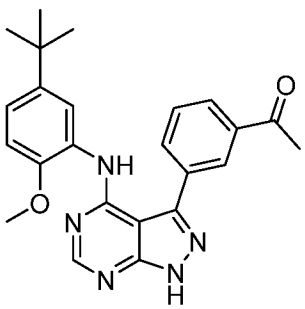
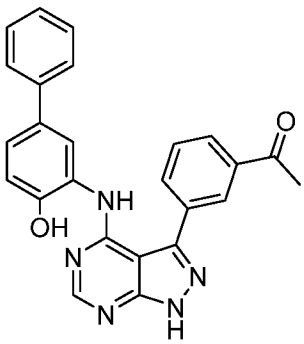
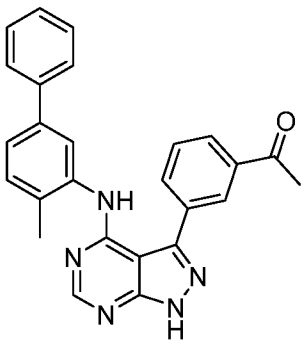
[0899] Embodiment 39. The compound of embodiment 38, wherein R^{16A} and R^{16B} are independently unsubstituted methyl.

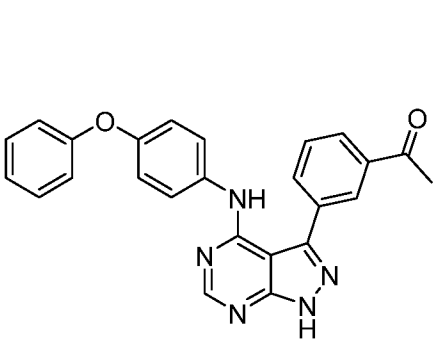
[0900] Embodiment 40. The compound of embodiment 37, wherein R^{15} is hydrogen; R^{16} is hydrogen; R^{17} is hydrogen, $-CH_3$, or $-CH_2NR^{17A}R^{17B}$; and R^{17A} and R^{17B} are independently hydrogen or unsubstituted alkyl.

[0901] Embodiment 41. The compound of embodiment 40, wherein R^{17A} and R^{17B} are independently unsubstituted methyl.

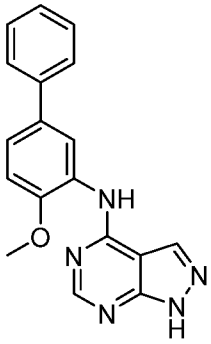
[0902] Embodiment 42. The compound of embodiment 37, wherein R^{15} is hydrogen, $-CH_3$, or $-CH_2NR^{15A}R^{15B}$; R^{16} is hydrogen; R^{17} is hydrogen; and R^{15A} and R^{15B} are independently hydrogen or unsubstituted alkyl.

[0903] Embodiment 43. The compound of embodiment 42, wherein R^{15A} and R^{15B} are independently unsubstituted methyl.

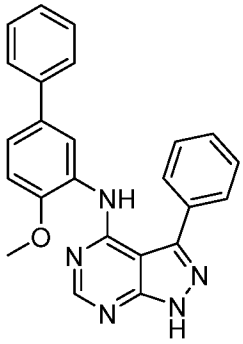
[0904] Embodiment44. The compound of embodiment 1,wherein the compound has the formula:  187A ,  187B ,  186A ,  186B ,  188A ,  188B ,  190D ,  191A ,  5-001A ,



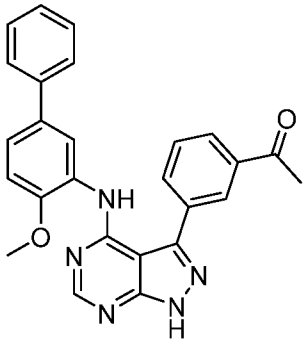
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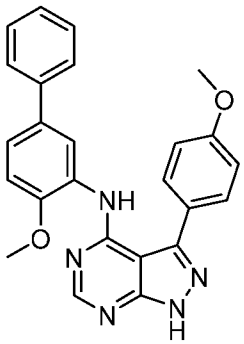
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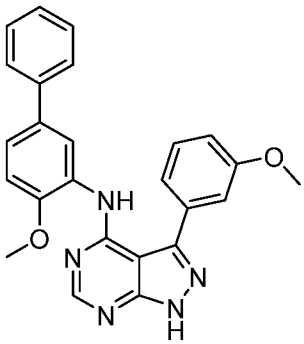
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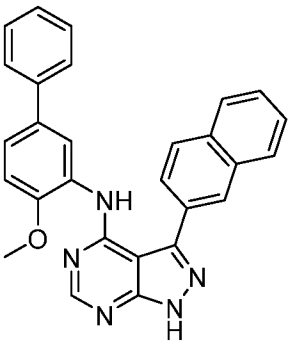
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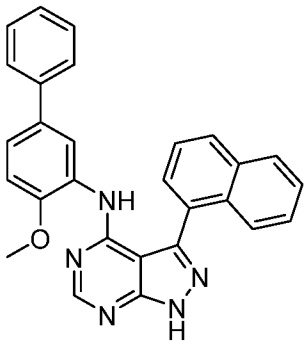
189B ,



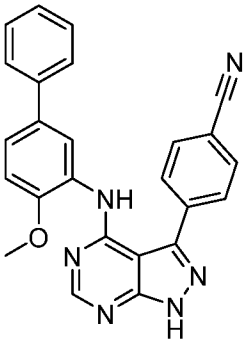
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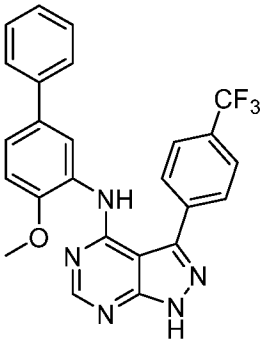
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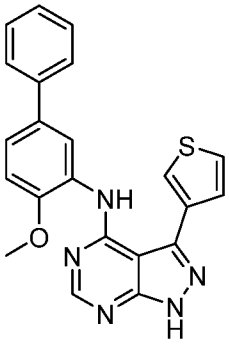
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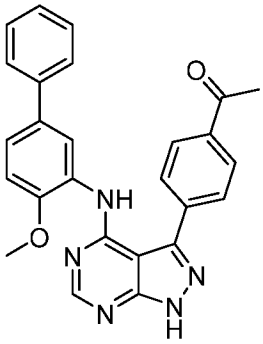
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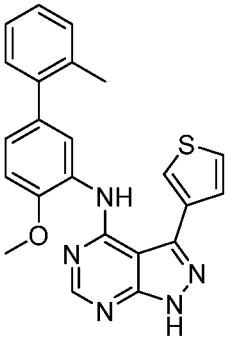
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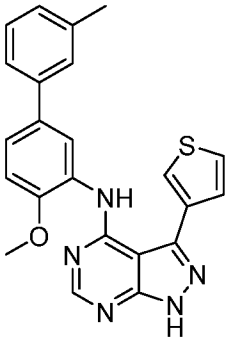
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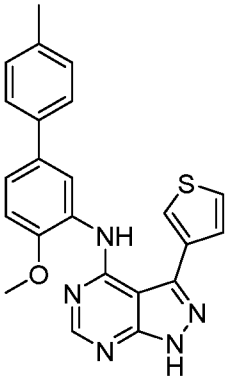
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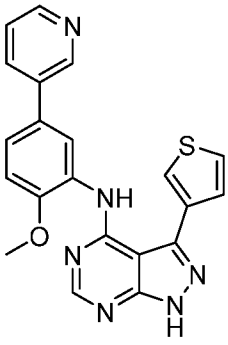
39A ,



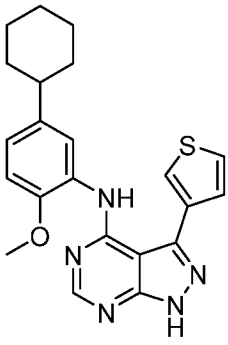
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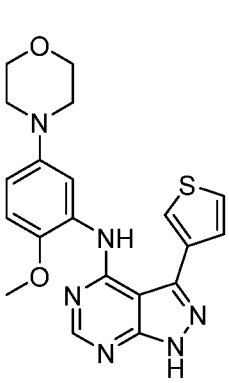
39C ,



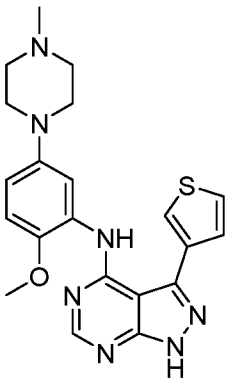
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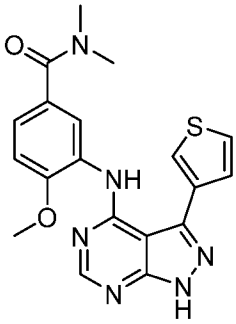
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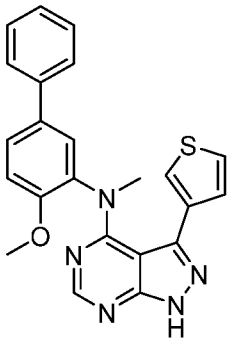
41A ,



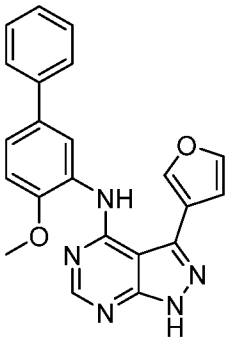
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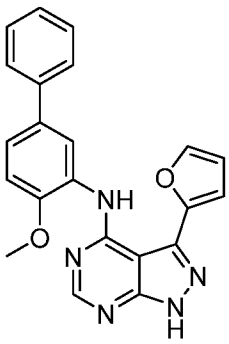
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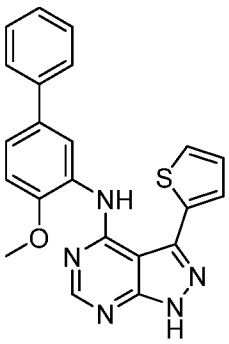
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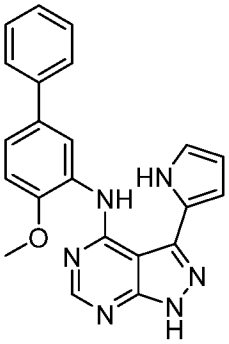
13 ,



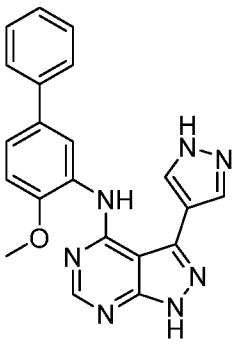
45A ,



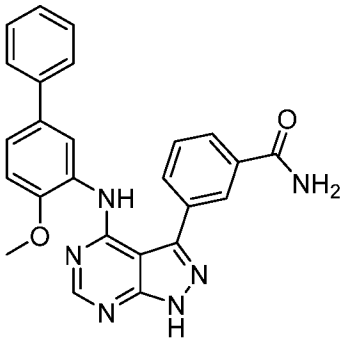
45B ,



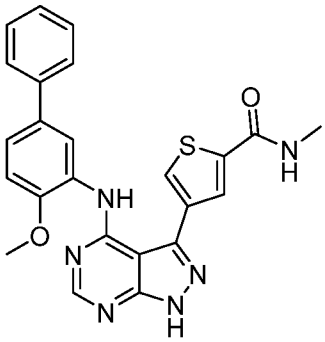
45C ,



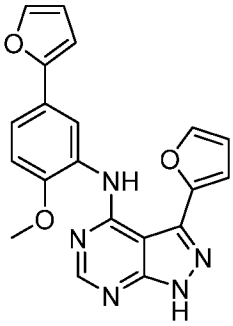
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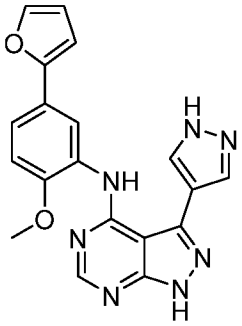
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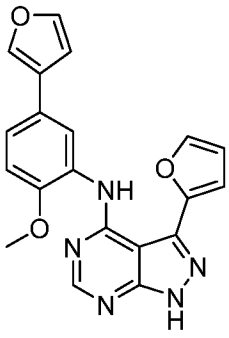
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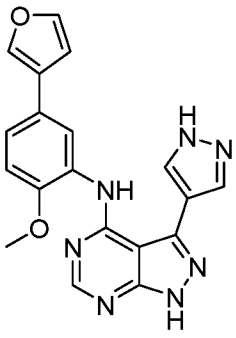
55A ,



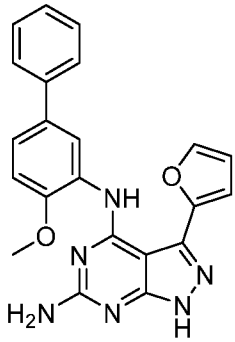
53B ,



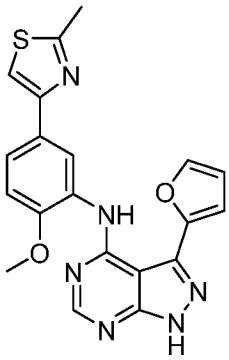
57A ,



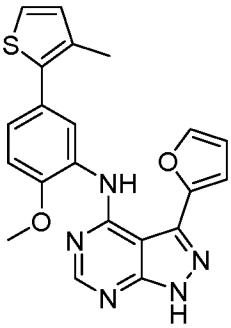
57B ,



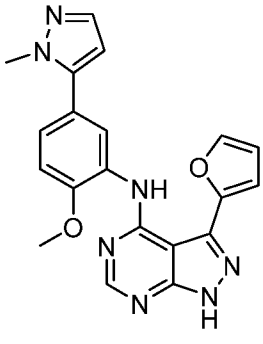
65 ,



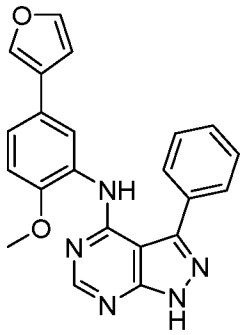
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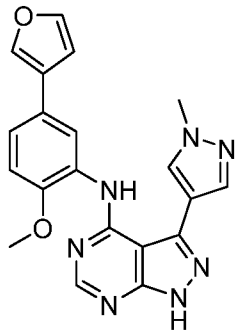
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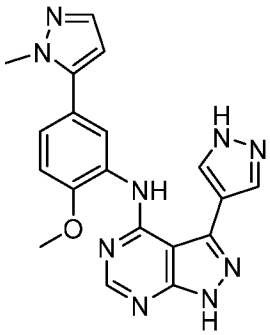
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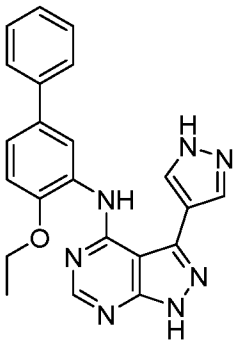
144A ,



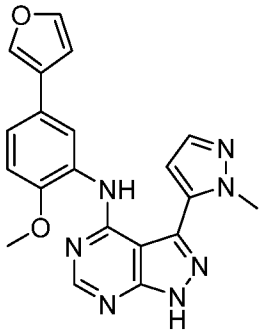
144B ,



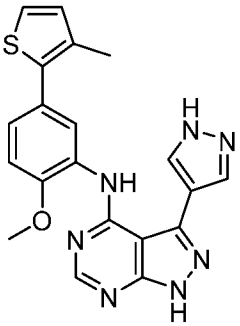
154A ,



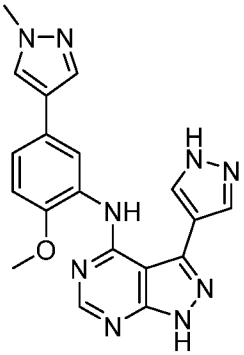
147 ,



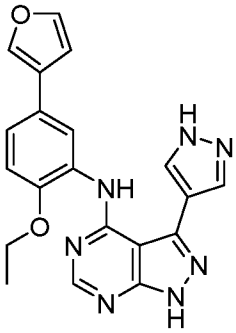
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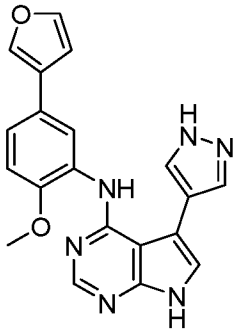
154B ,



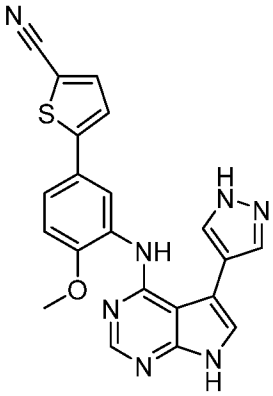
154C ,



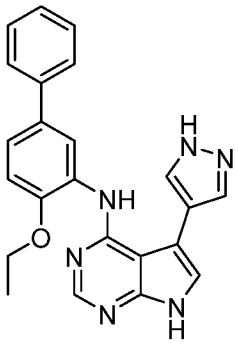
153 ,



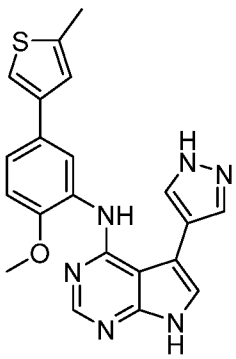
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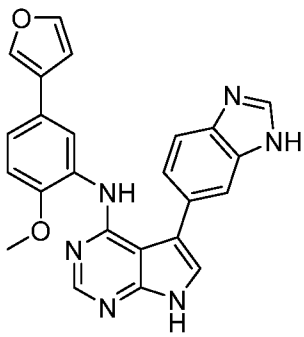
170 ,



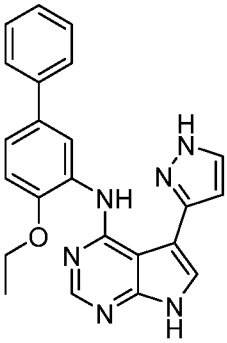
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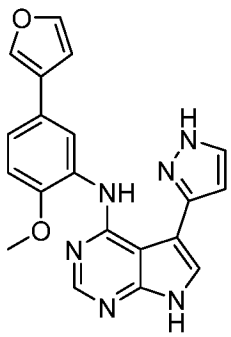
172 ,



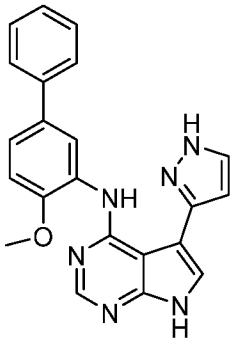
173B ,



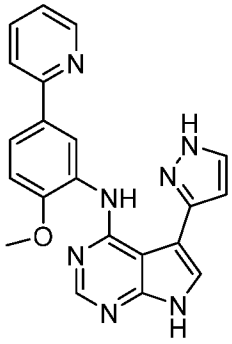
176 ,



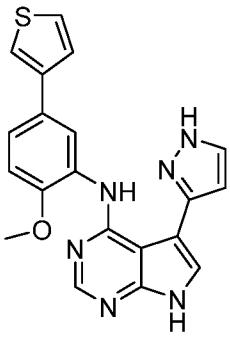
178 ,



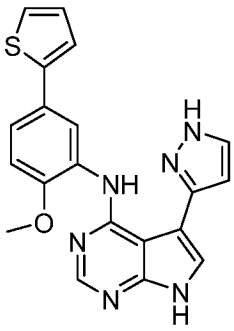
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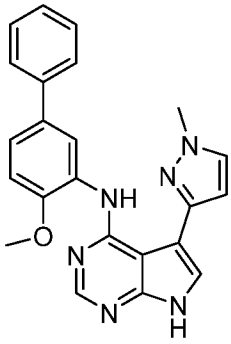
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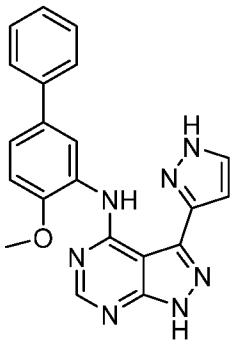
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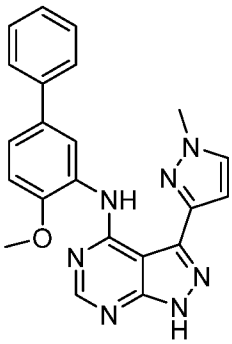
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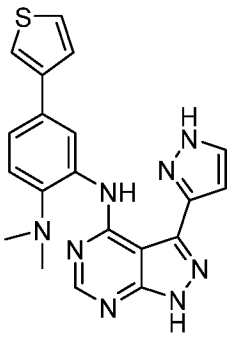
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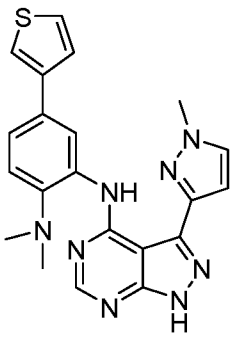
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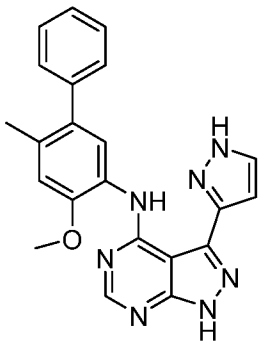
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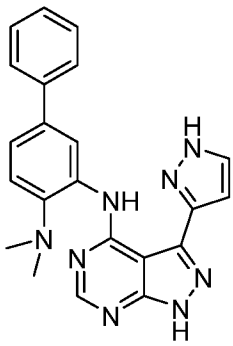
104A,



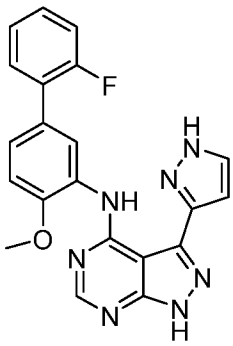
104B,



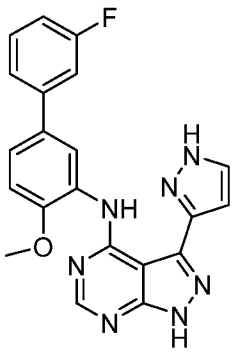
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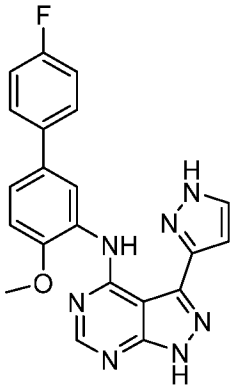
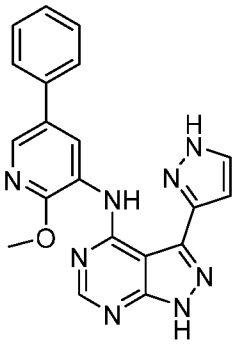
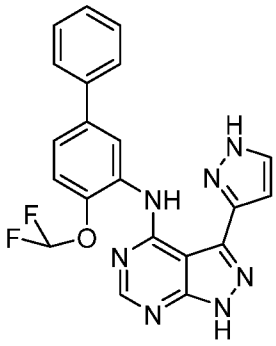
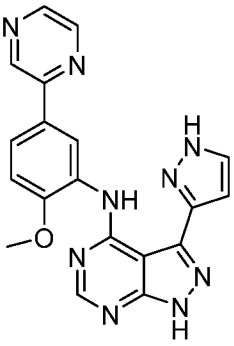
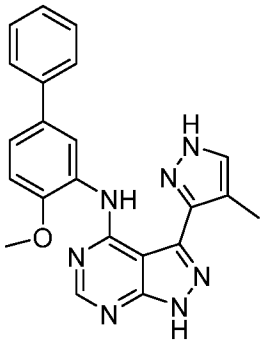
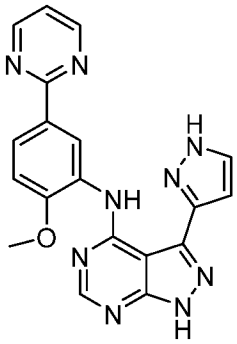
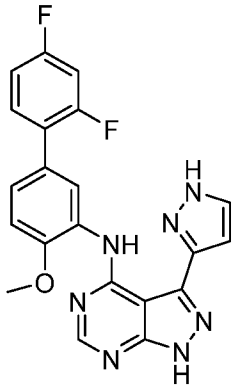
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8168A,

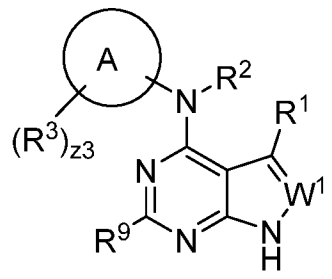


8168B,


8168C ,

8177 ,

8179 ,

8184 ,

8186 ,

8185 , or

8168A8168C .

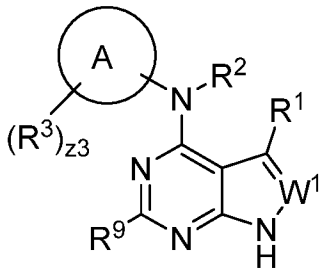
[0905] Embodiment 45. A pharmaceutical composition comprising a compound of one of embodiments 1 to 44 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0906] Embodiment 46. The pharmaceutical composition of embodiment 45, further comprising an anti-cancer agent.

[0907] Embodiment 47. A method of treating a disease associated with HER2 activity in a patient in need of such treatment, said method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:  (I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or

substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, $-C(O)O-$, $-OC(O)-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, $-C(O)O-$, $-OC(O)-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently

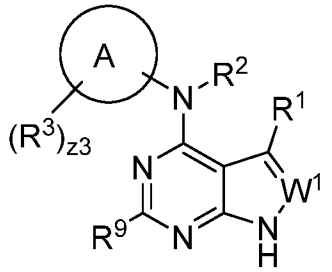
hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0908] Embodiment 48. A method of treating a disease associated with EGFR activity in a patient in need of such treatment, said method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:  (I); wherein; Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^6$-, -O-, -S-, -C(O)-, $-C(O)NR^6$-, $-NR^6C(O)$-, $-NR^6C(O)NH$-, $-NHC(O)NR^6$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted

heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0909] Embodiment 49. A method of treating cancer in a patient in need of such treatment, said method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:



(I);

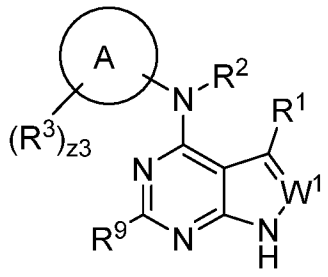
wherein; Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^6$-, -O-, -S-, -C(O)-, $-C(O)NR^6$-, $-NR^6C(O)$-, $-NR^6C(O)NH$-, $-NHC(O)NR^6$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^7$-, -O-, -S-, -C(O)-, $-C(O)NR^7$-, $-NR^7C(O)$-, $-NR^7C(O)NH$-, $-NHC(O)NR^7$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted

heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0910] Embodiment 50. The method of embodiment 49, wherein the cancer is resistant to a HER2 inhibitor.

[0911] Embodiment 51. The method of embodiment 49, wherein the cancer is resistant to an EGFR inhibitor.

[0912] Embodiment 52. A method of inhibiting HER2 activity, said method comprising contacting HER2 with an effective amount of a compound, or a pharmaceutically acceptable salt

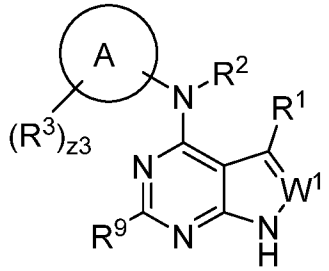


thereof, having the formula: (I); wherein; Ring A is aryl or heteroaryl; W^1 is N or C(H); R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, -C(O)-OR^{3C}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^6$-, -O-, -S-, -C(O)-, $-C(O)NR^6$-, $-NR^6C(O)$-, $-NR^6C(O)NH$-, $-NHC(O)NR^6$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, -C(O)-OR^{6C}, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^7$-, -O-, -S-, -C(O)-, $-C(O)NR^7$-, $-NR^7C(O)$-, $-NR^7C(O)NH$-, $-NHC(O)NR^7$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, -C(O)-OR^{7C}, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0913] Embodiment 53. The method of embodiment 52, wherein HER2 is in an active conformation.

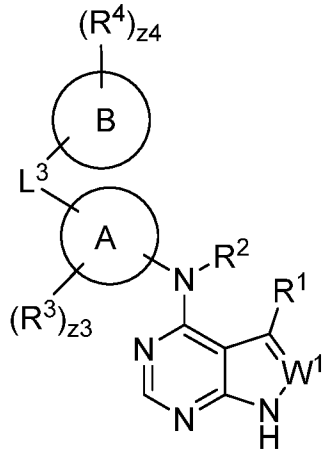
[0914] Embodiment 54. The method of embodiment 53, wherein HER2 is in a HER2-HER3 heterodimer.

[0915] Embodiment 55. A method of inhibiting EGFR activity, said method comprising contacting EGFR with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:  (I); wherein; Ring A is aryl or heteroaryl;

W^1 is N or C(H); R^1 is hydrogen, $-L^1-L^2-E$, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted

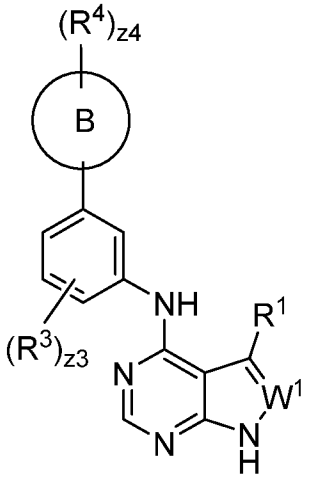
heteroaryl; E is an electrophilic moiety; each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0916] Embodiment 56. The method of embodiment 55, wherein EGFR is in an active conformation.

[0917] Embodiment 57. A method of one of embodiments 47 to 56, wherein the compound has the formula:  (II) wherein Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; L^3 is a bond, $-S(O)_2-$, $-NR^8-$, -O-, -S-, -C(O)-, $-C(O)NR^8-$, $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-NHC(O)NR^8-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^4$

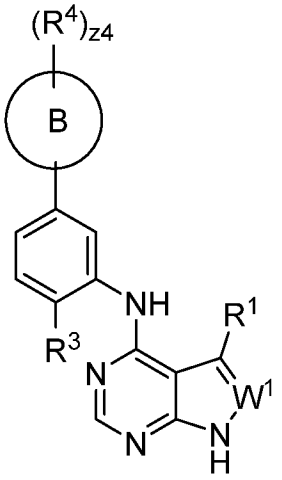
$^{A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^8 is independently halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, $-CN$, $-SO_{n8}R^{8D}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-C(O)R^{8C}$, $-C(O)-OR^{8C}$, $-C(O)NR^{8A}R^{8B}$, $-OR^{8D}$, $-NR^{8A}SO_2R^{8D}$, $-NR^{8A}C(O)R^{8C}$, $-NR^{8A}C(O)OR^{8C}$, $-NR^{8A}OR^{8C}$, 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; z4 is an integer from 0 to 5; Each R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{8A}, R^{8B}, R^{8C}, and R^{8D} is independently hydrogen, $-CX_3$, $-CN$, $-COOH$, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} 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^4 and X^8 are independently –F, -Cl, -Br, or –I; n4 and n8 are independently an integer from 0 to 4; and m4, m8, v4, and v8, are independently an integer from 1 to 2.

[0918] Embodiment 58. A method of one of embodiments 47 to 56, wherein the compound has the formula:



(III).

[0919] Embodiment 59. A method of one of embodiments 47 to 56, wherein the compound has the formula:



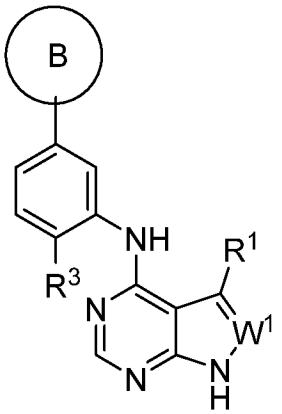
(IV).

[0920] Embodiment 60. The method of one of embodiments 47 to 59, wherein R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, or –CN.

[0921] Embodiment 61. The method of one of embodiments 47 to 59, wherein R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, or $-CH_2X^4$.

[0922] Embodiment 62. The method of one of embodiments 47 to 59, wherein R^4 is independently halogen.

[0923] Embodiment 63. A method of one of embodiments 47 to 62, wherein the compound has the formula:



(V).

[0924] Embodiment 64. The method of one of embodiments 47 to 63, wherein W^1 is C(H).

[0925] Embodiment 65. The method of one of embodiments 47 to 63, wherein W^1 is N.

[0926] Embodiment 66. The method of one of embodiments 47 to 65, wherein R^3 is an unsubstituted heteroalkyl.

[0927] Embodiment 67. The method of one of embodiments 47 to 65, wherein R^3 is unsubstituted 2 to 5 membered heteroalkyl.

[0928] Embodiment 68. The method of one of embodiments 47 to 65, wherein R^3 is –OCH_3, -OCH_2CH_3, -$N(CH_3)_2$, -NH_2, -$NH(CH_3)$, -$N(CH_2CH_3)_2$, -$NH(CH_2CH_3)$, -OCX^3_3, -OCH_2X^3, -$OCHX^3_2$, or -SH.

[0929] Embodiment 69. The method of one of embodiments 48 to 68, wherein Ring B is substituted or unsubstituted aryl or heteroaryl.

[0930] Embodiment 70. The method of one of embodiments 48 to 68, wherein Ring B is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0931] Embodiment 71. The method of one of embodiments 48 to 68, wherein Ring B is substituted or unsubstituted phenyl.

[0932] Embodiment 72. The method of one of embodiments 48 to 68, wherein Ring B is substituted or unsubstituted 5 to 6 membered heteroaryl.

[0933] Embodiment 73. The method of one of embodiments 48 to 68, wherein Ring B is substituted or unsubstituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

[0934] Embodiment 74. The method of one of embodiments 47 to 73, wherein R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0935] Embodiment 75. The method of one of embodiments 47 to 73, wherein R^1 is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0936] Embodiment 76. The method of one of embodiments 47 to 73, wherein R^1 is substituted or unsubstituted phenyl.

[0937] Embodiment 77. The method of one of embodiments 47 to 73, wherein R^1 is an unsubstituted phenyl.

[0938] Embodiment 78. The method of one of embodiments 47 to 73, wherein R^1 is a substituted or unsubstituted 5 to 6 membered heteroaryl.

[0939] Embodiment 79. The method of one of embodiments 47 to 73, wherein R^1 is an unsubstituted 5 to 6 membered heteroaryl.

[0940] Embodiment 80. The method of one of embodiments 47 to 73, wherein R^1 is substituted or unsubstituted pyridinyl, substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted

imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, or substituted or unsubstituted thiazolyl.

[0941] Embodiment 81. The method of one of embodiments 47 to 73, wherein R^1 is an unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl.

[0942] Embodiment 82. The method of one of embodiments 47 to 81, wherein R^1 is –L^1-L^2-E.

[0943] Embodiment 83. The method of one of embodiments 47 to 82, wherein L^1 is a bond, -C(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0944] Embodiment 84. The method of one of embodiments 47 to 82, wherein L^1 is a substituted or unsubstituted C_1-C_4 alkylene.

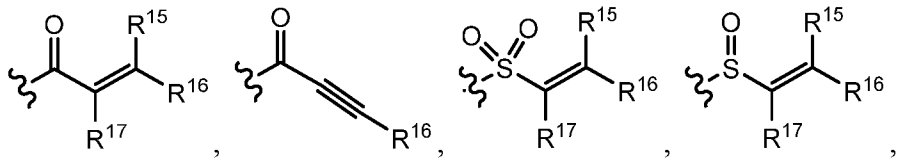
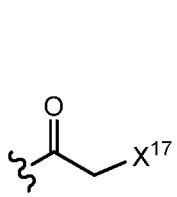
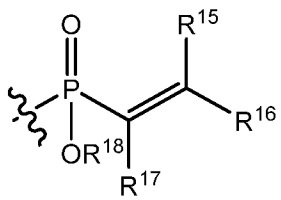
[0945] Embodiment 85. The method of one of embodiments 47 to 82, wherein L^1 is –$C(O)CH_2CH_2CH_2$-, –$C(O)CH_2CH_2$-, or –$C(O)CH_2$-.

[0946] Embodiment 86. The method of one of embodiments 47 to 85, wherein L^2 is -NR^7-, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heterocycloalkylene.

[0947] Embodiment 87. The method of one of embodiments 47 to 85, wherein L^2 is -NH-.

[0948] Embodiment 88. The method of one of embodiments 47 to 87, wherein E is a covalent cysteine modifier moiety.

[0949] Embodiment 89. The method of one of embodiments 47 to 87, wherein E is:

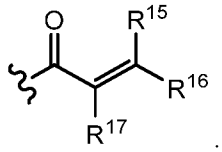
, or ; R^{15} is independently hydrogen, halogen, CX^{15}_3, -CHX^{15}_2, -CH_2X^{15}, -CN, -$SO_{n15}R^{15D}$, -$SO_{v15}NR^{15A}R^{15B}$, –$NHNR^{15A}R^{15B}$, –$ONR^{15A}R^{15B}$,

$-NHC=(O)NHNR^{15A}R^{15B}$,
$-NHC(O)NR^{15A}R^{15B}$, $-N(O)_{m15}$, $-NR^{15A}R^{15B}$, $-C(O)R^{15C}$, $-C(O)-OR^{15C}$, $-C(O)NR^{15A}R^{15B}$, $-OR^{15D}$, $-NR^{15A}SO_2R^{15D}$, $-NR^{15A}C(O)R^{15C}$, $-NR^{15A}C(O)OR^{15C}$, $-NR^{15A}OR^{15C}$, $-OCX^{15}_3$, $-OCHX^{15}_2$, 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^{16} is independently hydrogen, halogen, CX^{16}_3, $-CHX^{16}_2$, $-CH_2X^{16}$, -CN, $-SO_{n16}R^{16D}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHNR^{16A}R^{16B}$, $-ONR^{16A}R^{16B}$, $-NHC=(O)NHNR^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16C}$, $-C(O)-OR^{16C}$, $-C(O)NR^{16A}R^{16B}$, $-OR^{16D}$, $-NR^{16A}SO_2R^{16D}$, $-NR^{16A}C(O)R^{16C}$, $-NR^{16A}C(O)OR^{16C}$, $-NR^{16A}OR^{16C}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, 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^{17} is independently hydrogen, halogen, CX^{17}_3, $-CHX^{17}_2$, $-CH_2X^{17}$, -CN, $-SO_{n17}R^{17D}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC=(O)NHNR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17C}$, $-C(O)-OR^{17C}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17D}$, $-NR^{17A}SO_2R^{17D}$, $-NR^{17A}C(O)R^{17C}$, $-NR^{17A}C(O)OR^{17C}$, $-NR^{17A}OR^{17C}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{18} is independently hydrogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-C(O)R^{18C}$, $-C(O)OR^{18C}$, $-C(O)NR^{18A}R^{18B}$, 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^{15A}, R^{15B}, R^{15C}, R^{15D}, R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B}, R^{17C}, R^{17D}, R^{18A}, R^{18B}, R^{18C}, R^{18D}, are independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{15A} and R^{15B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; each X, X^{15}, X^{16}, X^{17} and X^{18} is independently –F, -Cl, -Br, or –I; n15, n16, n17, v15, v16, and v17, are independently an integer from 0 to 4; and m15, m16, and m17 are independently and integer from 1 to 2.

[0950] Embodiment 90. The method of embodiment 89, wherein R^{15}, R^{16}, R^{17}, and R^{18} are hydrogen.

[0951] Embodiment 91. The method of one of embodiments 89 to 90, wherein E is:



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[0952] Embodiment 92. The method of embodiment 91, wherein R^{15} is hydrogen; R^{16} is hydrogen, $-CH_3$, or $-CH_2NR^{16A}R^{16B}$; R^{17} is hydrogen; and R^{16A} and R^{16B} are independently hydrogen or unsubstituted alkyl.

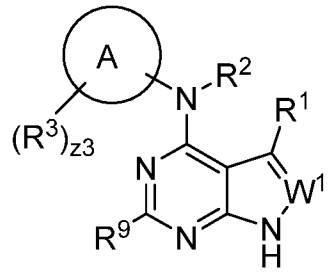
[0953] Embodiment 93. The method of embodiment 92, wherein R^{16A} and R^{16B} are independently unsubstituted methyl.

[0954] Embodiment 94. The method of embodiment 91, wherein R^{15} is hydrogen; R^{16} is hydrogen; R^{17} is hydrogen, $-CH_3$, or $-CH_2NR^{17A}R^{17B}$; and R^{17A} and R^{17B} are independently hydrogen or unsubstituted alkyl.

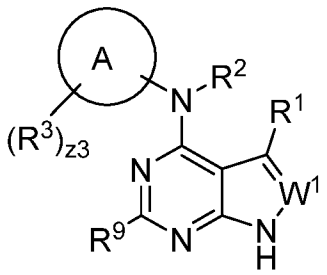
[0955] Embodiment 95. The method of embodiment 94, wherein R^{17A} and R^{17B} are independently unsubstituted methyl.

[0956] Embodiment 96. The compound of embodiment 91, wherein R^{15} is hydrogen, $-CH_3$, or $-CH_2NR^{15A}R^{15B}$; R^{16} is hydrogen; R^{17} is hydrogen; and R^{15A} and R^{15B} are independently hydrogen or unsubstituted alkyl.

[0957] Embodiment 97. The method of embodiment 96, wherein R^{15A} and R^{15B} are independently unsubstituted methyl.

[0958] Embodiment 98. An EGFR protein covalently bonded to a compound having the formula:  (I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H) R^1 is $–L^1$-L^2-E; R^2 is hydrogen, -CX^2_3, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, -CX^3_3, -CHX^3_2, -CH_2X^3, -OCX^4_3, -OCH_2X^3, -$OCHX^3_2$, -CN, -$SO_{n3}R^{3D}$, -$SO_{v3}NR^{3A}R^{3B}$, -NHC(O)$NR^{3A}R^{3B}$, -$N(O)_{m3}$, -$NR^{3A}R^{3B}$, -C(O)R^{3C}, -C(O)-OR^{3C}, -C(O)$NR^{3A}R^{3B}$, -OR^{3D}, -$NR^{3A}SO_2R^{3D}$, -NR^{3A}C(O)R^{3C}, -NR^{3A}C(O)OR^{3C}, -$NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, -$S(O)_2$-, -$S(O)_2$-Ph-, -NR^6-, -O-, -S-, -C(O)-, -C(O)NR^6-, -NR^6C(O)-, -NR^6C(O)NH-, -NHC(O)NR^6-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, -CX^6_3, -CHX^6_2, -CH_2X^6, -OCX^6_3, -OCH_2X^6, -$OCHX^6_2$, -CN, -$SO_{n6}R^{6D}$, -$SO_{v6}NR^{6A}R^{6B}$, -NHC(O)$NR^{6A}R^{6B}$, -$N(O)_{m6}$, -$NR^{6A}R^{6B}$, -C(O)R^{6C}, -C(O)-OR^{6C}, -C(O)$NR^{6A}R^{6B}$, -OR^{6D}, -$NR^{6A}SO_2R^{6D}$, -NR^{6A}C(O)R^{6C}, -NR^{6A}C(O)OR^{6C}, -$NR^{6A}OR^{6C}$, 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; L^2 is a bond, -$S(O)_2$-, -$S(O)_2$-Ph-, -NR^7-, -O-, -S-, -C(O)-, -C(O)NR^7-, -NR^7C(O)-, -NR^7C(O)NH-, -NHC(O)NR^7-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, -CX^7_3, -CHX^7_2, -CH_2X^7, -OCX^7_3, -OCH_2X^7, -$OCHX^7_2$, -CN, -$SO_{n7}R^{7D}$, -$SO_{v7}NR^{7A}R^{7B}$, -NHC(O)$NR^{7A}R^{7B}$, -$N(O)_{m7}$, -$NR^{7A}R^{7B}$, -C(O)R^{7C}, -C(O)-OR^{7C}, -C(O)$NR^{7A}R^{7B}$, -OR^{7D}, -$NR^{7A}SO_2R^{7D}$, -NR^{7A}C(O)R^{7C}, -NR^{7A}C(O)OR^{7C}, -$NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0959] Embodiment 99. A HER2 protein covalently bonded to a compound having the formula:  (I) wherein Ring A is aryl or heteroaryl; W^1 is N or C(H) R^1 is $–L^1-L^2-E$; R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl; R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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; z3 is an integer from 0 to 4; L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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; L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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; E is an electrophilic moiety; each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I; n3, n6, n7, and n9 are independently an integer from 0 to 4; and m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

[0960] 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 embodiments. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

EXAMPLES

A. Overcoming Resistance to HER2 Inhibitors

[0961] Within the EGFR family, HER2 and HER3 are unique. HER3 is classified as a pseudokinase with only residual kinase activity, whereas HER2 has no known activating ligand but is constitutively able to dimerize with other active family members. In this way HER2 and HER3 together form a functional RTK unit, with HER3 responding to activating ligands such as neuregulin (NRG), HER2 providing the intracellular kinase activity, and both intracellular domains providing phosphorylation sites. Additionally, HER2 and HER3 are each other's preferred heterodimerization partners and also form the most mitogenic complex among all possible EGFR family dimers[11]. Because of this co-dependence, HER3 is equally important for the formation, proliferation, and survival of HER2 overexpressing tumors[12].

[0962] Although HER2 amplification and overexpression is the most well studied means of oncogenic activation of the HER2/HER3 heterodimer, improper signaling can also be caused by secretion of the HER3 ligand NRG to stimulate HER2/HER3 heterodimers in an autocrine manner as well as by mutations in HER3 that stabilize and activate heterodimers independently of ligand[13, 14]. In addition, mutations that activate the HER2 kinase domain have also been reported[15-17].

[0963] Inhibition of HER2 using small molecule kinase inhibitors such as lapatinib or HER2-targeted antibodies such as ado-trastuzumab emtansine (T-DM1), have shown efficacy against

HER2-driven cancers in the clinic[18, 19]. However, recent studies have demonstrated that the presence of NRG induces resistance against currently-approved HER2 targeted mono-therapies through HER2/HER3 signaling[20, 21]. Additionally, inhibition of HER2/HER3 signaling at either the RTK level or of the downstream PI3K/Akt pathway releases a negative feedback loop that increases the transcription, translation, and membrane localization of HER3[22-24]. This increase in the level of HER3 causes a rebound in its phosphorylation and reactivation of the PI3K/Akt pathway even in the continued presence of lapatinib, indicating that formation of HER2/HER3 heterodimers is crucial for intrinsic cellular resistance to current HER2 targeted therapies[25]. This severe limitation illustrates why more effective therapies targeting the active HER2/HER3 dimer are required.

[0964] Here, we evaluated the ability of current reversible HER2 inhibitors to inhibit signaling and proliferation in cancer cell lines driven by HER2/HER3 heterodimers activated by different oncogenic mechanisms. Across several cell lines, stabilization of HER2 in the active conformation led to severely diminished activity of both lapatinib and TAK-285. We therefore aimed to identify a novel HER2/HER3 inhibitor that would preferentially target the active state of the heterodimer. Reasoning that a biochemical screen would be unable to capture the relevant cellular conformation of the fully formed transmembrane complex, we turned to a cell based screening strategy. A high throughput screen of 950,000 small molecules against an engineered Ba/F3 cell line dependent on NRG stimulated HER2/HER3 heterodimers yielded a hit scaffold that we optimized to create a next generation HER2 inhibitor. The optimized inhibitor is capable of potently inhibiting signaling from the HER2/HER3 heterodimer regardless of the activating oncogenic mechanism.

B. Active HER2/HER3 Heterodimers are Resistant to DFG in/α-C out binding Inhibitors

[0965] We first confirmed that the addition of the HER3 activating ligand NRG 1, hereafter referred to as NRG, is able to dramatically rescue the proliferation of HER2 over-expressing breast cancer cell lines treated with the HER2 kinase inhibitors lapatinib and TAK-285 (FIGS. 1A-1B). This rescue of cell proliferation was dose dependent and effective at pM concentrations of NRG in the presence of either HER2 inhibitor at 1 μM (FIG. 1C). To determine how NRG was able to so profoundly rescue cellular proliferation we examined a time course of HER2/HER3 signaling in SK-BR-3 cells exposed to either lapatinib, NRG, or the combination of the two. While lapatinib alone was able to rapidly and sustainably inhibit all signaling from HER2 and HER3, the addition of NRG prevented the complete inhibition of p-HER3 and all

downstream signaling pathways at all time points examined, although HER2 phosphorylation remained inhibited (FIG. 1D). Analysis of signaling from alternative EGFR family members that could potentially contribute to this phenotype revealed that p-EGFR actually decreased in response to NRG and was still able to be inhibited by lapatinib while HER4, which is thought to function as a tumor suppressor, was undetectable in this cell line [26,27] (FIG. 8).

[0966] The ability of NRG to rescue phosphorylation of HER3, but not of HER2, in the presence of lapatinib could have several origins. The very weak kinase activity of HER3 itself is unlikely to be sufficient – although it is not inhibited by lapatinib. A more likely explanation is that NRG-induced heterodimerization of HER2 and HER3 stabilizes a conformation of the HER2 kinase domain that is resistant to inhibition by the inhibitors tested. Both lapatinib and TAK-285 bind to the DFG in/α-C out kinase conformation and occupy the back hydrophobic pocket of HER2 that is only available when the kinase domain is in an inactive conformation with the αC-helix in the characteristic 'out' position. This mode of binding has the advantage of giving these inhibitors slow off-rates and increased selectivity, but could also explain their ineffectiveness in the presence of NRG. Crystal structures of EGFR family homodimers and of a HER3/EGFR kinase complex have shown that only the 'activator' kinase in the asymmetric dimer can retain the inactive conformation (FIG. 1E) [30,31]. In HER2/HER3 complexes HER3 will adopt this position exclusively, whereas HER2 will take the 'receiver' kinase position and become stabilized in the active conformation. Thus, in a HER2/HER3 complex, the size and accessibility of the back hydrophobic pocket of the HER2 kinase domain will be greatly reduced, preventing lapatinib or TAK-285 from binding.

[0967] To determine if NRG induced heterodimerization prevents lapatinib binding, we treated serum-starved SK-BR-3 cells with lapatinib either 15 min before or simultaneously with NRG stimulation, and then rapidly examined HER2/HER3 signaling to monitor the on-rate of lapatinib in these cells. Lapatinib concentrations greater than 100 nM were sufficient to inhibit the entire RTK signaling pathway when added before NRG (FIG. 2A), i.e. in the absence of HER2/HER3 heterodimers. By contrast, lapatinib was much less effective when added simultaneously with NRG – where lapatinib would need to bind to the NRG-induced HER2/HER3 heterodimer to inhibit signaling – with significant levels of p-HER3, p-Akt and p-Erk remaining even in the presence of 1 μM lapatinib (FIG. 2A). A similar trend was seen in MCF-7 cells, which express modest levels of HER2 and HER3, demonstrating that this effect does not require HER2 overexpression (FIG. 2A). The same trend was also observed when cells were first treated with either NRG or vehicle for 15 min followed by 15 min of lapatinib treatment (FIG. 9).

[0968] To assess if NRG's ability to rescue the cellular proliferation of cell lines where the HER2/HER3 dimer may be activated by alternative mechanisms we assessed signaling and proliferation in CW-2 cells, which contain an activating mutation in the C-lobe of HER3 (E928G) as well as an N-lobe mutation in HER2 (L755S). Such HER3 mutations have been reported to activate HER2 by stabilizing HER2/HER3 heterodimers independently of NRG[13, 30]. Similar to the HER2 overexpressing cell lines, the addition of NRG rescued the viability of the HER3 mutant line in a 72h proliferation assay from both HER2 inhibitors and rescued HER2/HER3 signaling from lapatinib even after 1h of drug exposure (FIGS. 2B-2C).

[0969] We next sought to determine whether this apparent resistance to lapatinib is specific to NRG-induced HER2/HER3 heterodimers or if mutations that bias HER2 towards its active conformation in the absence of NRG can elicit a similar effect. We monitored HER2 and HER3 signaling 15 min after the addition of lapatinib in the lung cancer cell line NCI-H1781, which contains an insertion in the HER2 kinase domain at a position known to increase HER2 kinase activity[16]. As shown in FIG. 2D, lapatinib, even at a concentration of 1μM, was unable to fully inhibit signaling demonstrating that this activating mutation is sufficient to hinder lapatinib binding to HER2.

[0970] Taken together, these data argue that NRG rescues HER2/HER3 driven cells from DFG in/α-C out inhibitors by stabilizing HER2 in the active conformation within HER2/HER3 heterodimers. This inability to directly target the active state of HER2 places a major limitation on the effectiveness of a majority of current HER2 inhibitors since inhibition of HER2/HER3 signaling triggers feedback loops that lead to the increased membrane expression of HER2 and HER3, which increases the number of active HER2/HER3 heterodimers that then rescue signaling and proliferation [22, 23, 25]. Our findings indicate that inhibitors which target the active HER2/HER3 heterodimer will have significant advantages, especially in situations that increase the number of active HER2/HER3 heterodimers.

C. Identification of a Novel Inhibitor of HER2/HER3 Heterodimers

[0971] In order to find a small molecule inhibitor capable of binding to the active HER2/HER3 signaling complex we developed a high throughput cellular screen using a Ba/F3 cell line engineered to be dependent on NRG-induced HER2/HER3 heterodimers. Ba/F3 cells are normally dependent on IL-3 signaling for their proliferation and survival, but can be made dependent on introduced oncogenic signals[32]. We sequentially selected transduced Ba/F3 cells for populations stably expressing HER3 and then HER2. To ensure that all of the proliferative

signal could be attributed to HER2/HER3 heterodimers, rather than HER2 homodimers, the 9 C-terminal tyrosines in HER2 were mutated to phenylalanine (HER2YF). We then withdrew IL-3 and supplemented the media with NRG to select for NRG dependent HER2YF/HER3wt cells (2YF/3wt). The resulting 2YF/3wt cell line was completely dependent on NRG for survival and allowed us to screen for inhibitors of full length HER2/HER3 heterodimers in their native cellular conformations using a cell viability assay. In addition to allowing us to identify potential inhibitors of active HER2, this cellular system also has the potential to uncover compounds with novel mechanisms of action – such as inhibitors of HER3's ability to allosterically activate HER2. This system could also identify inhibitors of HER3's weak kinase activity in the unlikely event that this is important for proliferation of 2YF/3wt cells.

[0972] To validate the screen and test the effectiveness of counter-screening with either the same 2YF/3wt Ba/F3 cell line or the parental Ba/F3's in the presence of IL-3 to remove cytotoxic primary hits, we first tested a panel of kinase inhibitors with established mechanisms of action. This panel of inhibitors demonstrated that MAPK pathway inhibitors (e.g. vemurafenib) would not score as hits in NRG-treated 2YF/3wt cells, whereas mTOR inhibitors (e.g. MLN0128) are ruled out in our toxicity counter screen, showing equal activity in the presence of either NRG or IL-3 (FIG. 10). By contrast, HER2 and PI3K inhibitors showed a clear window for selective inhibition of NRG driven cells over IL-3 driven cells (FIG. 3B). In order to rapidly remove any hit compounds that do not directly inhibit the HER2/HER3 heterodimer, we created a separate Ba/F3 cell line dependent on the overexpression of full-length wt Axl, which also signals through the PI3K pathway. As shown in FIG. 3B, this panel of Ba/F3 cell lines was suitable to segregate lapatinib from the PI3K inhibitor PIK-93.

[0973] The 48h proliferation assay of 2YF/3wt + NRG cells was miniaturized and optimized for 1536 well plates, which we used to screen a diverse collection of 950,000 drug-like molecules (Z' $\geq$0.75). This primary screen resulted in 14,012 hits (>50% inhibition vs DMSO) that was reduced to 1,423 compounds after triplicate confirmation and the parental Ba/F3 + IL-3 counter-screen (<30% inhibition vs DMSO), which were then assayed in dose response against all 3 cell lines (2YF/3wt + NRG, parental Ba/F3 + IL-3, and Axl+) (Table 1).

[0974] Table 1. Small molecule screening data

Category	Parameter	Description
Assay	Type of assay	Cell-based
	Target	ERBB3 (UniProt P21860, KEGG 2065), ERBB2 (UniProt P04626,

		KEGG 2064)
	Primary measurement	Detection of cell viability
	Key reagents	CellTiter-Glo Luminescent Cell Viability Assay (Promega)
	Assay protocol	Described in the Methods section
	Additional comments	
Library	Library size	950,000 compounds
	Library composition	Diverse set of small-molecule compounds, composing of known drug library, bioactive library with known mechanism of action (MOA) and also 750,000 proprietary compounds with unknown MOA
	Source	Commercially available and proprietary sources
	Additional comments	The compounds were stored at room temperature for max 6 months during HTS
Screen	Format	White 1,536-well solid bottom plates from Greiner or Corning
	Concentration(s) tested	4 μM compound, 0.4% DMSO
	Plate controls	4 uM lapatinib, 0.4% DMSO
	Reagent/ compound dispensing system	Compounds: Echo 555 Liquid Handler from Labcyte; cells, CellTiter-Glo reagent: Bottle valve dispenser from Kalypsys
	Detection instrument and software	ViewLux uHTS Microplate Imager (PerkinElmer)
	Assay validation/QC	Z' ≥ 0.75
	Correction factors	-
	Normalization	DMSO control
	Additional comments	
Post-HTS analysis	Hit criteria	>50% inhibition of the luminescence signal as compared to the DMSO control
	Hit rate	1.5%
	Additional assay(s)	Hit confirmation in triplicate with the screening assay. Counter screens: Ba/F3 and Ba/F3 Axl cell viability
	Confirmation of hit purity and structure	Compounds were re-synthesized

[0975] Compounds were first screened for the ability to inhibit the proliferation of the 2YF/3wt + NRG cells, counter-screened against the parental cells in the presence of IL-3, and then screened in dose response against all 3 cell lines. This screening and triaging process led to the identification of 3 compounds that share the same scaffold, exemplified by compound 1 (also referred to herein as compound 185) in FIG. 3C, which reproducibly showed preferential

inhibition of 2YF/3wt + NRG cell proliferation. Optimization of the scaffold through 5 iterations of analog synthesis, each consisting of approximately 10 compounds, led to exemplary compound 2 (also referred to herein as compound 55A), which shows a marked preference for the inhibition of the NRG driven cells (FIG. 3D).

D. THE CELLULAR ACTIVITY OF COMPOUND 2 RESULTS FROM HER2 INHIBITION

[0976] The specificity of compound 2 for the NRG-driven 2YF/3wt cells over Axl+ or 2YF/3wt cells in the presence of IL-3 indicated that the compound was likely interfering with signaling at the RTK level. This was confirmed by *in vitro* profiling against a panel of kinases, with compound 2 only showing potent inhibition of EGFR and Abl (Table 2).

[0977] Table 2. Complete profiling of compound 2 at 100nM conducted by Nanosyn.

Kinase	% Inhibition		
EGFR	95.595	CDK2	4.145
ABL1	95.195	PIM-1-KINASE	4.075
LCK	74.16	DYRK1B	4.01
SRC	63.24	MST1	3.855
FLT-3	59.99	PYK2	3.805
BLK	59.895	CK1-EPSILON	3.45
FGFR1	48.3	EPH-B4	3.44
MAP4K4	36.53	TYRO3	3.29
KDR	27.32	AMP-A1B1G1	2.685
GSK-3-BETA	20.465	EPH-A2	2.42
JAK3	20.43	TRKA	2.385
TRKC	15.655	MET	2.045
SGK1	14.44	IKK-BETA	1.915
AKT1	14.27	NEK2	1.53
IGF1R	13.315	IRAK4	1.465
TIE2	12.835	ITK	1.24
PDGFR-ALPHA	11.85	PKC-ALPHA	1.24
AURORA-A	9.945	JNK2	1.075
P70S6K1	8.875	CHEK1	0.965
CSK	6.955	TSSK1	0.665
P38-ALPHA	6.605	ROCK1	0.155
ALK	6.145	MAPKAPK-2	0.12
PRKD2	5.465	PAK2	0.085

DYRK1A	5	DAPK1	-0.52
PDK1	4.58	SYK	-2.115

[0978] To determine the mechanism of action of compound 2, we evaluated its ability to interact with HER2 or HER3 using an *in vitro* kinase assay or thermofluor respectively. In embodiments, compound 2 was equipotent to lapatinib against HER2 *in vitro* (FIG. 4A) and, surprisingly, was also capable of binding to HER3 (FIG. 4B). Moreover, compound 2 was also able to inhibit the small amount of HER3 auto-phosphorylation seen when the purified HER3 intracellular domain is clustered, indicating that it binds to the HER3 active site (FIG. 11).

[0979] To determine how compound 2 is able to interact with multiple members of the EGFR family, we determined the X-ray crystal structure of compound 2 bound to the EGFR kinase domain (FIG. 4D, Table 3).

[0980] Table 3. Data collection and refinement statistics (molecular replacement). [1] Each dataset was collected from a single crystal; [2] Values for highest resolution shell are shown in parenthesis; [3] $CC^{1/2}$ is 0.562 on highest resolution shell.

	EGFR/**2**
Data collection[1]	
Space group	P 3_1 2 1
Cell dimensions	
a, *b*, *c* (Å)	69.4, 69.4, 192
α, β, γ (°)	90, 90, 120
Resolution (Å)	50-3.30
R_{sym}[2]	0.057 (0.982)[3]
I/σ	21.4 (1.26)
Completeness (%)	99.7 (99.7)
Redundancy	3.4 (3.5)
Refinement	
Resolution (Å)	50-3.30
No. reflections	8562
R_{work} / R_{free}	0.24/0.27
No. atoms	
Protein	2333
Ligand	38
B-factors	
Protein	154.5
Ligand	128.5
R.m.s. deviations	
Bond lengths (Å)	0.003
Bond angles (°)	0.630

[0981] Although crystals were obtained with both the wild-type kinase domain and a V924R-mutated variant, the latter were optimized most readily. The V924R kinase domain crystallizes

in the inactive (autoinhibited) conformation in the absence of inhibitor or even when bound to the type I EGFR inhibitor erlotinib, because this mutation places a polar arginine side-chain in the middle of the hydrophobic patch used to form the asymmetric dimer required for EGFR to act as an activator[33, 34] (FIG. 4D). Strikingly, compound 2 was able to stabilize the active conformation of this mutated EGFR kinase domain in crystals, as evidenced by the "in conformation" of the α-C helix, which allows formation of the characteristic salt-bridge between the β3 lysine and the α-C glutamate, as well as the ordered extension of the activation loop (FIGS. 4D-4E). This finding indicates that this scaffold has a strong preference for binding and stabilizing the active conformation of EGFR family kinase domains. Interestingly, the HER3 kinase domain has only ever been crystallized in the inactive conformation, and failed to crystallize after introducing mutations designed to destabilize the inactive state or in the presence of compound 2 [35, 36]. This suggests that compound 2 may be stabilizing an alternate HER3 kinase domain conformation that could potentially prevent its ability to allosterically activate HER2.

[0982] In order to determine whether binding to HER2, HER3, or to both, is responsible for the anti-proliferative activity of compound 2 we created a series of Ba/F3 cell lines dependent on NRG-induced HER2/HER3 heterodimers that possessed methionine gatekeeper mutations (TM) in either kinase (2YF/3TM and 2YFTM/HER3wt) or both (2YFTM/3TM). The methionine gatekeeper mutation has been shown to prevent lapatinib from binding to HER2, and was able to reduce the ability of compound 2 to bind to either kinase in isolation (FIGS. 12A-12B).

[0983] Both lapatinib and gefitinib (an EGFR inhibitor capable of inhibiting HER2 to a lesser extent) were unable to inhibit the proliferation of either Ba/F3 cell line that contained the gatekeeper mutation in HER2 (FIG. 4F). Similarly, inhibition by compound 2 was only affected by the HER2 gatekeeper mutation, whereas the gatekeeper mutation in HER3 had little influence (FIG. 4F). These data indicate that the cellular activity of compound 2 is due to inhibition of HER2 kinase activity.

E. TYPE I INHIBITORS OF HER2 ARE INSENSITIVE TO NRG MEDIATED RESISTANCE

[0984] Further experimentation was performed to optimize the potency of these inhibitors against the Ba/F3 cell line panel. The crystal structure suggested that the extra-cyclic NH linker could form an intramolecular hydrogen bond with the 2-furan, which would help to stabilize the inhibitor in a conformation necessary for binding to the active kinase. The structure also

suggested that limiting the charge density on the other 2-furan ring would prevent negative interactions with the kinase. With these parameters in mind, the second optimization effort led to compound 3 (also referred to herein as compound 178), which showed superior activity to lapatinib in the 2YF/3wt + NRG cells, and specificity for this cell line over the others by multiple orders of magnitude (FIGS. 5A-5B, Table 4).

[0985] Table 4. Table of IC_{50} values (nM ± S.D., n=3 for 2YF/3wt + IL-3, Axl, and 2YF/3wt + NRG. n=2 for 2YF-L755S/3wt + NRG, 2YF-YVMA/3wt + NRG, and 2YF-VC/3wt + NRG).

	2YF/3wt + IL-3	**Axl**	**2YF/3wt + NRG**	**2YF-L755S/3wt + NRG**	**2YF-YVMA/3wt + NRG**	**2YF-VC/3wt + NRG**
Lapatinib	>3,333	>3,333	63.6 ± 12.5	>3,333	>10,000	>3,333
TAK-285	>10,000	>3,333	398.6 ± 110.7	NT	NT	NT
Compound 3	2536.7 ± 217.2	1172.3 ± 106.0	6.8 ± 0.2	38.2±2.9	11.4±0.1	7.7±1.0

[0986] *In vitro* kinase profiling of compound 3 revealed a similar profile to compound 2 as well as similar potency against HER2 (Table 5 and Table 6, and FIG. 13).

[0987] Table 5. Complete profiling of compound 2 at 1 μM conducted by Nanosyn.

Kinase	**% Inhibition**	**Kinase**	**% Inhibition**
ABL1	97.22	PYK2	20.195
EGFR	96.945	MST1	19.93
LCK	93.57	ALK	19.825
BLK	90.405	PDK1	18.29
FLT-3	89.42	CDK2	17.555
SRC	88.935	DYRK1A	16.68
FGFR1	86.27	ITK	13.945
MAP4K4	78.705	AMP-A1B1G1	12.91
KDR	71.28	P38-ALPHA	12.91
JAK3	69.355	MET	10.14
GSK-3-BETA	68.82	PIM-1-KINASE	8.705
TIE2	59.745	JNK2	6.62
SGK1	53.445	PKC-ALPHA	5.57
IGF1R	53.275	TYRO3	5.56
PDGFR-ALPHA	52.5	TRKA	4.495
AURORA-A	47.18	NEK2	2.985
TRKC	46.91	IKK-BETA	2.91

P70S6K1	38.41	CHEK1	2.265
AKT1	33.05	DAPK1	1.425
PRKD2	26.63	IRAK4	1.42
CSK	24.82	ROCK1	1.16
CK1-EPSILON	24.12	PAK2	1.07
DYRK1B	22.625	MAPKAPK-2	0.575
EPH-B4	21.67	TSSK1	-3.06
EPH-A2	20.97	SYK	-6.41

[0988] Table 6. Complete profiling of compound 3 at 1 μM conducted by Nanosyn.

Kinase	**% inhibition**	**Kinase**	**% inhibition**
MAP4K4	100	ITK	24
EGFR	99	AMP-A1B1G1	20
ABL1	98	PRKACA	20
LCK	98	CDK1	18
SRC	95	MET	16
FGFR1	93	ROCK1	16
MST1	84	CK1-EPSILON	11
MST2	84	CDK2	10
JAK2	83	CHEK1	10
FLT-3	78	IKK-BETA	8
KDR	74	JNK2	7
MEK2	70	PIM-1-KINASE	7
MEK1	66	PI3K-ALPHA	6
PDGFR-ALPHA	66	PDK1	5
CSK	62	PAK2	3
JAK1	52	P38-ALPHA	2
TYK2	51	CAMK4	0
IGF1R	46	DAPK1	-1
DYRK1A	41	MAPK1	-2
PYK2	41	MAPKAPK-2	-6
GSK-3-BETA	40	NEK2	-9
SYK	35	FAK	-10
IRAK4	34		
AURORA-A	31		
SGK1	31		
PKC-ALPHA	30		
EPH-A2	28		
PRKD2	28		

[0989] Compound 3 showed little to no shift in its ability to inhibit the growth or signaling of HER2 over-expressing cell lines in the presence of NRG (FIG. 5C, and FIG. 14). Additionally,

unlike lapatinib and TAK-285, 1μM compound 3 was able to inhibit the proliferation of HER2 overexpressing cells over a dose response of NRG, and was also able to induce cell death in the presence of NRG (FIGS. 15A-15C). To confirm that compound 3 could bind to the actively signaling HER2/HER3 heterodimer we looked at signaling 15 min after the addition of NRG in SK-BR-3 cells either pre-treated with compound 3 followed by NRG stimulation or simultaneously treated with compound 3 and NRG. The minimal influence of NRG on the ability of compound 3 to inhibit all levels of signaling with or without pre-incubation, especially when compared to lapatinib (such as comparing FIG. 5D to FIG. 2A), suggests that it is fully capable of binding to and inhibiting the active HER2/HER3 complex, which were not disrupted by compound 3 (FIG. 16). A similar result was obtained in the non-HER2 amplified MCF-7 cells, and when NRG or vehicle was added prior to a dose response of compound 3 (FIG. 17 and FIG. 18).

[0990] Consistent with the results in the HER2 overexpressing cell lines, CW-2 cells that harbor a HER3-activating mutation were equally sensitive to compound 3 +/- NRG in both proliferation and signaling assays (FIGS. 6A-6B). This superior activity of compound 3 compared to lapatinib towards the CW-2 cells was not due solely to the L755S mutation in HER2, as a similar trend was also seen in a Ba/F3 cell line dependent on the HER3 mutant, HER2YF/HER3E928G (2YF/3EG), which can grow independently of NRG. In these cells the addition of NRG reduces lapatinib and TAK-285 sensitivity by 55 and 40 fold respectively, but affects sensitivity to compound 3 by less than 5-fold (FIGS. 19A-19D). The ability of compound 3 to inhibit the activated form of HER2 was not limited to growth factor-induced heterodimers, as the mutationally activated form of HER2 in NCI-H1781 cells was rapidly and fully inhibited by compound 3, which translated into its ability to inhibit the proliferation of this cell line (FIGS. 6C-6D). To further evaluate the potential of compound 3 against HER2 mutants within a HER2/HER3 heterodimer we transduced wt HER3 containing Ba/F3 cells with reported HER2 oncogenic mutants in the HER2YF construct[15,16]. The resulting cell lines L755S (2YF-L755S/3wt), Y772_A775 dup (2YF-YVMA/3wt), and G776del insVC(2YF-VC/3wt) remained sensitive to compound 3 but showed complete resistance to lapatinib (Table 4).

[0991] An additional mechanism by which cancers can become dependent on HER2/HER3 dimers is through NRG mediated autocrine signaling. Proliferation of the NRG autocrine dependent CHL-1 cell line was similar between lapatinib and compound 3 when measured at 72h using Cell Titer Glo (FIG. 6E). However, monitoring the growth of CHL-1 cells using microscopy over the same time period showed that the anti-proliferative activity of compound 3

is immediate and more potent when compared to lapatinib, which takes some time to begin exerting its weaker anti-proliferative effect (FIG. 6F).

[0992] We next examined signaling in CHL-1 cells after 24h drug treatment and found that compound 3 was able to inhibit NRG autocrine signaling in the presence of feedback, evidenced by the increasing expression of HER2 and HER3 with increasing concentration of drug (FIG. 6G). To further examine the differing abilities of compound 3 and lapatinib to inhibit feedback-released signaling in the NRG autocrine cells, we pre-treated CHL-1 cells with lapatinib for 24h to induce feedback signaling, washed the cells, and then treated with a dose response of either lapatinib or compound 3 for an additional 24h. Whereas the ability of lapatinib to inhibit feedback signaling was reduced as compared to the 24h treatment by itself, compound 3 showed little to no shift in its ability to inhibit signaling – and showed complete inhibition at 1μM (FIG. 6H). Similar results were obtained in FaDu cells, which are also dependent on NRG autocrine signaling (FIGS. 20A-20B).

[0993] To determine the feasibility of using compound 3 *in vivo* we analyzed the pharmacokinetics after either IV or IP administration in mice (FIG. 14) and also reported for two compounds in Example I.

[0994] The conformational dynamics of protein kinases are critical for their function, and for many of the adaptable characteristics of kinase-driven signaling pathways such as hypersensitivity, insulation, feed-back inhibition, feed-forward activation, and desensitization. Particular kinase conformations also offer access to distinctive structural features that can be exploited in the design of inhibitors to gain selectivity even among well conserved protein families. The DFG in/α-C out binding inhibitor lapatinib targets the inactive state of a kinase with its benzyl ether substituent. What has so far been largely unappreciated is the vulnerability of type I inhibitors to mechanisms that stabilize the active state of the targeted kinases, which lead to drug resistance as we describe here.

[0995] The challenge is therefore to develop a potent inhibitor of the HER2/HER3 heterodimer whose selectivity is independent of binding to the inactive state. In order to discover such an inhibitor we turned to a cell-based screen, which have shown a unique ability to identify novel kinase inhibitors that target the relevant conformation of a protein in its endogenous environment. A screen of approximately one million small molecules revealed a novel inhibitor whose potency and selectivity were improved through iterative rounds of medicinal chemistry. The resulting EGFR family inhibitor demonstrates the striking ability to inhibit the mutationally-

activated form of HER2 as well as NRG-stabilized HER2/HER3 signaling complexes, both of which are insensitive to the clinical inhibitor lapatinib.

[0996] One unique trait of our inhibitors is their ability to interact with not only HER2, but with the kinase domain of HER3 as well.

[0997] While our approach sought to find a single agent that could address the challenge of inhibiting the active HER2/HER3 heterodimer alternative strategies using the HER2 targeting antibody pertuzumab in conjunction with T-DM1 have also been shown to be efficacious. This treatment regimen would require sufficient doses of both drugs to be consistently present for activity as either agent by itself is unable to inhibit signaling or growth of HER2 driven cells in the presence of NRG[20]. Additionally, this dual anti-body based strategy would be unable to target the p95 fragment of HER2, which is associated with trastuzumab resistance [42,43] and poorer clinical outcomes [44, 45].

[0998] Another potential strategy to target the NRG stimulated HER2/HER3 heterodimers is to use irreversible inhibitors of HER2, for example neratinib.

F. Materials and Methods

[0999] **Cell Culture and Reagents.** BT-474, MCF-7, NCI-H1781, CHL-1, FaDu, were purchased from ATCC, CW-2 cells were purchased from Riken Cell Bank, HEK293T cells were purchased from the UCSF cell culture facility, and EcoPack-293 cells were purchased from Clontech. SK-BR-3 cells and parental Ba/F3 cells were obtained from UCSF. All cell lines were maintained at 37°C and 5% CO_2. BT-474, NCI-H1781, CW-2, Axl+ Ba/F3, and 2YF/3EG Ba/F3 cells were maintained in RPMI-1640 (Gibco) + 10% FBS. MCF-7, CHL-1, FaDu, HEK293T, and EcoPack-293 cells were maintained in DMEM (Gibco) + 10% FBS. SK-BR-3 cells were maintained in McCoy's 5A (Gibco) + 10% FBS. Parental Ba/F3's were maintained in RPMI-1640 + 10% FBS supplemented with 10ng/mL IL-3. 2YF/3wt, 2YF/3TM, 2YFTM/3wt, 2YFTM/3TM, 2YF-L755S/3wt, 2YF-YVMA/3wt, and 2YF-VC/3wt Ba/F3 cells were maintained in RPMI-1640 + 10% FBS supplemented with 6.25ng/mL NRG.

[1000] Lapatinib and TAK-285 were purchased from Selleckchem and were aliquoted and stored as 10mM DMSO stocks at -20°C. Anti-phospho-EGFR (Y1068) (cat#3777), anti-EGFR (cat#4267), anti-phospho-HER2 (Y1221/Y1222) (cat#2243), anti-HER2 (cat#2165), anti-phospho-HER3(Y1289) (cat#2842), anti-HER3 (cat#12708), anti-HER4 (cat#4795), anti-phospho-Akt(T308) (cat#2965), anti-Akt (cat#2920), anti-phospho-ERK (cat#9101), anti-ERK (cat#4695), anti-phospho-S6 (S240/244) (cat#2215), anti-S6 (cat#2217), anti-phospho-4-EBP1

(T37/46) (cat#2855), anti-4EBP1 (cat#9644), anti-α-tubulin (cat#3873), and human neuregulin-1 (cat#5218) were purchased from cell signaling technologies. Mouse IL-3 (cat#PMC0034) was purchased from Gibco.

[1001] Cloning and Ba/F3 Cell Selection. Site-directed mutagenesis was performed according to standard protocols on the human HER2 and HER3 sequences in pcDNA3.1. The desired constructs were Gibson cloned into the pMSCV plasmid (Clontech) containing the puro resistance (HER3, Axl) or neo resistance (HER2) gene[46]. The sequences of all constructs were confirmed with DNA sequencing. To produce virus, EcoPack-293 cells in a 6-well plate were transfected with the desired pMSCV plasmid using lipofectamine LTX (Invitrogen) according to the manufacturer's protocol. Media was exchanged 8h after transfection. 48h after transfection the viral supernatant was filtered through a 0.2μM filter and added to one well of a 6 well plate containing $2x10^6$ Ba/F3 cells in 1 mL of RPMI media containing 40% FBS, 10 ng of IL-3, and 4 μg of polybrene (Sigma). The cells were then centrifuged at 2,000 x g for 90 min at room temperature, placed back in the incubator for 24h, and then added to a T-75 flask containing fresh RPMI-1640 media supplemented with 10 ng/mL of IL-3 and incubated for an additional 24h.

[1002] For the 2YF/3wt cells, the parental cells were first transduced with HER3 according to the protocol above and were then spun down at 500xg for 5 min and re-suspended in media supplemented with 10 ng/mL IL-3 and 3 μg/mL puromycin (Invitrogen). Cells were maintained in these conditions for seven days, passaging as required. After seven days the cells were spun down, washed with fresh media, and then used for a subsequent round of transduction according to the protocol above with HER2YF virus. 48h after the second transduction, the cells were re-suspended in RPMI-1640 containing 10 ng/mL IL-3 and 800 μg/mL G418 (Invitrogen). The cells were maintained in these conditions for seven days, passaging as required. After seven days the cells were spun down, washed with fresh media, and then suspended in media supplemented with 10 ng/mL of NRG. Cells were maintained in these conditions for seven days to select for a NRG dependent population of 2YF/3wt Ba/F3 cells that were then maintained as described above. The same protocol was used for the 2YF-L755S/3wt, 2YF-YVMA/3wt, and 2YF-VC/3wt cell lines using the indicated constructs.

[1003] For the HER2YF/3TM, HER2YFTM/3wt, and HER2YFTM/3TM Ba/F3 cell lines, an identical protocol was used with the exception that the populations were first selected for

expression of the indicated HER2 construct (G418 resistance), followed by the expression of the indicated HER3 construct (puromycin resistance).

[1004] For HER2YF/3EG Ba/F3 cells were selected according to the protocol for the HER2YF/3TM Ba/F3's with the exception that no NRG was supplemented in the media during IL-3 independent selection.

[1005] For Axl+ cells, the transduced cells were spun down at 500xg for 5 min and resuspended in media supplemented with 10 ng/mL IL-3 and 3 μg/mL puromycin (Invitrogen). Cells were maintained in these conditions for 7 days, passaging as required. After 7 days the cells were spun down, washed with fresh media, and then suspended in IL-3 free media. The cells were maintained in these conditions for 2 weeks to select for an IL-3 independent population of Axl+ driven cells.

[1006] **Proliferation Assays.** For adherent cell lines, cells were plated onto opaque white 96 well plates (Greiner cat#655083) and allowed to adhere overnight. The following day media was changed to fresh media that contained either DMSO or the indicated concentration of drug plus NRG (50ng/mL final concentration) as indicated. Plates were incubated at 37°C for 72h and proliferation was read out using Cell Titer Glo (Promega) according to the manufacturer's protocol. For Ba/F3 cell proliferation, cells, drug dilution, and any necessary growth factors (10 ng/mL IL-3 or 6.25 ng/mL NRG) were combined in a well of a 96 well plate. Plates were incubated at 37°C for 48h and proliferation was read out using Cell Titer Glo according to the manufacturer's protocol. For all normalized assays, proliferation was normalized to the DMSO control condition. All graphs were plotted in GraphPad Prism 6 and fit with a non-linear regression of the log(inhibitor) vs response with a variable slope where shown. All graphs are averages (+/- standard deviation) of biological triplicates each performed in technical triplicate unless otherwise noted. If only one biological replicate was performed standard deviations were derived from the technical replicates.

[1007] **Immunoblotting.** Cells were grown in 6 well plates and treated according to the indicated conditions at which point the media was aspirated, cells were washed with 1mL of cold PBS, which was then aspirated and the plates were frozen at -80°C. The frozen cells were thawed on the plates in a buffer containing 50mM Tris pH 7.5, 150mM NaCl, 1mM EDTA, and 1% Triton X-100 supplemented with 1x phosphatase (PhoSTOP, Roche) and 1x protease (complete-mini tablets, Roche) inhibitors. Lysates were scraped, transferred to Eppendorf tubes, and cleared by centrifugation at 20,000xg for 20 min at 4°C. The clarified lysates were

transferred to chilled, clean tubes, and normalized for protein concentration by Bradford (Bio-Rad). The normalized lysates were diluted with Laemmli loading buffer, and 10µg of total protein was run on a 4-12% gradient gel (Invitrogen), which was then transferred to .45 µM nitrocellulose (Bio-Rad) and analyzed using the indicated primary antibodies according to the manufacturer's recommendations. Primary antibodies were detected using IRDye secondary antibodies (Li-Cor) according to the manufacturer's recommendations and scanned on an Odyssey imager (Li-Cor). Scanned images were cropped and assembled in Adobe Illustrator 6.

[1008] For the HER3 immunoprecipitation cells were treated the same as above but lysed in a buffer containing 20 mM Tris pH=7.5, 150mM NaCl, 1mM EDTA, and 1% Triton X-100 supplemented with 1x phosphatase (PhoSTOP, Roche) and 1x protease (complete-mini tablets, Roche) inhibitors. 1 mg of of the total protein was immunoprecipitated with the HER3 anti-body (CST, cat#12708) at 4°C overnight, followed by incubation with protein A beads (CST cat#8687) for 30 min at room temperature. The beads were washed 3x with lysis buffer, eluted by boiling in 3x laemmli buffer and analyzed by western blot as detailed above.

[1009] **High Throughput Screening and Analysis.** For compound screening, 20 nL of 1 mM compound solutions in DMSO were transferred (Echo Labcyte) into white 1,536-well plates. Subsequently, cells were seeded in 5 µL of growth medium (500 cells per well) using an automated plate filler (Kalypsys), resulting in 4 µM compound concentration. Each assay plate included neutral (DMSO only) and inhibitor (lapatinib) control wells. CellTiter-Glo Reagent (Promega, 2 µL/well) was added two days later. Luminescence signal was read after 10 minutes using an automated plate reader (ViewLux or Envision, Perkin-Elmer). The data were analyzed using the Genedata Screener software, normalized by neutral control. The percentage inhibition for each tested compound was calculated on per-plate basis, and all compounds that showed over 50% inhibition of the luminescence signal as compared to the DMSO control were picked as primary hits for triplicate confirmation. Hits confirmed with > 50% inhibition in two out of the three replicates were subsequently assayed in parental Ba/F3 +IL3 cells and non-toxic hits (< 30% inhibition in parental cells) were further assayed in dose response in 2YF/3wt + NRG, parental BaF3 +IL-3, and BaF3-Axl cells in order to identify hits that selectively inhibit the 2YF/3wt cells in the presence of NRG.

[1010] ***In vitro*** **Kinome Screen**. In vitro profiling of compound 2 at 100 nM was conducted by Nanosyn.

[1011] Real Time Cell Growth Assay. CHL-1 cells were plated in clear bottom black 96 well plates (Corning cat# 3904) and allowed to adhere overnight. The following day media was changed to fresh media that contained either DMSO or the indicated concentration of drug. Confluence was measured every 2h for 96h using 2 bright field images per well taken on an IncuCyte Zoom (Essen BioScience). Data were graphed in GraphPad Prism 6 and are averages of biological duplicates, each performed in technical triplicate.

[1012] *In vitro* HER2 Kinase Assay. *In vitro* kinase assays with the HER2 kinase domain (SignalChem) were performed in triplicate as follows. To 9 µL of a 2.5x solution of kinase and substrate in reaction buffer was added 3µL of a 5x DMSO or inhibitor dilution in 10% DMSO:water. The inhibitor/kinase solution was incubated at room temperature for 10 minutes. The kinase assay was initiated by the addition of 3 µL of a 5x solution of ATP, and ran for 15 minutes. The final reaction conditions were 50mM Tris (pH7.4), 5mM $MnCl_2$, 0.01% Tween-20, 2mM DTT, 100 µM E_4Y substrate (SignalChem), 15 nM HER2, 2% DMSO, 50 µM ATP, and 1 µCi γ^{32}P-ATP. After 15 minutes, 3 µL of each reaction was pipetted onto phosphocellulose sheets (P81, Whatman) and allowed to dry. The sheets were then washed 4 x 5 min with a solution of 0.5% phosphoric acid, dried, and exposed to a phosphor screen overnight. Phosphorimaging was conducted on a Typhoon 9500, image intensities were quantified in ImageQuant 5.2, normalized to the DMSO control and plotted in GraphPad Prism 6.

[1013] HER3 Thermofluor Assay. The HER3 gatekeeper mutation (T787M) was introduced into the HER3 tyrosine kinase domain in the pFastBac plasmid using standard protocols. Both wt and T787M HER3 were purified according to the previously published protocols[35]. Thermofluor reactions were performed in duplicate and set up as follows. 1 µL of an inhibitor or DMSO dilution in 40% DMSO:water was added to 19 µL of the HER3 kinase domain in reaction buffer. The final reaction solution contained 100mM MOPS, 200mM NaCl, 5% glycerol, 5mM MgCl2, 0.1mM DTT, 5x SYPRO orange, 2µM kinase, 2% DMSO and 20µM inhibitor in the wells of a 96-well, low profile, white, PCR plate (USA scientific). The solution was pipetted up and down to mix, sealed with TempAssure clear PCR flat caps (USA Scientific), centrifuged at 500xg for 30s, and heated in a Stratagene Mx3005P RT-PCR machine from 25°C to 95°C in 0.5°C increments every 30s after an initial incubation at 25°C for 10 min. Fluorescence was measured at the end of each 30s period with an excitation wavelength of 492 nm and an emission wavelength of 610 nm. To obtain the melting temperature, fluorescent signals were normalized to the maximum fluorescent signal for that well. Values after the well had reached a maximum signal were discarded and the signals were fit to the Boltzmann

equation in Graphpad Prism 6. ΔT_m was calculated as the difference in melting temperature between the compound treated kinase compared to the DMSO control.

[1014] Transfected HER2 kinase Activity. The HER2 gatekeeper mutation (T798M) was introduced into the HER2 gene in pcDNA3.1 using standard protocols. HEK293T cells were transfected with the indicated pcDNA3.1 constructs of HER2 using Lipofectamine LTX according to the manufacturers protocol. 24h after transfection the media was exchanged for fresh drug containing media. After 1h of drug treatment the cells were processed for immunoblots according to the above protocol.

[1015] Cell Death Assay. Cells were plated in clear bottom, black, 96 well plates (Corning cat#3904) and allowed to adhere overnight. The following day media was changed to fresh media that contained 1x concentration of CellTox green (Promega) and either DMSO or the indicated concentration of drug and NRG. Cells were allowed to grow for 72h after which the number of dead cells was measured using the IncuCyte Zoom. Immediately after the 72h read, 5 µL of 1.25% Triton X-100 was added to each well, which were then incubated at 37°C for 30 min to lyse all cells that were then counted by the IncuCyte. The percent cell death was calculated by dividing the number of dead cells counted at 72h by the number of total DNA containing cells after the detergent treatment. Values are the average of biological triplicate each performed in technical triplicate and were plotted in GraphPad Prism 6.

[1016] Crystallization and Structure Determination. $EGFR^{672-998}$/V924R protein expression and purification was performed exactly as previously described[34]. For the EGFR TKD^{V924R}/55A structure, EGFR TKD protein was concentrated to 8 mg/ml in 20 mM Tris-HCl, pH 8.0, containing 150 mM NaCl and 2 mM DTT. Protein was co-crystallized with excess of a drug **2** (1:2 molar ratio) in a reservoir solution of 1.34M ammonium sulfate, 1.34% (v/v) PEG 400, and 0.1 M sodium acetate/acetic acid pH 5.5 in the hanging drop at 21˚C. Crystals were cryo-protected in reservoir solution with added 20% (w/v) glycerol and flash frozen in liquid nitrogen. Diffraction data were collected at beamline 23ID-B of GM/CA@APS (Advanced Photon Source), where crystals diffracted to 3.3 Å, and were processed using HKL2000 (see Table 2). The structure was solved by molecular replacement using Phaser with the active EGFR (WT) TKD structure (PDB 1M17) as an initial search model. Repeated cycles of manual building/rebuilding using Coot were alternated with rounds of refinement employing REFMAC and PHENIX, plus composite omit maps calculated using PHENIX. Coordinates, parameter files

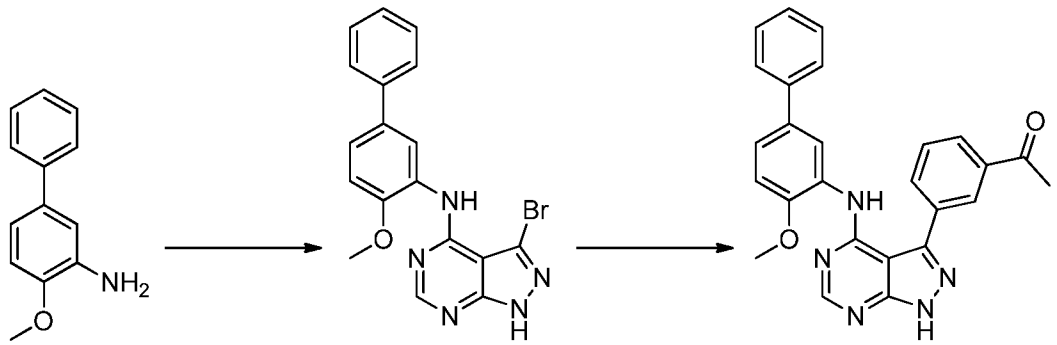
and molecular topology of compound 2 were generated by PRODRG[47]. Data collection and refinement statistics are shown in Table 2, and structural figures were generated with PyMOL.

[1017] HER3 Autophosphorylation Assay. ErbB3-ICD$^{665-1323}$ wild-type expression and purification was performed exactly as previously described[35]. To monitor the change in autophosphorylation, 1μM ErbB3-ICD$^{665-1323}$ protein was incubated with inhibitors (varied concentrations noted in the figure) and DOGS-Ni-NTA (prepared as described in Zhang et al.[4]) in 100 mM MOPS pH 7.4, containing 200 mM NaCl, divalent cations (2 mM $MnCl_2$ plus 5 mM $MgCl_2$), 5 % glycerol, 0.1 mM DTT and 200 μM ATP for 1 hour at 25℃, and the reactions were stopped by adding 50 mM EDTA and SDS-PAGE gel-loading buffer for rapid qualitative comparison of autophosphorylation by SDS-PAGE and immunoblotting with anti-phosphotyrosine (pY20) and anti-$(His)_5$.

[1018] Pharmacokinetic Evaluation of Compound 3. Pharmacokinetic profiling of compound 3 was performed by Biotranex.

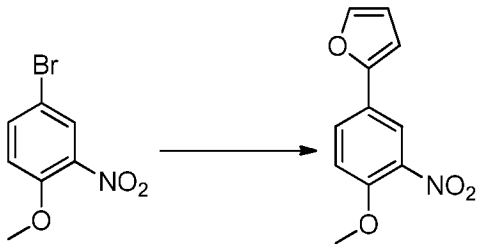
G. Chemical Synthesis

[1019] General Methods: Reactions were performed in sealed vials with magnetic stirring. All commercial reagents were used without further purification. All microwave reactions were performed on a discover system (CEM). Silica gel chromatography was performed on a Combiflash Rf + using column cartridges pre-packed with 40-60 micron silica (Teledyne Isco). All RP-HPLC were performed with a Waters 2545 binary gradient module equipped with an XBridge prep C18 column using H2O + 0.1% formic acid and CH3CN + 0.1% formic acid (5-95% gradient) while monitoring at 254 nm. Low resolution mass spectra (LC/ESI-MS) were recorded in positive and negative mode on a Waters TQ detector with an Acquity UPLC equipped with a BEH C18 column. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer or a Bruker Avance DRX500 spectrometer and referenced to solvent peaks. Coupling constants (*J*) are reported in hertz, chemical shifts are reported in δ (ppm) as either s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets), or m (multiplet).



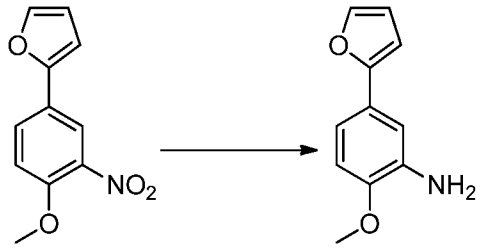
4 1

[1020] 1-(3-(4-((4-methoxy-[1,1'-biphenyl]-3-yl)amino)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone (**1**): A microwave tube containing 19.3 mg of 5-phenyl-o-anisidine (0.097 mmol), 25.1 mg of 3-bromo-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (0.11 mmol), 9.2 µL of glacial acetic acid (0.16 mmol) and 1 mL of n-butanol with a stir bar was capped and heated to 130°C for 15 min in a microwave reactor. The reaction was cooled and concentrated by rotary evaporation. The residue was recrystallized in ethanol to give 30.7 mg of crude **4** as a white solid. The crude **4** was added to a microwave tube containing 54.2 mg of 3-acetylphenyl-boronic acid (0.31 mmol), and 68.5 mg of potassium phosphate (0.31 mmol) in 1.5 mL of dioxane:H_2O (3:1) with a stir bar, which was sparged with argon for 5 min. 6.3 mg of XPhos Pd G2 (.0078 mmol) and 7.8 mg of SPhos (.016 mmol) were then added to the microwave tube which was purged with argon and heated to 150°C for 20 min in a microwave. The reaction was cooled, concentrated *in vacuo*, and the residue was purified by silica gel chromatography (eluent, Hex:EtOAc = 3:1 to 1:3) to give 26.4 mg (62.5% over 2 steps) of **1** as a white powder. MS (ES+) *m/z* 436.9 $(M + H)^{+1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.66 (s, 3H), 3.60 (s, 3H), 7.08 (d, 1H, *J*=8.6 Hz), 7.33 (m, 2H), 7.47 (t, 2H, *J* =7.7 Hz), 7.62 (m, 2H), 7,84 (t, 1H, *J*=7.7 Hz), 7.98 (s, 1H), 8.06 (dt, 1H, *J*=7.7, 1.3 Hz), 8.21 (dt, 1H, *J*=7.8, 1.3 Hz), 8.33 (t, 1H, *J*=1.5 Hz), 8.60 (s, 1H), 9.12 (d, 1H, *J*=2.2 Hz), 14.04 (s, 1H) ; ^{13}C NMR(DMSO-d6, 400 MHz) δ 27.29, 56.19, 99.25, 111.45, 118.68, 121.87, 126.84, 127.38, 128.70, 128.86, 129.08, 129.40, 130.35, 133.3, 133.73, 133.97, 137.98, 140.71, 143.5, 148.09, 154.45, 155.99, 156.1, 198.1.



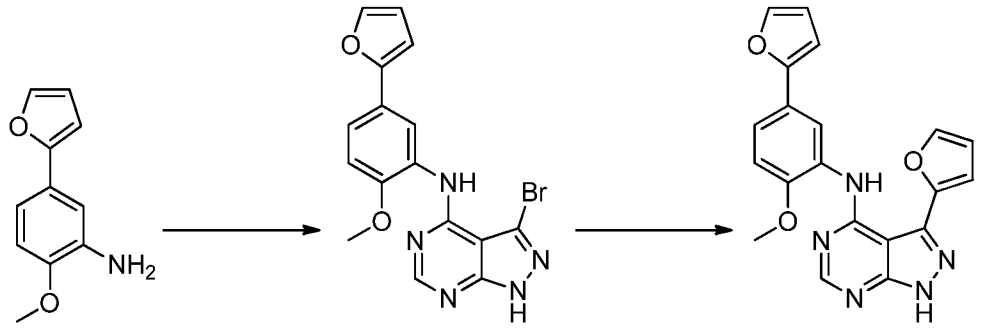
5

[1021] 2-(4-methoxy-3-nitrophenyl)furan (**5**): A vial containing a stir bar and a solution of 166.3mg of 4-bromo-2-nitroanisole (.72 mmol) and 247.6 mg 2-Furanylboronic acid MIDA ester (1.11 mmol) in 4.35 mL of 1,2 dimethoxyethane and 2.9 mL of 1M Na_2CO_3 in H_2O was sparged with argon for 5 min. 172 mg of Tetrakis(triphenylphosphine)palladium(0) (0.15 mmol) was added and the reaction, which was purged with argon and stirred at 80°C for 12h. The reaction was cooled and water was added to the reaction mixture, which was extracted 3 times with dichloromethane. The combined organic layer was washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (eluent, Hex:EtOAc = 1:0 to 3:1) to give 140.4 mg (89%) of **5** as a yellow solid. MS (ES+) *m/z* 220.4 $(M + H)^{+1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.96, (s, 3H), 6.62 (dd, 1H, *J*=3.4, 1.8 Hz). 7.03 (dd, 1H, *J*=3.4, 0.7 Hz), 7.44 (d, 1H, *J*=9.1 Hz), 7.77 (dd, 1H, *J*=1.8, 0.7 Hz), 7.97 (dd, 1H, *J*=8.8, 2.3 Hz), 8.17 (d, 1H, *J*=2.3 Hz); ^{13}C NMR(DMSO-d6, 500 MHz) δ 57.31, 106.85, 112.74, 115.50, 120.06, 123.67, 129.43, 140.11, 143.72, 151.28, 151.37.



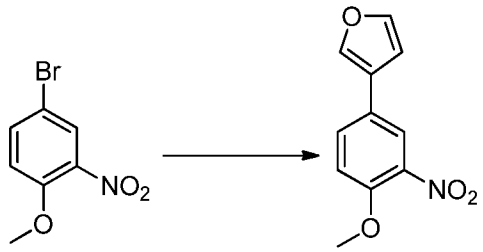
5 **6**

[1022] 5-(furan-2-yl)-2-methoxyaniline (**6**): To a vial containing a stir bar and 131.4 mg of **5** (0.6 mmol) in 2 mL THF was added 686 μL glacial acetic acid (12 mmol). The solution was stirred at 0°C for 5 min and 1.178 g of powdered zinc (18 mmol) was added. The reaction was allowed to warm to room temperature over 1h. The reaction was then diluted with MeOH, filtered, and concentrated *in vacuo*. The resulting residue was extracted from saturated sodium bicarbonate with 3 portions of dichloromethane. The pooled organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated to give 94.4 mg (83%) of **6** as an off white solid. MS (ES+) *m/z* 190.6 $(M + H)^{+1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.79 (s, 3H), 4.82 (s, 2H), 6.51 (dd, 1H, *J*= 3.3, 1.8 Hz), 6.6 (dd, 1H, *J*=3.3, 0.7 Hz), 6.83 (d, 1H, *J*=8.5 Hz), 6.9 (dd, 1H, *J*=8.3, 2.1 Hz), 6.99 (d, 1H, *J*=2.07 Hz), 7.63 (dd, 1H, 1.7, 0.7 Hz); ^{13}C NMR(DMSO-d6, 400 MHz) δ 55.82, 103.8, 109.44, 111.17, 112.22, 112.42, 123.95, 138.32, 142.08, 146.58, 154.45.



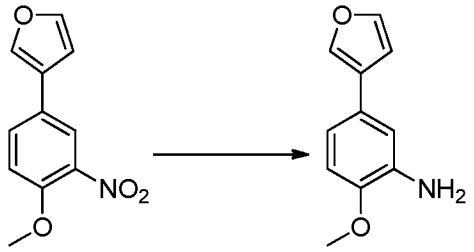
6 7 2

[1023] 3-(furan-2-yl)-N-(5-(furan-2-yl)-2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**2**): **2** was obtained in 66% yield over 2 steps as a white powder by a method similar to the one described for compound **1**. MS (ES+) *m/z* 374.2 $(M + H)^{+1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.02 (s, 3H), 6.60 (dd, 1H, *J*=3.3, 1.8Hz), 6.81 (dd, 1H, *J*=3.3, 0.7 Hz), 6.83 (dd, 1H, *J*=3.4, 1.8 Hz), 7.09 (dd, 1H, *J*=3.5, 0.7 Hz), 7.21 (d, 1H, *J*=8.7Hz), 7.45 (dd, 1H, *J*=8.5, 2.1Hz), 7.75 (dd, 1H, *J*=1.7, 0.6Hz), 8.02 (dd, 1H, *J*=1.8, 0.7Hz), 8.57 (s, 1H), 9.25 (d, 1H, *J*=2.2Hz), 9.64 (s, 1H), 14.05 (s, 1H); ^{13}C NMR(DMSO-d6, 400 MHz) δ 56.97, 97.96, 104.93, 108.49, 111.7, 112.45, 113.15, 116.44, 119.34, 123.71, 128.84, 142.76, 143.88, 147.91, 148.54, 153.77, 154.03, 155.92, 156.15.



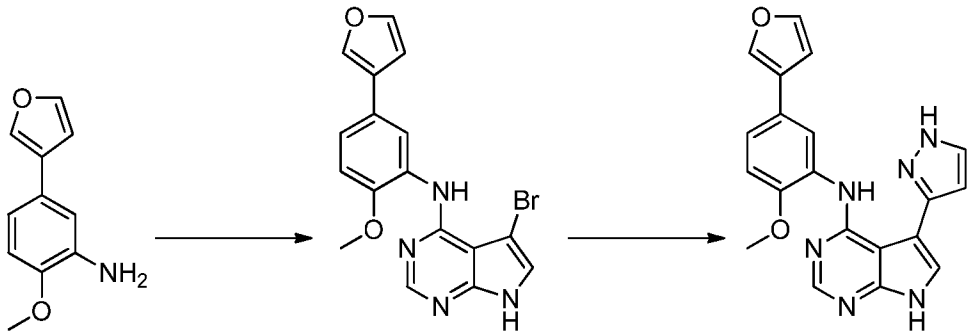
8

[1024] 3-(4-methoxy-3-nitrophenyl)furan (**8**): **8** was obtained in 90% yield as a yellow solid by a method similar to the one described for compound **5**. MS (ES+) *m/z* 220.4 $(M + H)^{+1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.95 (s, 3H), 7.04 (dd, 1H, *J*=1.9,0.9), 7.39 (d, 1H, *J*=8.8), 7.76 (t, 1H, *J*=1.7), 7.91 (dd, 1H, *J*=8.7, 2.4), 8.12 (d, 1H, *J*=2.4Hz), 8.27 (m, 1H); ^{13}C NMR(DMSO-d6, 500 MHz) δ 57.23, 109.05, 115.23, 121.8, 124.26, 125.26, 131.50, 140.17, 145.00, 150.94.



8 9

[1025] 5-(furan-3-yl)-2-methoxyaniline (**9**): **9** was obtained in 92% yield as a pale yellow solid by a method similar to the one described for compound **6**. MS (ES+) *m/z* 190.7 $(M + H)^{+1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.77 (s, 3H), 4.71 (s, 2H), 6.75 (m, 1H), 6.77 (d, 1H, 2.10), 6.80 (d, 1H, 8.35 Hz), 6.85 (d, 1H, *J*=2.0Hz), 7.67 (t, 1H, *J*=1.7Hz), 7.90 (m, 1H); ^{13}C NMR(DMSO-d6, 400 MHz) δ 58.82, 109.26, 111.27, 111.60, 114.23, 125.06, 126.74, 138.20, 138.24, 144.28, 146.18.

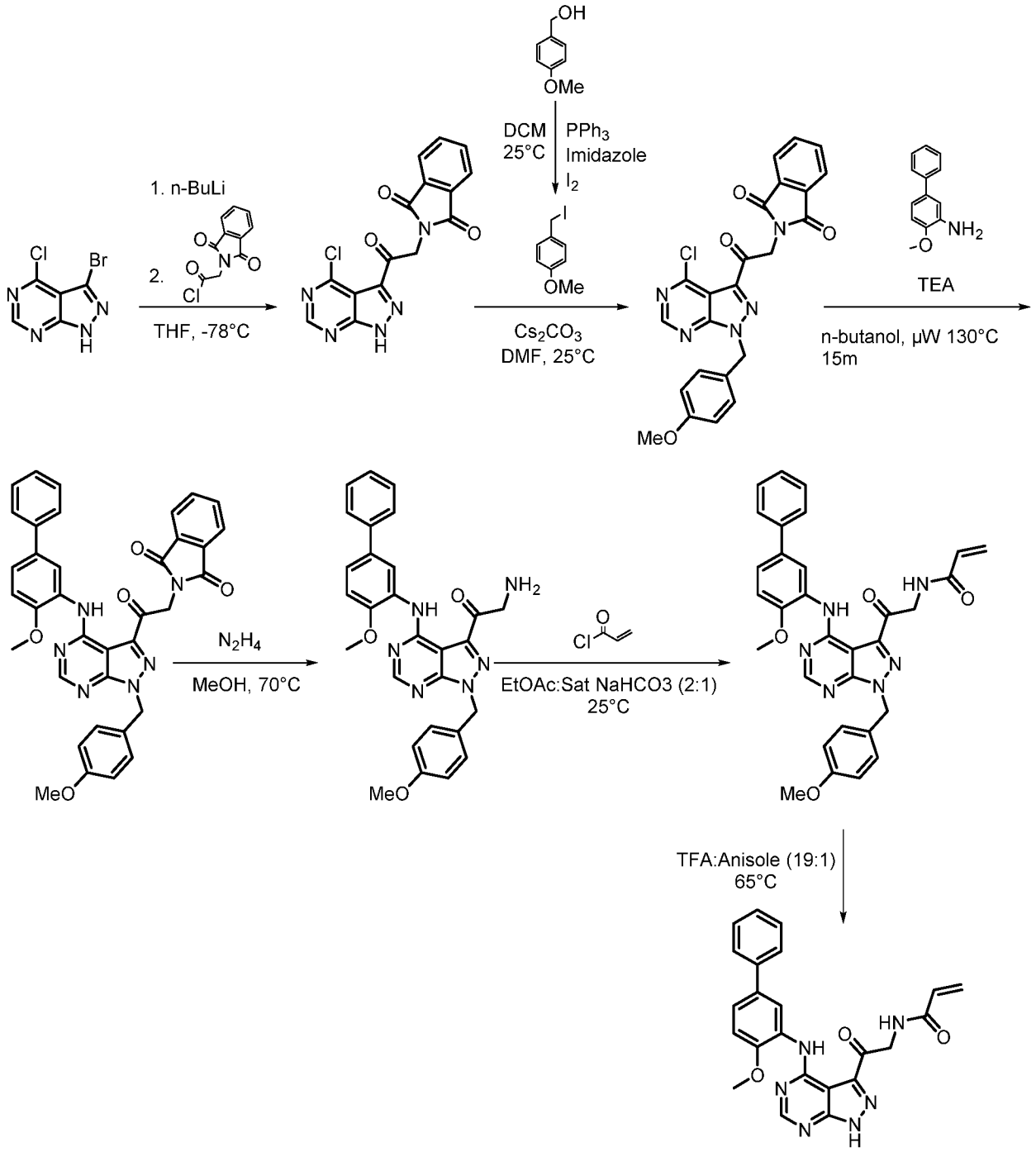


9 10 3

[1026] N-(5-(furan-3-yl)-2-methoxyphenyl)-5-(1H-pyrazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**3**): A microwave vial containing 45.0 mg of **9** (0.24 mmol), 62.7 mg of 7-Bromo-6-chloro-7-deazapurine (0.27 mmol), 22.2 µL of glacial acetic acid (0.39 mmol) and 2.5 mL of n-butanol with a stir bar was capped and heated to 130°C for 17 min in a microwave reactor. The reaction was cooled and concentrated by rotary evaporation. The residue was recrystallized in ethanol to give 35.5 mg of crude **10** as a brown solid. The crude **10** was added to a microwave tube containing 70.2 mg of 1H-Pyrazole-5-boronic acid pinacol ester (0.36 mmol), and 81 mg of potassium phosphate (0.38 mmol) in 1 mL of dioxane:H_2O (3:1) with a stir bar, which was sparged with argon for 5 min. 7.5 mg of XPhos Pd G2 (.0097 mmol) and 7.3 mg of SPhos (0.018 mmol) were then added to the microwave tube which was purged with argon and heated to 150°C for 20 min in a microwave. The reaction was cooled and run on RP-HPLC. The product containing fractions were concentrated *in vacuo*, and the residue was purified by silica gel

chromatography (eluent, Hex:EtOAc = 3:1 to 0:1) to give 12.4 mg (15% over 2 steps) of **3** as an off white powder. MS (ES-) *m/z* 371.6 $(M - H)^{-1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.92 (s, 3H), 6.72 (d, 1H, *J*=2.2), 6.87 (dd, 1H, *J*=1.8, 0.8 Hz), 7.08 (d, 1H, *J*=8.60 Hz), 7.27 (dd, 1H, *J*=8.3, 2.2Hz), 7.73 (m, 2H), 7.83 (d, 1H, *J*=2.3Hz), 8.04 (m, 1H), 8.28 (s, 1H), 8.78 (d, 1H, *J*=2.2Hz), 11.67 (s, 1H), 11.93 (s, 1H), 12.79 (s, 1H);); ^{13}C NMR(DMSO-d6, 400 MHz) δ56.63, 101.33, 101.94, 109.20, 109.40, 111.79, 120.34, 120.62, 121.11, 124.46, 126.60, 130.01, 130.65, 138.67, 144.51, 146.87, 149.99, 151.86, 152.14, 154.94.

[1027] Irreversible inhibitor design and synthesis for compound 8156:



H. Inhibition data

[1028] Table 7. Assay results.

	Ba/F3 line IC50 (nm)			
Cmpd	**Parental + IL-3**	**HER2YF/HER3 + NRG**	**HER2+/2VE**	**Axl+**
184	9950	386	1290	527
185	1487	148	243	257
186A	>10,000	>10,000	>10,000	>10,000

	Ba/F3 line IC50 (nm)			
Cmpd	**Parental + IL-3**	**HER2YF/HER3 + NRG**	**HER2+/2VE**	**Axl+**
186B	>10,000	>10,000	>10,000	>10,000
187A	>10,000	>10,000	>10,000	>10,000
187B	>10,000	>10,000	>10,000	>10,000
188A	>10,000	>10,000	>10,000	>10,000
188B	>10,000	>10,000	>10,000	>10,000
189A	1120	361	613	362
189B	>10,000	>10,000	>10,000	>10,000
190A	450	86.8	229	171
190C	1510	862	1840	643
190D	>10,000	>10,000	>10,000	>10,000
191A	2910	150	769	506
191B	>1,000	>1,000	>1,000	>1,000
191D	1740	884	1111	1010
191E	>10,000	>10,000	>10,000	>10,000
191F	2510	376	1700	2150
191H	>10,000	>10,000	>10,000	>10,000
5-001A	>10,000	>3,333	>3,333	>3,333
5-001B	>10,000	>10,000	>10,000	>10,000
5-004	>3,333	2590	3150	6940
39A	>10,000	>3,333	>10,000	>10,000
39B	>3,333	>3,333	>3,333	1757
39C	>10,000	>10,000	>10,000	>10,000
39D	>10,000	>10,000	>10,000	>10,000
6	>10,000	>10,000	>10,000	>10,000
41A	>10,000	>3,333	>10,000	>10,000
41B	>3,333	>3,333	>1,000	>1,000
42	>10,000	>10,000	>10,000	>10,000
43	>3,333	>3,333	>3,333	>3,333
13	>10,000	839	3396	2957
45A	>10,000	43	978	1206
45B	>10,000	745	3607	4025
45C	>10,000	952	>3,333	>3,333
45D	3014	270	869	880
45E	>10,000	53	1349	>10,000
45F	>10,000	739	1022	535
53B	>10,000	13.9	83.5	>10,000
55A	>10,000	39.5	908.3	>3,333
57A	>10,000	21	459.9	>10,000
57B	>10,000	12.6	82.9	>10,000
65	8.4	4	11	
66A		1560	2336	
66B		31	2 10	
66C		362	642	

	Ba/F3 line IC50 (nm)			
Cmpd	**Parental + IL-3**	**HER2YF/HER3 + NRG**	**HER2+/2VE**	**Axl+**
144A	>3,333	170.7	1083	
144B	>3,333	21.4	307.5	
152	>10,000	822	2568	
154A	>10,000	>10,000	>10,000	
154B	>10,000	39.3	294.7	
154C	>10,000	>10,000	>10,000	
147	1360	58.7	359	
153	>3,333	17.53333333	285	
170		687	673	
171		45	183	
172		910	422	
173B		32	228	
176	2288	29	216.9	
178	2536.7	6.8	70.3	1172.3

[1029] Table 8. Assay data. Compounds in the table below may be written with a dash, e.g., 8-089, or without a dash, e.g., 8089, and it is understood these represent identical compounds.

	Ba/F3 line IC50 (nm)						
Cmpd	**Parental + IL-3**	**HER2YF/HER3 + NRG**	**HER2+/2VE**	**Axl+**	**HCC827 (%viable at 1 nM)**	**A431**	**NCI-H1975**
8-089	2443	20.8	118	1155	99.9±14.6% (3)	914±134 (3)	2248±54 (3)
8-090	2252	227	895	1567	102% (1)	911 (1)	2544 (1)
8-091	2586	9.25	120	696.5	80.9±24% (3)	634±188 (3)	1418±117 (3)
8-092	>3333	20.5	231.5	1197.5	81.6±21.1% (3)	762±215 (3)	1900±134 (3)
8-095	>3333	5	46.7	1314.5	49.2±13.7% (3)	1116±59.0 (3)	1740±157 (3)
8-096	1538.5	2	31.4	501	30.6±4.2% (3)	471±63.4 (3)	891±18.6 (3)
8-097	1769	1	13.7	611.5	29.5±7.1% (3)	290±71 (3)	507±85.1 (3)
104A	1595.5	1.5	48.5	843.9	29.8±2.7% (3)	330±125 (3)	720±30 (3)
104B	~2000	1.5	46.4	1558	25.2±3.4% (3)	343±169 (3)	814±59 (3)

I. Pharmacokinetics and stability studies

[1030] Table 9A. A pharmacokinetic study for compound 8168B following IV administration in Male CD-1 mice. Study details include: Animal Species/ Strain/ Sex: Mice/CD-1/Male; Number of Animals: 3; Route of Administration: IV; Sampling Method: Retro-Orbital; Feeding Condition: Fasted; Dose (mg/kg): 2; Dose Volume (mL/kg): 5; Concentration (mg/mL): 0.4; Formulation Vehicle: Solution in 22% PEG300 / 15% DMSO / 63% PBS; Sample/Collection - Type: Blood collection ; Anti-coagulant: K2EDTA; Sampling Time points: Blood: 0.083, 0.25 h, 1h, 3 h, 5h, 8h, 24h.

Test Article Name (IV)	Compound 8168B					
Formulation IV solution	Solution in 22% PEG300 / 15% DMSO / 63% PBS					
Species	Male CD-1 mice					
Study Design	Pharmacokinetic Study					
Matrix	Plasma					
Bioanalytical Details						
Analyte 8168B						
LLOQ (Plasma)	1.05 ng/mL		ULOQ		1044.00 ng/mL	
Plasma Concentration (ng/mL) of 8168B (IV-2.0 mg/kg)						
Time (h)	M1	M2	M3	Mean	Std Dev	% CV
0.08	55.13	53.28	64.54	58.91	7.96	13.52
0.25	31.90	29.14	34.06	31.60	3.48	11.01
1.00	12.34	22.71	12.93	17.82	6.92	38.81
3.00	6.96	11.36	8.08	9.72	2.32	23.86
5.00	7.32	7.57	6.55	7.06	0.72	10.22
8.00	6.02	7.32	9.38	8.35	1.46	17.44
24.00	6.79	5.33	3.54	4.44	1.27	28.54
Dose (mg/kg)*	2.00	2.00	2.00	2.00	0.00	0.00
C0 (ng/mL)	72.36	71.91	88.67	77.65	11.85	15.26
T1/2 (h)#	302.57	36.64	18.98	27.81	12.49	44.92
AUC0-last (ng·h/mL)	183.16	205.32	185.37	191.28	14.11	7.37
AUCall (ng·h/mL)	183.16	205.32	185.37	191.28	14.11	7.37
AUC0-inf (ng·h/mL)#	3147.06	487.06	282.28	384.67	144.80	37.64
AUCExtra(%)	94.18	57.85	34.33	46.09	16.63	36.08
Cl (ml/min/kg)#	10.59	68.44	118.09	93.26	35.11	37.64
Vd (L/kg)#	277.41	217.05	193.96	205.51	16.33	7.95
MRT0-last (h)	10.30	9.04	9.04	9.46	0.00	0.03
Rsq	0.4805	0.9963	0.9744	0.99	0.02	1.58
After dose formulation is 87% so under the inhouse formulation accuracy limits. PK Parameters were calculated by considering 100% formulation accuracy.						

[1031] Table 9B. A pharmacokinetic study for compound 8168B following IP administration in Male CD-1 mice. Study details include: Animal Species/ Strain/ Sex: Mice/CD-1/Male; Test

Item: sCCX155; Number of Animals: 3; Route of Administration: IP; Sampling Method: Retro-Orbital; Feeding Condition: Fasted; Dose (mg/kg): 2; Dose Volume (mL/kg): 5; Concentration (mg/mL): 0.4; Formulation Vehicle: Solution in 22% PEG300 / 15% DMSO / 63% PBS; Sample/Collection - Type: Blood collection ; Anti-coagulant: K2EDTA; Sampling Time points: Blood: 0.25 h, 1h, 3 h, 5h, 8h, 24h.

Test Article Name (IP)	Compound 8168B					
Formulation IP solution	Solution in 22% PEG300 / 15% DMSO / 63% PBS					
Species	Male CD-1 mice					
Study Design	Pharmacokinetic Study					
Matrix	Plasma					
Bioanalytical Details						
Analyte 8168B						
LLOQ (Plasma)	1.05 ng/mL		ULOQ		1044.00 ng/mL	
Plasma Concentration (ng/mL) of 8168B (IP-2.0 mg/kg)						
Time (h)	M1	M2	M3	Mean	Std Dev	% CV
0.25	241.92	189.54	198.56	210.01	28.00	13.33
1.00	100.58	69.73	76.68	82.33	16.18	19.66
3.00	2.25	4.17	2.33	2.92	1.09	37.24
5.00	BLQ	BLQ	BLQ	BLQ	NA	NA
8.00	BLQ	BLQ	BLQ	BLQ	NA	NA
24.00	BLQ	BLQ	BLQ	BLQ	NA	NA
Dose (mg/kg)*	2.00	2.00	2.00	2.00	0.00	0.00
Cmax (ng/mL)	241.92	189.54	198.56	210.01	28.00	13.33
Tmax (h)	0.25	0.25	0.25	0.25	0.00	0.00
Oral T1/2 (h)	0.40	0.50	0.42	0.44	0.05	11.89
AUC0-last (ng·h/mL)	202.77	160.10	163.46	175.44	23.73	13.52
AUCall (ng·h/mL)	202.77	160.10	163.46	175.44	23.73	13.52
AUC0-inf (ng·h/mL)	204.07	163.10	164.87	177.35	23.16	13.06
AUCExtra(%)	0.63	1.84	0.86	1.11	0.64	57.63
MRT0-last (h)	0.76	0.81	0.76	0.78	0.03	4.04
Rsq	0.9920	0.9999	0.9961	0.9960	0.00	0.39
After dose formulation is 90% so PK Parameters were calculated by considering 100% formulation accuracy.						

[1032] Table 10A. A pharmacokinetic study for compound 8168C following IV administration in Male CD-1 mice. Study details include: Animal Species/ Strain/ Sex: Mice/CD-1/Male; Test Item: sCCX156; Number of Animals: 3; Route of Administration: IV; Sampling Method: Retro-Orbital; Feeding Condition: Fasted; Dose (mg/kg): 2; Dose Volume (mL/kg): 5; Concentration (mg/mL): 0.4; Formulation Vehicle: Solution in 22% PEG300 / 15% DMSO / 63% PBS; Sample/Collection - Type: Blood collection ; Anti-coagulant: K2EDTA; Sampling Time points: Blood: 0.083, 0.25 h, 1h, 3 h, 5h, 8h, 24h.

Test Article Name (IV)	Compound 8168C					
Formulation IV solution	Solution in 22% PEG300 / 15% DMSO / 63% PBS					
Species	Male CD-1 mice					
Study Design	Pharmacokinetic Study					
Matrix	Plasma					
Bioanalytical Details						
Analyte 8168C						
LLOQ (Plasma)	1.03 ng/mL		ULOQ		1029.60 ng/mL	
Plasma Concentration (ng/mL) of 8168C (IV-2.0 mg/kg)						
Time (h)	M1	M2	M3	Mean	Std Dev	% CV
0.08	601.37	643.79	668.53	637.90	33.97	5.32
0.25	381.91	361.85	533.91	425.89	94.08	22.09
1.00	180.89	124.19	132.77	145.95	30.56	20.94
3.00	14.30	16.88	24.59	18.59	5.35	28.80
5.00	4.53	8.17	9.69	7.46	2.65	35.53
8.00	1.79	BLQ	4.14	2.97	1.66	56.04
24.00	BLQ	BLQ	BLQ	BLQ	NA	NA
Dose (mg/kg)*	2.00	2.00	2.00	2.00	0.00	0.00
C0 (ng/mL)	753.60	857.24	747.58	786.14	61.65	7.84
T1/2 (h)	1.70	0.79	1.98	1.49	0.62	41.64
AUC0-last (ng·h/mL)	495.61	441.82	554.77	497.40	56.50	11.36
AUCall (ng·h/mL)	495.61	441.82	554.77	497.40	56.50	11.36
AUC0-inf (ng·h/mL)	500.01	451.15	566.58	505.91	57.94	11.45
AUCExtra(%)	0.88	2.07	2.08	1.68	0.69	41.21
Cl (ml/min/kg)	66.67	73.89	58.83	66.46	7.53	11.33
Vd (L/kg)	9.82	5.06	10.07	8.32	2.82	33.92
MRT0-last (h)	0.94	0.87	1.09	0.96	0.11	11.73
Rsq	0.9692	0.9371	0.9802	0.9622	0.02	2.33
After dose formulation is 85.4% so under the inhouse formulation accuracy limits. PK Parameters were calculated by considering 100% formulation accuracy. In house limit for formulation accuracy is ±20%.						

[1033] Table 10B. A pharmacokinetic study for compound 8168C following IP administration in Male CD-1 mice. Study details include: Animal Species/ Strain/ Sex: Mice/CD-1/Male; Test Item: sCCX156; Number of Animals: 3; Route of Administration: IP; Sampling Method: Retro-Orbital; Feeding Condition: Fasted; Dose (mg/kg): 2; Dose Volume (mL/kg): 5; Concentration (mg/mL): 0.4; Formulation Vehicle: Solution in 22% PEG300 / 15% DMSO / 63% PBS; Sample/Collection - Type: Blood collection ; Anti-coagulant: K2EDTA; Sampling Time points: Blood: 0.25 h, 1h, 3 h, 5h, 8h, 24h.

Test Article Name (IP)	8168C
Formulation IP solution	Solution in 22% PEG300 / 15% DMSO / 63% PBS
Species	Male CD-1 mice

Study Design	Pharmacokinetic Study					
Matrix	Plasma					
Bioanalytical Details						
Analyte 8168C						
LLOQ (Plasma)	1.03 ng/mL		ULOQ		1029.60 ng/mL	
Plasma Concentration (ng/mL) of 8168C (IP-2.0 mg/kg)						
Time (h)	M1	M2	M3	Mean	Std Dev	% CV
0.25	206.62	306.24	169.92	227.59	70.54	30.99
1.00	85.20	69.88	66.74	73.94	9.88	13.36
3.00	9.75	2.05	BLQ	5.90	5.44	92.28
5.00	2.52	BLQ	BLQ	BLQ	NA	NA
8.00	BLQ	BLQ	BLQ	BLQ	NA	NA
24.00	BLQ	BLQ	BLQ	BLQ	NA	NA
Dose (mg/kg)*	2.00	2.00	2.00	2.00	0.00	0.00
Cmax (ng/mL)	206.62	306.24	169.92	227.59	70.54	30.99
Tmax (h)	0.25	0.25	0.25	0.25	0.00	0.00
Oral T1/2 (h)	0.79	0.38	NC	0.59	0.29	48.85
AUC0-last (ng·h/mL)	208.92	196.69	104.05	169.89	57.35	33.76
AUCall (ng·h/mL)	208.92	196.69	104.05	169.89	57.35	33.76
AUC0-inf (ng·h/mL)	211.79	197.83	NC	204.81	9.87	4.82
AUCExtra(%)	1.35	0.57	NC	0.96	0.55	57.24
MRT0-last (h)	1.06	0.67	0.50	0.74	0.29	38.40
Rsq	0.9825	0.9994	NC	0.9909	0.01	1.21
After dose formulation is 110% so PK Parameters were calculated by considering 100% formulation accuracy. In house limit for formulation accuracy is ±20%.						
NC:- Not calculated due to insufficient data point post Cmax.						

[1034] Table 11. HER3 Mouse Liver Microsome stability assay study results.

WuXi Microsomal stability (Mouse Extraction Ratio)	Compound name
<0.3	8168B
0.4	8168C
0.6	8179
0.7	8134

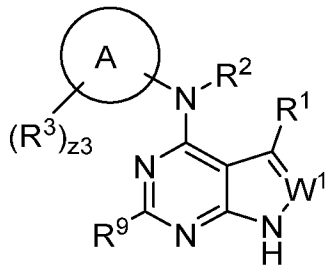
0.7	8186
0.8	8168A
0.8	8177
0.8	8185
0.837	96
0.87	104A
0.9	8164
0.9	8184
0.928	91
0.939	97
0.948	178

[1035] References: 1. Lemmon, M. A. *et al. Cold Spring Harbor Perspectives in Biology* **6,** a020768–a020768 (2014). 2. Kovacs, E., Zorn, J. A., Huang, Y., Barros, T. & Kuriyan, J. *Annu Rev Biochem* **84,** 739–764 (2015). 3. Doerner, A., Scheck, R. & Schepartz, A. *Chem Biol* **22,** 776–784 (2015). 4. Zhang, X., Gureasko, J., Shen, K., Cole, P. A. & Kuriyan, J. *Cell* **125,** 1137–1149 (2006). 5. Schneider, M. R. & Yarden, Y. *Oncogene* (2015). doi:10.1038/onc.2015.372; 6. Yarden, Y., Yarden, Y., Sliwkowski, M. X. & Sliwkowski, M. X. *Nat Rev Mol Cell Biol* **2,** 127–137 (2001). 7. Brewer, M. R. *et al. Proceedings of the National Academy of Sciences* **110,** E3595 (2013). 8. Wang, Z. *et al. Nat Struct Mol Biol* **18,** 1388–1393 (2011). 9. Foster, S. A. *et al. Cancer Cell* doi:10.1016/j.ccell.2016.02.010. 10. Lee-Hoeflich, S. T. *et al. Cancer Res* **68,** 5878–5887 (2008). 11. Tzahar, E. *et al. Mol. Cell. Biol.* **16,** 5276–5287 (1996). 12. Russo, P. *et al. Cancer Res* **72,** 2672–2682 (2012). 13. Jaiswal, B. S. *et al. Cancer Cell* **23,** 603–617 (2013). 14. Lee, D. Y., Wilson, T. R., Shames, D. S., Berry, L. & Settleman, J. *Cancer Cell* **20,** 158–172 (2011). 15. Bose, R. *et al. Cancer Discovery* **3,** 224 (2012). 16. Wang, S. E. *et al. Cancer Cell* **10,** 25–38 (2006). 17. Greulich, H. *et al. Proc Natl Acad Sci USA* **109,** 14476–14481 (2012). 18. Geyer, C. E. *et al. N Engl J Med* **355,** 2733–2743 (2006). 19. Verma, S. *et al. N Engl J Med* **367,** 1783–1791 (2012). 20. Lewis Phillips, G.D. *et al. Clinical Cancer Research* **20,** 456 (2013). 21. Wilson, T. R. *et al. Nature* **487,** 505–509 (2012). 22. Sergina, N. V. *et al. Nature* **445,** 437 (2007). 23. Chakrabarty, A., Sanchez, V., Kuba, M. G., Rinehart, C. & Arteaga, C. L. *Proceedings of the National Academy of Sciences* **109,** 2718 (2011). 24. Chandarlapaty, S. *et al. Cancer Cell* **19,** 58–71 (2011). 25. Amin, D. N. *et al. Sci Transl Med* **2,** 16ra7 (2010). 26. Das, P. M. *et al. Oncogene* **29,** 5214–5219 (2010). 27. Sartor, C. I. *et al. MCB* **21,** 4265-4275 (2001). 28. Aertgeerts, K. *et al. J Biol Chem* **286,** 18756–18765 (2011). 29. Wood, E. R. *et al. Cancer Res* **64,** 6652–6659 (2004). 30. Littlefield, P. *et al. Sci Signal* **7,** ra114–ra114 (2014). 31. Brewer, M. R. *et al. Mol Cell* **34,** 641 (2009). 32. Warmuth, M., Kim, S., Gu, X.-J., Xia, G. & Adrian,

Current Opinion in Oncology **19,** 55–60 (2006). 33. Jura, N. *et al. Cell* **137,** 1293–1307 (2009). 34. Park, J. H., Liu, Y., Lemmon, M. A. & Radhakrishnan, R. *Biochem J* **448,** 417–423 (2012). 35. Shi, F., Telesco, S. E., Liu, Y., Radhakrishnan, R. & Lemmon, M. A. *Proc Natl Acad Sci USA* **107,** 7692–7697 (2010). 36. Jura, N. *et al. Proc Natl Acad Sci USA* **106,** 21608–21613 (2009). 37. Rexer, B. N. *et al. Clin Cancer Res* **19,** 5390–5401 (2013). 38. Vivanco, I. *et al. Cancer Discovery* **2,** 458–471 (2012). 39. Yoshida, T., Kakegawa, J., Yamaguchi, T. & Hantani, Y. *Oncotarget* (2012). 40. Adrián, F. J. *et al. Nature Chemical Biology* **2,** 95–102 (2006). 41. Xie, T. *et al. Nature Chemical Biology* **10,** 1006 (2014). 42. Scaltriti, M. *et al. J Natl Cancer Inst* **99,** 628–638 (2007). 43. Chandarlapaty, S. *et al. Oncogene* **29,** 325–334 (2009). 44. Sperinde, J. *et al. Clin Cancer Res* **16,** 4226–4235 (2010). 45. Sáez, R. *et al. Clin Cancer Res* **12,** 424–431 (2006). 46. Gibson, D. G. *et al. Nat Meth* **6,** 343–345 (2009). 47. Schüttelkopf, A. W. & van Aalten, D. M. F. *Acta Crystallogr D Biol Crystallogr* **60,** 1355–1363 (2004).

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I);

wherein

Ring A is aryl or heteroaryl;

W^1 is N or C(H);

R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl;

R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)$-OR^{3C}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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;

z3 is an integer from 0 to 4;

L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^6$-, -O-, -S-, -C(O)-, $-C(O)NR^6$-, $-NR^6C(O)$-, $-NR^6C(O)NH$-, $-NHC(O)NR^6$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)$-OR^{6C}, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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;

L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)$-OR^{7C}, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)$-OR^{9C}, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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;

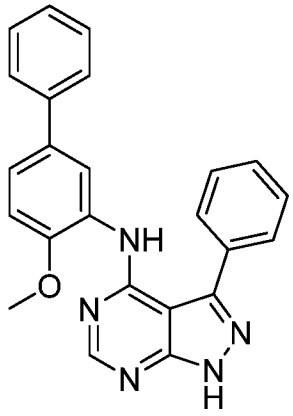
E is an electrophilic moiety;

each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

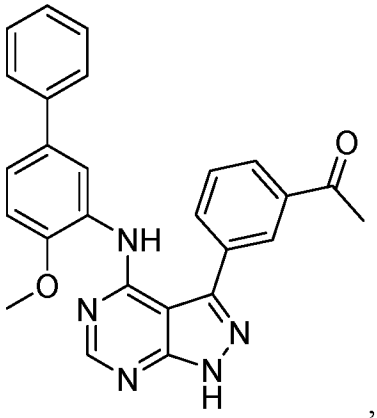
each X, X^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I;

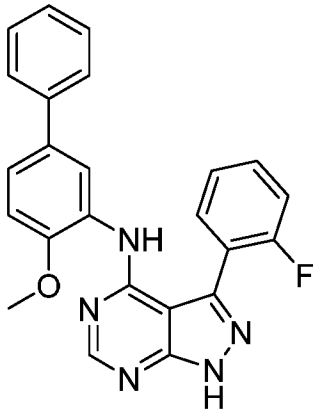
n3, n6, n7, and n9 are independently an integer from 0 to 4; and

m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2;

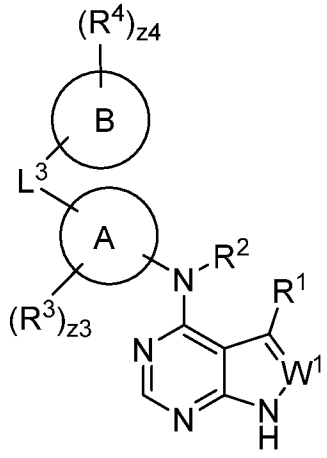


wherein the compound is not ,



, or  .

2. A compound of claim 1, having the formula:



(II);

wherein

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

L^3 is a bond, $-S(O)_2-$, $-NR^8-$, -O-, -S-, -C(O)-, $-C(O)NR^8-$, $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-NHC(O)NR^8-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, 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^8 is independently halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, -CN, $-SO_{n8}R^{8D}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-C(O)R^{8C}$, $-C(O)-OR^{8C}$, $-C(O)NR^{8A}R^{8B}$, $-OR^{8D}$, $-NR^{8A}SO_2R^{8D}$, $-NR^{8A}C(O)R^{8C}$, $-NR^{8A}C(O)OR^{8C}$, $-NR^{8A}OR^{8C}$, 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;

z4 is an integer from 0 to 5;

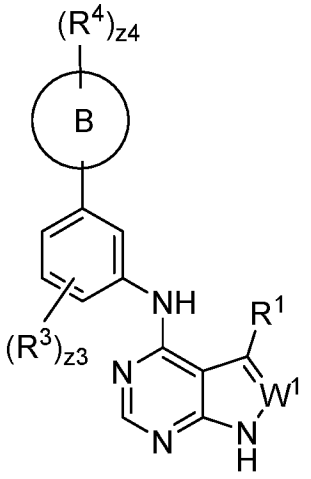
Each R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{8A}, R^{8B}, R^{8C}, and R^{8D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} 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^4 and X^8 are independently –F, -Cl, -Br, or –I;

n4 and n8 are independently an integer from 0 to 4; and

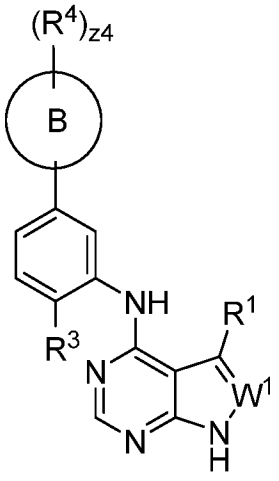
m4, m8, v4, and v8, are independently an integer from 1 to 2.

3. The compound of claim 2, having the formula:



(III).

4. The compound of claim 2, having the formula:



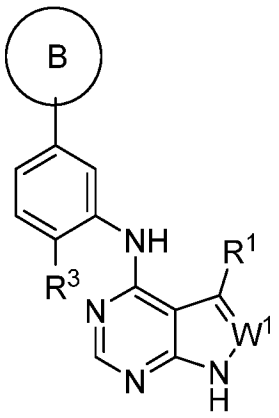
(IV).

5. The compound of claim 2, wherein R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, or –CN.

6. The compound of claim 2, wherein R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, or $-CH_2X^4$.

7. The compound of claim 2, wherein R^4 is independently halogen.

8. The compound of claim 2, having the formula:



(V).

9. The compound of claim 1, wherein W^1 is C(H).

10. The compound of claim 1, wherein W^1 is N.

11. The compound of claim 1, wherein R^3 is an unsubstituted heteroalkyl.

12. The compound of claim 1, wherein R^3 is an unsubstituted 2 to 5 membered heteroalkyl.

13. The compound of claim 1, wherein R^3 is – OCH_3, $-OCH_2CH_3$, $-N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, or -SH.

14. The compound of claim 1, wherein R^3 is – OCH_3, $-OCH_2CH_3$, $-N(CH_3)_2$, $-OCX^3_3$, $-OCH_2X^3$, or $-OCHX^3_2$.

15. The compound of claim 2, wherein Ring B is substituted or unsubstituted aryl or heteroaryl.

16. The compound of claim 2, wherein Ring B is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

17. The compound of claim 2, wherein Ring B is substituted or unsubstituted phenyl.

18. The compound of claim 2, wherein Ring B is substituted or unsubstituted 5 to 6 membered heteroaryl.

19. The compound of claim 2, wherein Ring B is substituted or unsubstituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

20. The compound of claim 1, wherein R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

21. The compound of claim 1, wherein R^1 is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

22. The compound of claim 1, wherein R^1 is substituted or unsubstituted phenyl.

23. The compound of claim 1, wherein R^1 is an unsubstituted phenyl.

24. The compound of claim 1, wherein R^1 is substituted or unsubstituted 5 to 6 membered heteroaryl.

25. The compound of claim 1, wherein R^1 is an unsubstituted 5 to 6 membered heteroaryl.

26. The compound of claim 1, wherein R^1 is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, or substituted or unsubstituted thiazolyl.

27. The compound of claim 1, wherein R^1 is an unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl.

28. The compound of claim 1, wherein R^1 is $-L^1$-L^2-E.

29. The compound of claim 1, wherein L^1 is a bond, -C(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

30. The compound of claim 1, wherein L^1 is a substituted or unsubstituted C_1-C_4 alkylene.

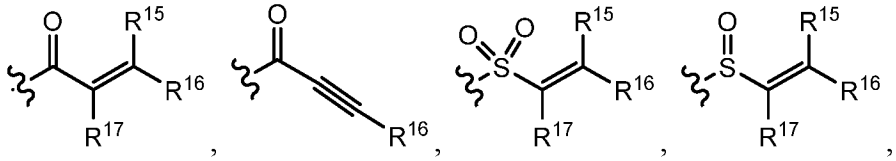
31. The compound of claim 1, wherein L^1 is $–C(O)CH_2CH_2CH_2-$, $–C(O)CH_2CH_2-$, or $–C(O)CH_2-$.

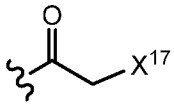
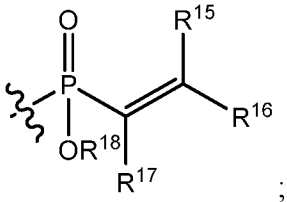
32. The compound of claim 1, wherein L^2 is $-NR^7-$, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heterocycloalkylene.

33. The compound of claim 1, wherein L^2 is -NH-.

34. The compound of claim 1, wherein E is a covalent cysteine modifier moiety.

35. The compound of claim 1, wherein E is:



, or ;

R^{15} is independently hydrogen, halogen, CX^{15}_3, $-CHX^{15}_2$, $-CH_2X^{15}$, -CN, $-SO_{n15}R^{15D}$, $-SO_{v15}NR^{15A}R^{15B}$, $–NHNR^{15A}R^{15B}$, $–ONR^{15A}R^{15B}$, $–NHC=(O)NHNR^{15A}R^{15B}$, $–NHC(O)NR^{15A}R^{15B}$, $-N(O)_{m15}$, $-NR^{15A}R^{15B}$, $-C(O)R^{15C}$, $-C(O)-OR^{15C}$, $-C(O)NR^{15A}R^{15B}$, $-OR^{15D}$, $-NR^{15A}SO_2R^{15D}$, $-NR^{15A}C(O)R^{15C}$, $-NR^{15A}C(O)OR^{15C}$, $-NR^{15A}OR^{15C}$, $-OCX^{15}_3$, $-OCHX^{15}_2$, 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^{16} is independently hydrogen, halogen, CX^{16}_3, $-CHX^{16}_2$, $-CH_2X^{16}$, -CN, $-SO_{n16}R^{16D}$, $-SO_{v16}NR^{16A}R^{16B}$, $–NHNR^{16A}R^{16B}$, $–ONR^{16A}R^{16B}$, $–NHC=(O)NHNR^{16A}R^{16B}$, $–NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16C}$, $-C(O)-OR^{16C}$, $-C(O)NR^{16A}R^{16B}$, $-OR^{16D}$, $-NR^{16A}SO_2R^{16D}$, $-NR^{16A}C(O)R^{16C}$, $-NR^{16A}C(O)OR^{16C}$, $-NR^{16A}OR^{16C}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, 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^{17} is independently hydrogen, halogen, CX^{17}_3, $-CHX^{17}_2$, $-CH_2X^{17}$, -CN, $-SO_{n17}R^{17D}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC=(O)NHNR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17C}$, $-C(O)-OR^{17C}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17D}$, $-NR^{17A}SO_2R^{17D}$, $-NR^{17A}C(O)R^{17C}$, $-NR^{17A}C(O)OR^{17C}$, $-NR^{17A}OR^{17C}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R^{18} is independently hydrogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-C(O)R^{18C}$, $-C(O)OR^{18C}$, $-C(O)NR^{18A}R^{18B}$, 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^{15A}, R^{15B}, R^{15C}, R^{15D}, R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B}, R^{17C}, R^{17D}, R^{18A}, R^{18B}, R^{18C}, R^{18D}, are independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{15A} and R^{15B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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;

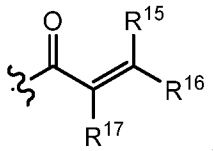
each X, X^{15}, X^{16}, X^{17} and X^{18} is independently –F, -Cl, -Br, or –I;

n15, n16, n17, v15, v16, and v17, are independently an integer from 0 to 4; and

m15, m16, and m17 are independently and integer from 1 to 2.

36. The compound of claim 35, wherein R^{15}, R^{16}, R^{17}, and R^{18} are hydrogen.

37. The compound of claim 35, wherein E is:



.

38. The compound of claim 37, wherein

R^{15} is hydrogen;

R^{16} is hydrogen, -CH_3, or –$CH_2NR^{16A}R^{16B}$;

R^{17} is hydrogen; and

R^{16A} and R^{16B} are independently hydrogen or unsubstituted alkyl.

39. The compound of claim 38, wherein R^{16A} and R^{16B} are independently unsubstituted methyl.

40. The compound of claim 37, wherein

R^{15} is hydrogen;

R^{16} is hydrogen;

R^{17} is hydrogen, -CH_3, or –$CH_2NR^{17A}R^{17B}$; and

R^{17A} and R^{17B} are independently hydrogen or unsubstituted alkyl.

41. The compound of claim 40, wherein R^{17A} and R^{17B} are independently unsubstituted methyl.

42. The compound of claim 37, wherein

R^{15} is hydrogen, -CH_3, or –$CH_2NR^{15A}R^{15B}$;

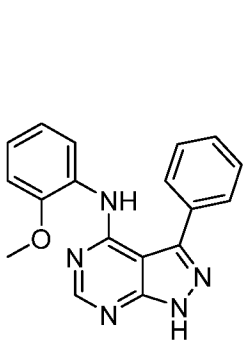
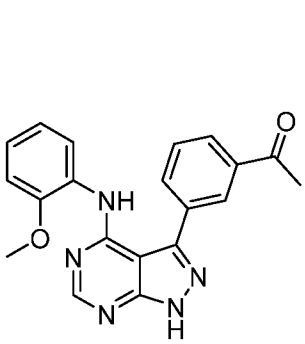
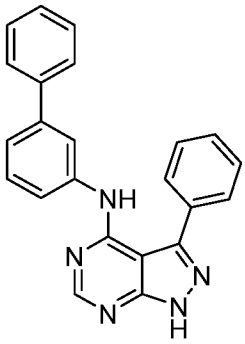
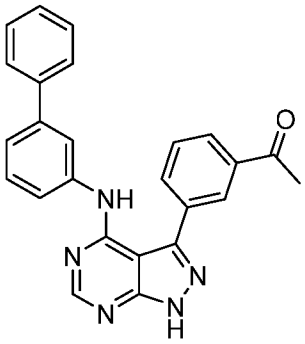
R^{16} is hydrogen;

R^{17} is hydrogen; and

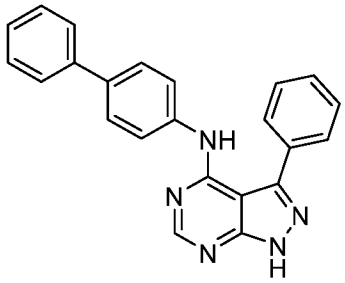
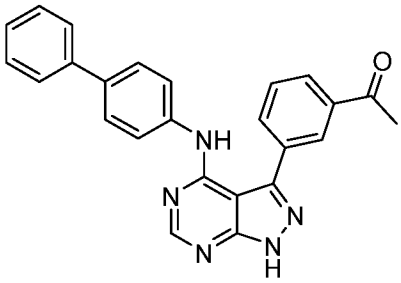
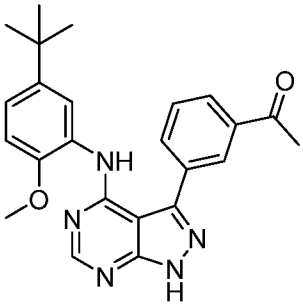
R^{15A} and R^{15B} are independently hydrogen or unsubstituted alkyl.

43. The compound of claim 42, wherein R^{15A} and R^{15B} are independently unsubstituted methyl.

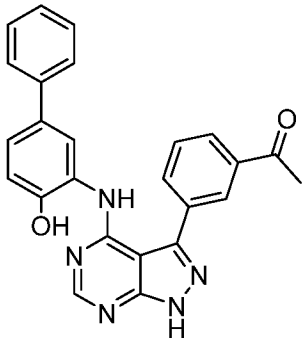
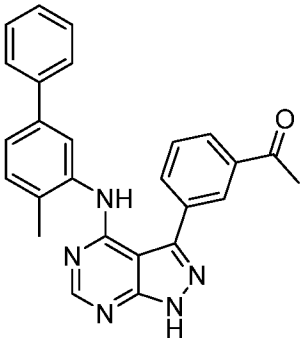
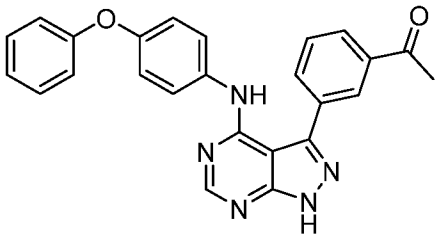
1 44. The compound of claim 1,wherein the compound has the formula:

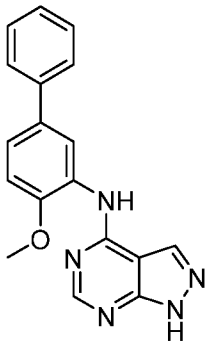
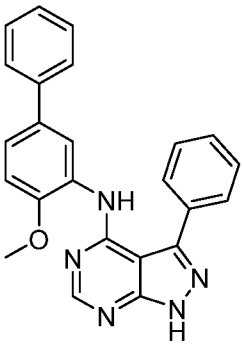
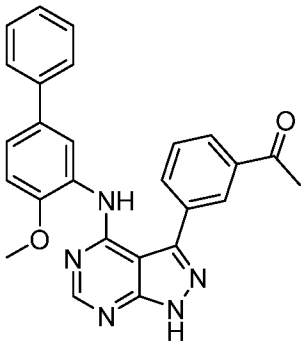
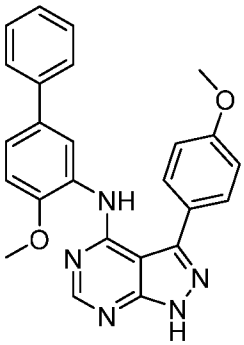
2 187A , 187B , 186A , 186B ,

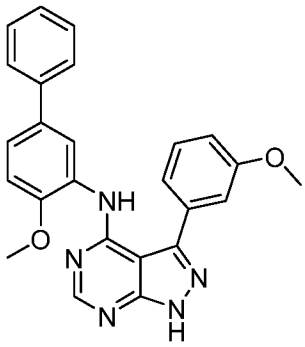
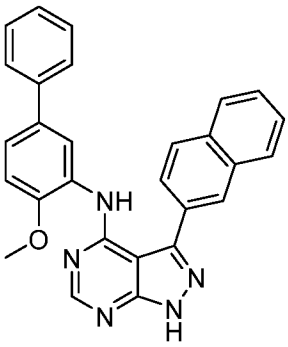
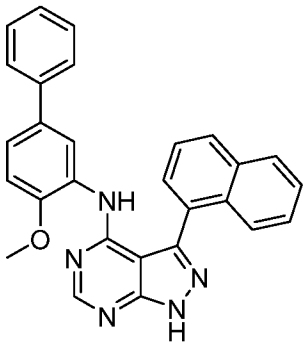
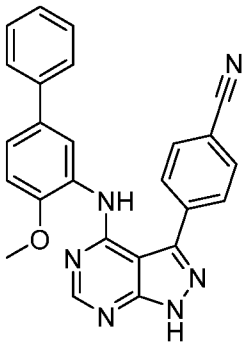
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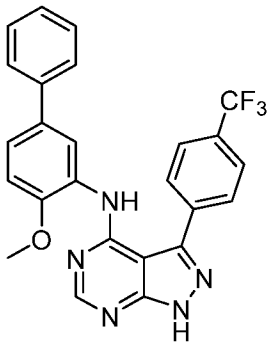
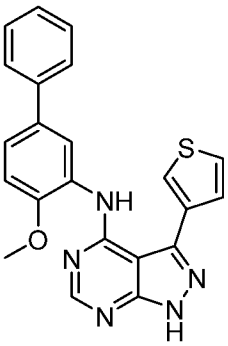
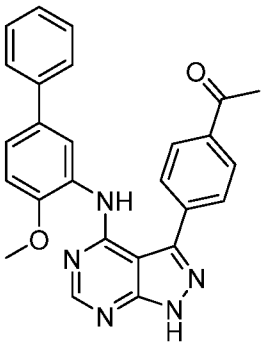
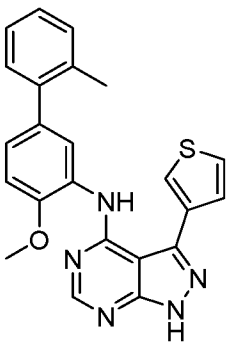




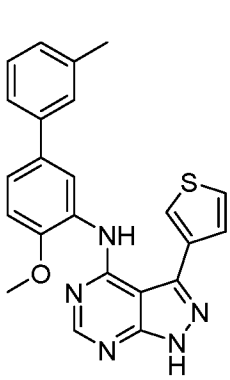
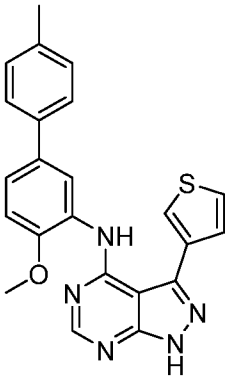
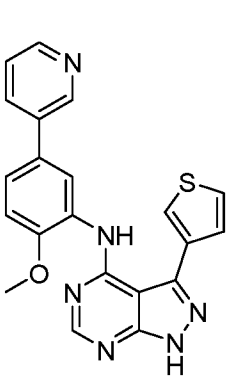
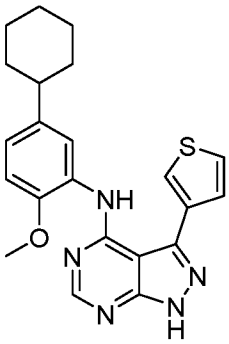
4 191A , 5-001A , 5-001B ,

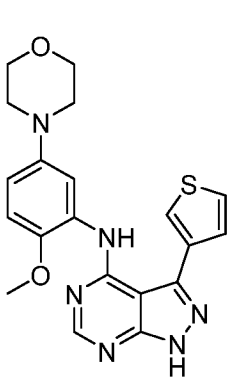
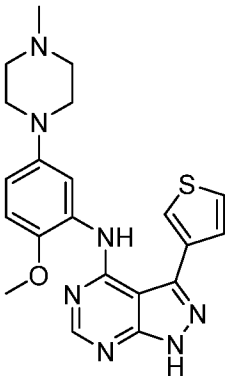
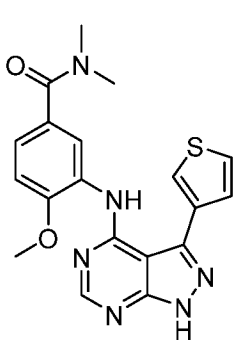
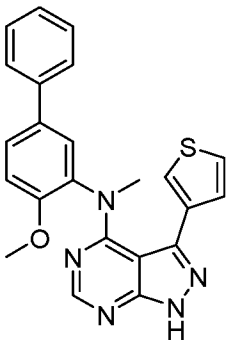





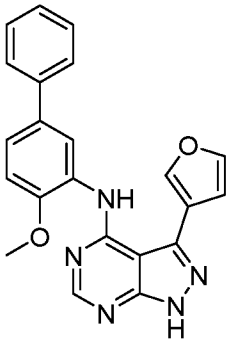
5 5-004 , 184 , 185 , 189B ,

6  190A ,  190C ,  191B ,  191D ,

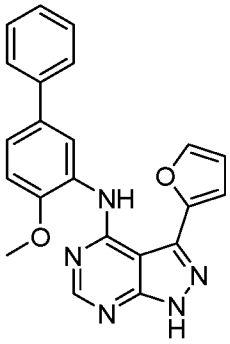
7  191E ,  191F ,  191H ,  39A ,

8  39B ,  39C ,  39D ,  6 ,

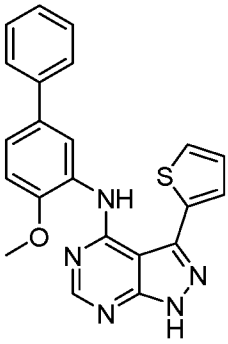
9  41A ,  41B ,  42 ,  43 ,



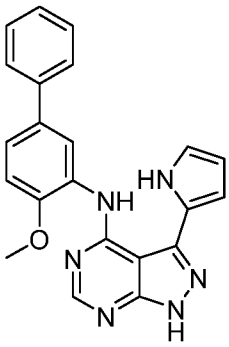
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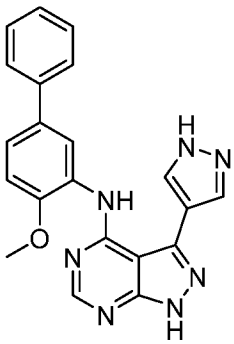
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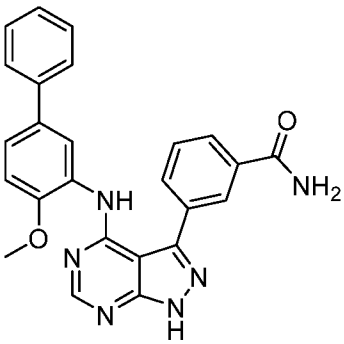
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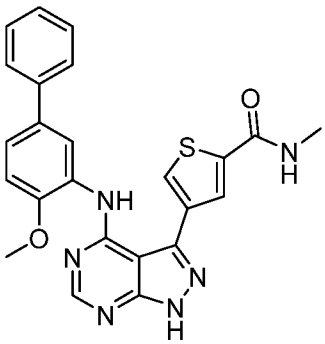
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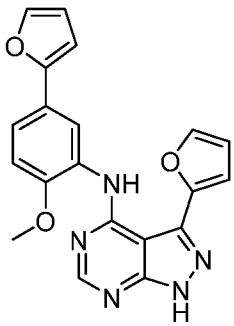
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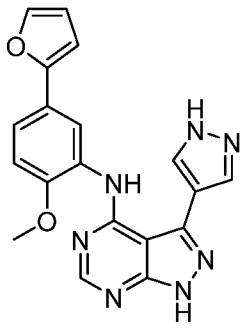
45D



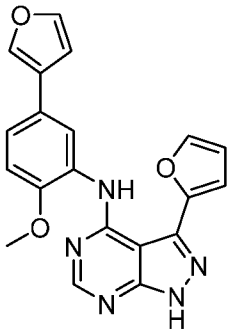
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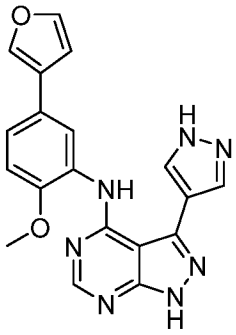
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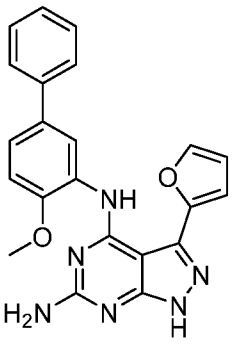
53B



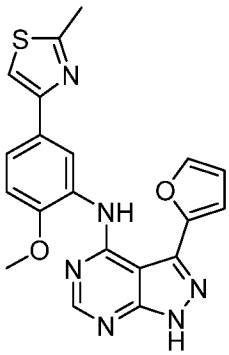
57A



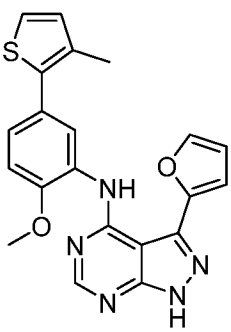
57B



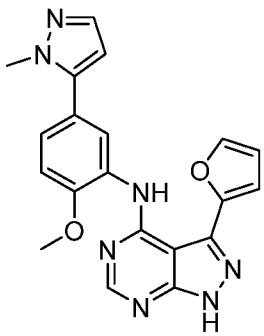
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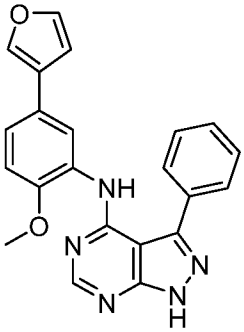
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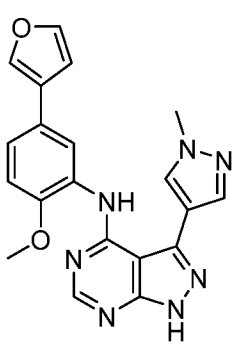
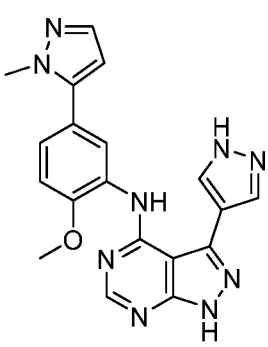
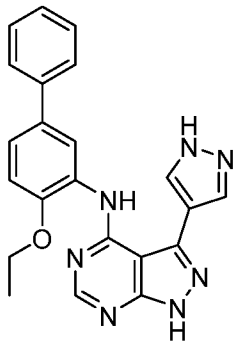
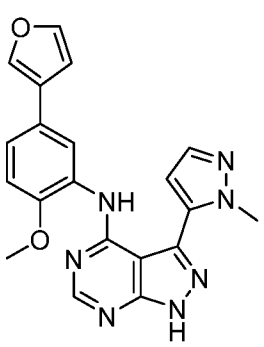
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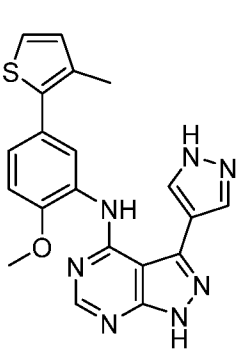
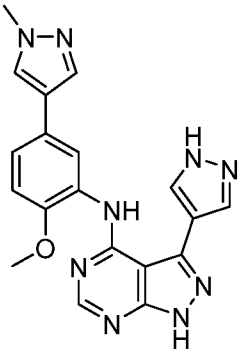
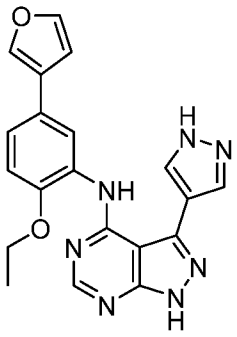
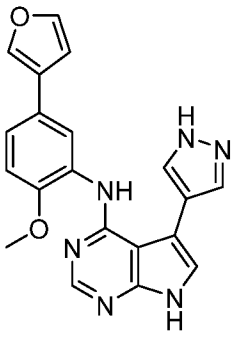


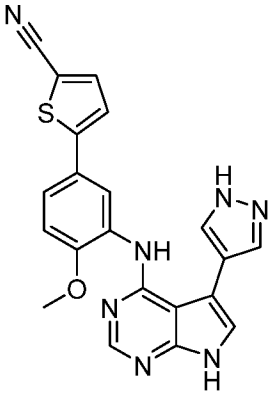
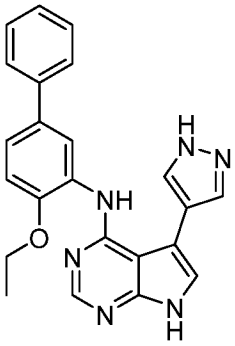
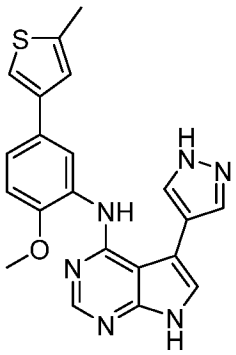
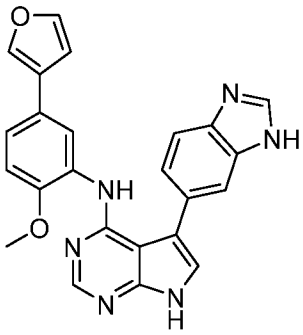
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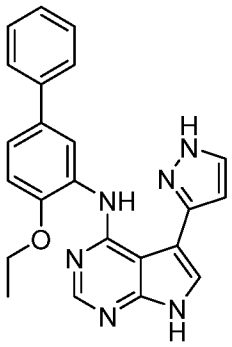
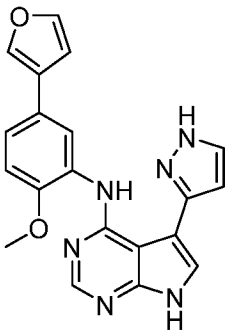
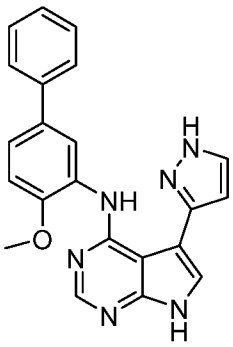
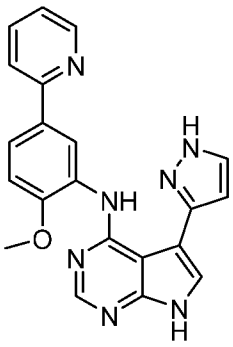


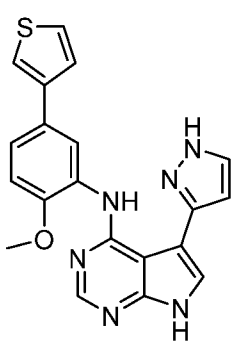
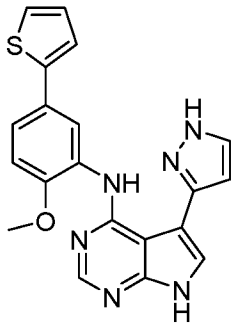
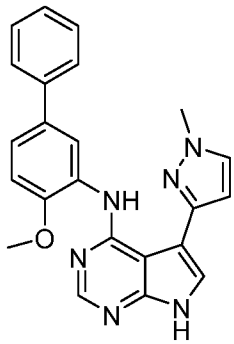
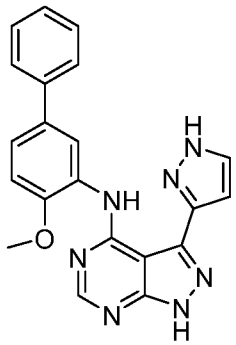
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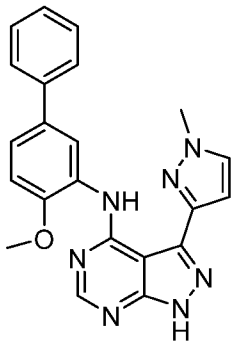
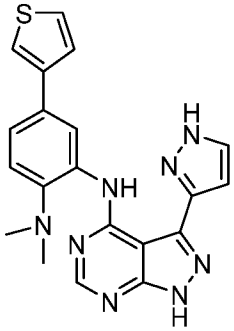
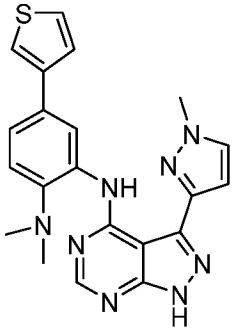
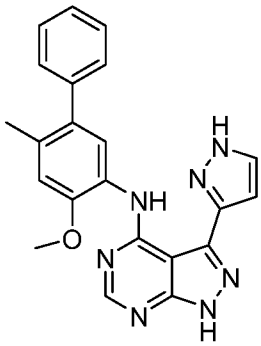

144B ,

154A ,

147 ,

152 ,

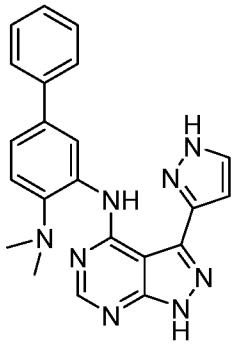
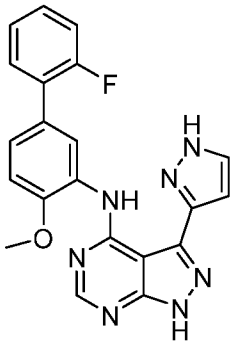
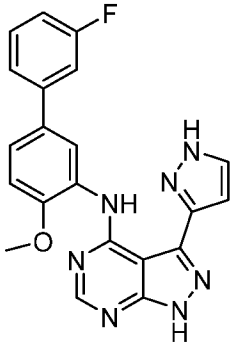
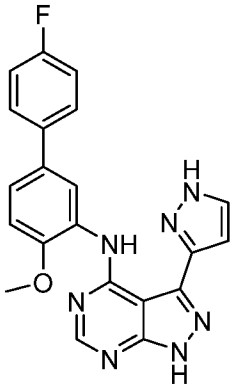

154B ,

154C ,

153 ,

155 ,

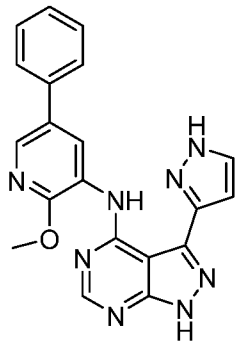
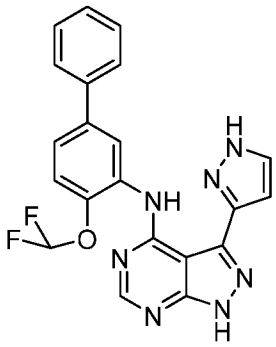
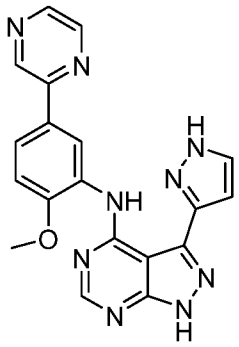
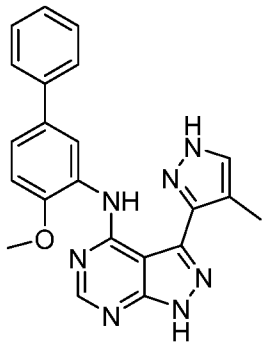
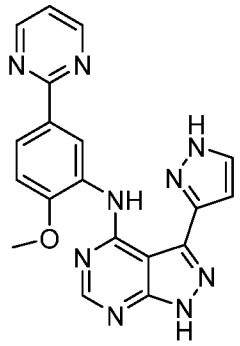
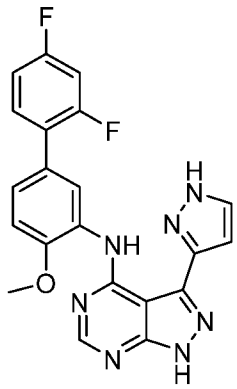

170 ,

171 ,

172 ,

173B ,


176 ,

178 ,

8-089 ,

8-090 ,


8-091,

8-092,

8-095,

8-096,


8-097,

104A,

104B,

8134,

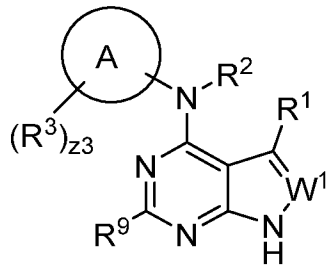

8164,

8168A,

8168B,

8168C,


8177 ,

8179 ,

8184 ,

8186 ,

8185 , or

8168A8168C .

45. A pharmaceutical composition comprising a compound of one of claims 1 to 44 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

46. The pharmaceutical composition of claim 45, further comprising an anti-cancer agent.

47. A method of treating a disease associated with HER2 activity in a patient in need of such treatment, said method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:


(I)

wherein

Ring A is aryl or heteroaryl;

W^1 is N or C(H);

R^1 is hydrogen, $-L^1-L^2-E$, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl;

R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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;

z3 is an integer from 0 to 4;

L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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;

L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)O$

R^{7C}, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, $-CN$, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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;

E is an electrophilic moiety;

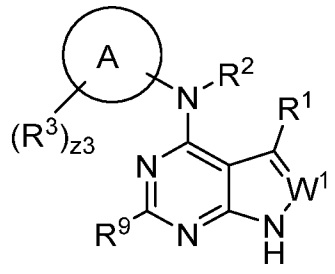
each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, $-CN$, $-COOH$, $-CONH_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I;

n3, n6, n7, and n9 are independently an integer from 0 to 4; and

m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

48. A method of treating a disease associated with EGFR activity in a patient in need of such treatment, said method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:



(I);

wherein;

Ring A is aryl or heteroaryl;

W^1 is N or C(H);

R^1 is hydrogen, $-L^1-L^2-E$, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl;

R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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;

z3 is an integer from 0 to 4;

L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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;

L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, -NH

$C(O)NR^7$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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;

E is an electrophilic moiety;

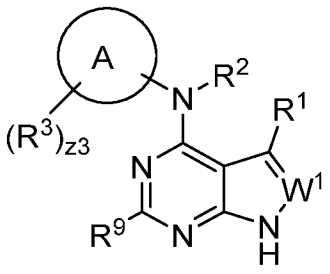
each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I;

n3, n6, n7, and n9 are independently an integer from 0 to 4; and

m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

49. A method of treating cancer in a patient in need of such treatment, said method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:



(I);

wherein;

Ring A is aryl or heteroaryl;

W^1 is N or C(H);

R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl;

R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)$-OR^{3C}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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;

z3 is an integer from 0 to 4;

L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^6$-, -O-, -S-, -C(O)-, $-C(O)NR^6$-, $-NR^6C(O)$-, $-NR^6C(O)NH$-, $-NHC(O)NR^6$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)$-OR^{6C}, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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;

L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, -C(O)-OR^{7C}, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, -C(O)-OR^{9C}, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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;

E is an electrophilic moiety;

each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I;

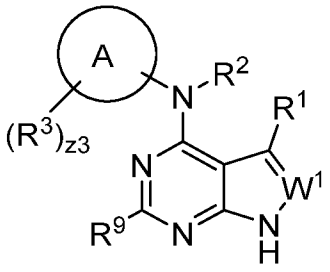
n3, n6, n7, and n9 are independently an integer from 0 to 4; and

m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

50. The method of claim 49, wherein the cancer is resistant to a HER2 inhibitor.

51. The method of claim 49, wherein the cancer is resistant to an EGFR inhibitor.

52. A method of inhibiting HER2 activity, said method comprising contacting HER2 with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:



(I);

wherein;

Ring A is aryl or heteroaryl;

W^1 is N or C(H);

R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is hydrogen, -CX^2_3, –CHX^2_2, –CH_2X^2, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl;

R^3 is independently halogen, -CX^3_3, -CHX^3_2, -CH_2X^3, -OCX^4_3, -OCH_2X^3, -$OCHX^3_2$, -CN, -$SO_{n3}R^{3D}$, -$SO_{v3}NR^{3A}R^{3B}$, -$NHC(O)NR^{3A}R^{3B}$, -$N(O)_{m3}$, -$NR^{3A}R^{3B}$, -$C(O)R^{3C}$, -C(O)-OR^{3C}, -$C(O)NR^{3A}R^{3B}$, -OR^{3D}, -$NR^{3A}SO_2R^{3D}$, -$NR^{3A}C(O)R^{3C}$, -$NR^{3A}C(O)OR^{3C}$, -$NR^{3A}OR^{3C}$, 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;

z3 is an integer from 0 to 4;

L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, -C(O)-OR^{6C}, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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;

L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, -C(O)-OR^{7C}, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, -C(O)-OR^{9C}, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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;

E is an electrophilic moiety;

each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I;

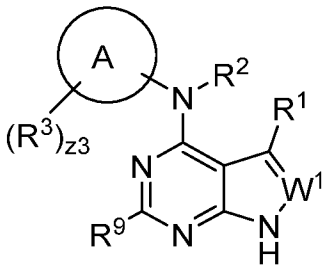
n3, n6, n7, and n9 are independently an integer from 0 to 4; and

m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

53. The method of claim 52, wherein HER2 is in an active conformation.

54. The method of claim 53, wherein HER2 is in a HER2-HER3 heterodimer.

55. A method of inhibiting EGFR activity, said method comprising contacting EGFR with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, having the formula:



(I);

wherein;

Ring A is aryl or heteroaryl;

W^1 is N or C(H);

R^1 is hydrogen, $–L^1$-L^2-E, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is hydrogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl;

R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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;

z3 is an integer from 0 to 4;

L^1 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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;

L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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;

E is an electrophilic moiety;

each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

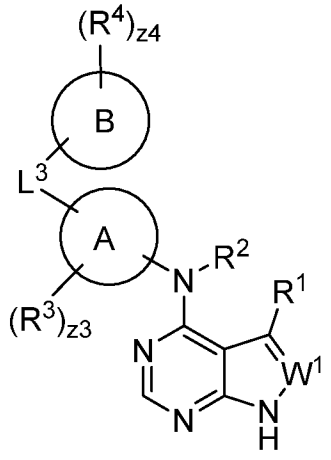
each X, X^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I;

n3, n6, n7, and n9 are independently an integer from 0 to 4; and

m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

56. The method of claim 55, wherein EGFR is in an active conformation.

57. A method of claim 47, wherein the compound has the formula:



(II)

wherein

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

L^3 is a bond, $-S(O)_2-$, $-NR^8-$, -O-, -S-, -C(O)-, $-C(O)NR^8-$, $-NR^8C(O)-$, $-NR^8C(O)NH-$, $-NHC(O)NR^8-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, 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^8 is independently halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, -CN, $-SO_{n8}R^{8D}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-C(O)R^{8C}$, $-C(O)-OR^{8C}$, $-C(O)NR^{8A}R^{8B}$, $-OR^{8D}$, $-NR^{8A}SO_2R^{8D}$, $-NR^{8A}C(O)R^{8C}$, $-NR^{8A}C(O)OR^{8C}$, $-NR^{8A}OR^{8C}$, 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;

z4 is an integer from 0 to 5;

Each R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{8A}, R^{8B}, R^{8C}, and R^{8D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{4A} and R^{4B} substituents bonded to the same nitrogen atom may

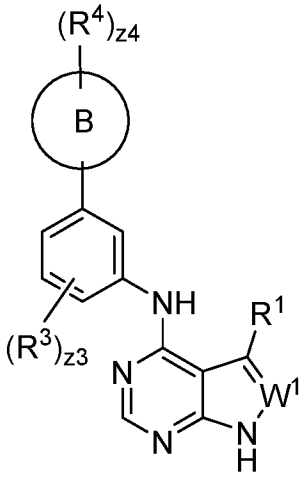
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl

each X^4 and X^8 are independently –F, -Cl, -Br, or –I;

n4 and n8 are independently an integer from 0 to 4; and

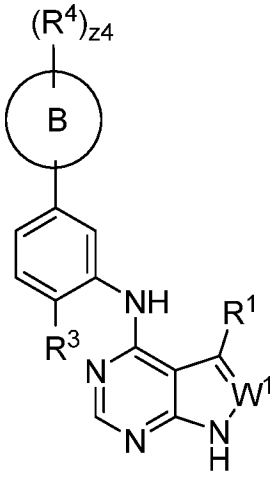
m4, m8, v4, and v8, are independently an integer from 1 to 2.

58. A method of claim 47, wherein the compound has the formula:



(III).

59. A method of claim 47, wherein the compound has the formula:



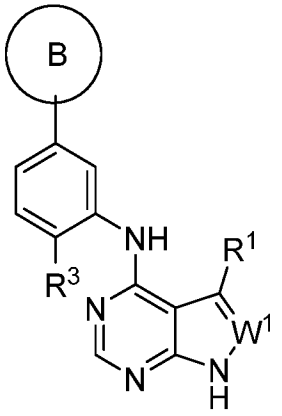
(IV).

60. The method of claim 57, wherein R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, or –CN.

61. The method of claim 57, wherein R^4 is independently halogen, $-CX^4_3$, $-CHX^4_2$, or $-CH_2X^4$.

62. The method of claim 57, wherein R^4 is independently halogen.

63. The method of claim 47, wherein the compound has the formula:



(V).

64. The method of claim 47, wherein W^1 is C(H).

65. The method of claim 47, wherein W^1 is N.

66. The method of claim 47, wherein R^3 is an unsubstituted heteroalkyl.

67. The method of claim 47, wherein R^3 is unsubstituted 2 to 5 membered heteroalkyl.

68. The method of claim 47, wherein R^3 is – OCH_3, $-OCH_2CH_3$, $-N(CH_3)_2$, $-NH_2$, $-NH(CH_3)$, $-N(CH_2CH_3)_2$, $-NH(CH_2CH_3)$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, or -SH.

69. The method of claim 57, wherein Ring B is substituted or unsubstituted aryl or heteroaryl.

70. The method of claim 57, wherein Ring B is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

71. The method of claim 57, wherein Ring B is substituted or unsubstituted phenyl.

72. The method of claim 57, wherein Ring B is substituted or unsubstituted 5 to 6 membered heteroaryl.

73. The method of claim 57, wherein Ring B is substituted or unsubstituted pyrazinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiazolyl.

74. The method of claim 47, wherein R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

75. The method of claim 47, wherein R^1 is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

76. The method of claim 47, wherein R^1 is substituted or unsubstituted phenyl.

77. The method of one of claims 47 to 73, wherein R^1 is an unsubstituted phenyl.

78. The method of claim 47, wherein R^1 is a substituted or unsubstituted 5 to 6 membered heteroaryl.

79. The method of claim 47, wherein R^1 is an unsubstituted 5 to 6 membered heteroaryl.

80. The method of claim 47, wherein R^1 is substituted or unsubstituted pyridinyl, substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, or substituted or unsubstituted thiazolyl.

81. The method of claim 47, wherein R^1 is an unsubstituted furanyl, unsubstituted thienyl, unsubstituted pyrrolyl, unsubstituted imidazolyl, unsubstituted pyrazolyl, unsubstituted oxazolyl, unsubstituted isoxazolyl, or unsubstituted thiazolyl.

82. The method of claim 47, wherein R^1 is $–L^1\text{-}L^2\text{-}E$.

83. The method of claim 47, wherein L^1 is a bond, -C(O)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

84. The method of claim 47, wherein L^1 is a substituted or unsubstituted C_1-C_4 alkylene.

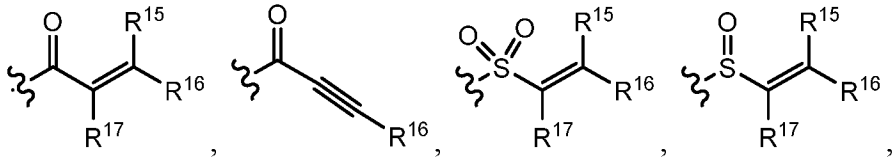
85. The method of claim 47, wherein L^1 is $–C(O)CH_2CH_2CH_2$-, $–C(O)CH_2CH_2$-, or $–C(O)CH_2$-.

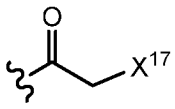
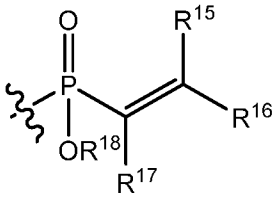
86. The method of claim 47, wherein L^2 is -NR^7-, substituted or unsubstituted heteroalkylene, or substituted or unsubstituted heterocycloalkylene.

87. The method of claim 47, wherein L^2 is -NH-.

88. The method of claim 47, wherein E is a covalent cysteine modifier moiety.

89. The method of claim 47, wherein E is:




, or  ;

R^{15} is independently hydrogen, halogen, CX^{15}_3, -CHX^{15}_2, -CH_2X^{15}, -CN, -$SO_{n15}R^{15D}$, -$SO_{v15}NR^{15A}R^{15B}$, $–NHNR^{15A}R^{15B}$, $–ONR^{15A}R^{15B}$, $–NHC=(O)NHNR^{15A}R^{15B}$, $–NHC(O)NR^{15A}R^{15B}$, -$N(O)_{m15}$, -$NR^{15A}R^{15B}$, -$C(O)R^{15C}$, -C(O)-OR^{15C}, -$C(O)NR^{15A}R^{15B}$, -OR^{15D}, -$NR^{15A}SO_2R^{15D}$, -$NR^{15A}C(O)R^{15C}$, -$NR^{15A}C(O)OR^{15C}$, -$NR^{15A}OR^{15C}$, -OCX^{15}_3, -$OCHX^{15}_2$, 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^{16} is independently hydrogen, halogen, CX^{16}_3, -CHX^{16}_2, -CH_2X^{16}, -CN, -$SO_{n16}R^{16D}$, -$SO_{v16}NR^{16A}R^{16B}$, $–NHNR^{16A}R^{16B}$, $–ONR^{16A}R^{16B}$, $–NHC=(O)NHNR^{16A}R^{16B}$,

–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}, -$NR^{16A}SO_2R^{16D}$, -$NR^{16A}C(O)R^{16C}$, -$NR^{16A}C(O)OR^{16C}$, -$NR^{16A}OR^{16C}$, -OCX^{16}_3, -$OCHX^{16}_2$, 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^{17} is independently hydrogen, halogen, CX^{17}_3, -CHX^{17}_2, -CH_2X^{17}, -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}, -$NR^{17A}SO_2R^{17D}$, -$NR^{17A}C(O)R^{17C}$, -$NR^{17A}C(O)OR^{17C}$, -$NR^{17A}OR^{17C}$, -OCX^{17}_3, -$OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R^{18} is independently hydrogen, -CX^{18}_3, -CHX^{18}_2, -CH_2X^{18}, -$C(O)R^{18C}$, -$C(O)OR^{18C}$, -$C(O)NR^{18A}R^{18B}$, 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^{15A}, R^{15B}, R^{15C}, R^{15D}, R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B}, R^{17C}, R^{17D}, R^{18A}, R^{18B}, R^{18C}, R^{18D}, are independently hydrogen, -CX_3, -CN, -COOH, -$CONH_2$, -CHX_2, -CH_2X, 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^{15A} and R^{15B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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;

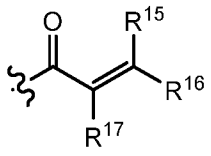
each X, X^{15}, X^{16}, X^{17} and X^{18} is independently –F, -Cl, -Br, or –I;

n15, n16, n17, v15, v16, and v17, are independently an integer from 0 to 4; and

m15, m16, and m17 are independently and integer from 1 to 2.

90. The method of claim 89, wherein R^{15}, R^{16}, R^{17}, and R^{18} are hydrogen.

91. The method of claim 89, wherein E is:



.

92. The method of claim 91, wherein

R^{15} is hydrogen;

R^{16} is hydrogen, -CH_3, or $-CH_2NR^{16A}R^{16B}$;

R^{17} is hydrogen; and

R^{16A} and R^{16B} are independently hydrogen or unsubstituted alkyl.

93. The method of claim 92, wherein R^{16A} and R^{16B} are independently unsubstituted methyl.

94. The method of claim 91, wherein

R^{15} is hydrogen;

R^{16} is hydrogen;

R^{17} is hydrogen, -CH_3, or $-CH_2NR^{17A}R^{17B}$; and

R^{17A} and R^{17B} are independently hydrogen or unsubstituted alkyl.

95. The method of claim 94, wherein R^{17A} and R^{17B} are independently unsubstituted methyl.

96. The compound of claim 91, wherein

R^{15} is hydrogen, -CH_3, or $-CH_2NR^{15A}R^{15B}$;

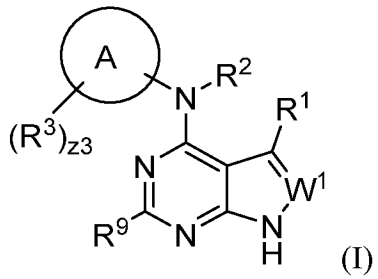
R^{16} is hydrogen;

R^{17} is hydrogen; and

R^{15A} and R^{15B} are independently hydrogen or unsubstituted alkyl.

97. The method of claim 96, wherein R^{15A} and R^{15B} are independently unsubstituted methyl.

98. An EGFR protein covalently bonded to a compound having the formula:



(I)

wherein

Ring A is aryl or heteroaryl;

W^1 is N or C(H)

R^1 is $–L^1$-L^2-E;

R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl;

R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)$-OR^{3C}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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;

z3 is an integer from 0 to 4;

L^1 is a bond, $-S(O)_2$-, $-S(O)_2$-Ph-, $-NR^6$-, -O-, -S-, -C(O)-, $-C(O)NR^6$-, $-NR^6C(O)$-, $-NR^6C(O)NH$-, $-NHC(O)NR^6$-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)$-OR^{6C}, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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;

L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)$-OR^{7C}, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)$-OR^{9C}, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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;

E is an electrophilic moiety;

each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} substituents bonded

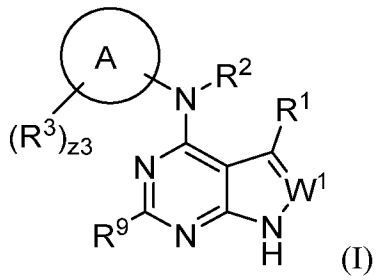
to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I;

n3, n6, n7, and n9 are independently an integer from 0 to 4; and

m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

99. A HER2 protein covalently bonded to a compound having the formula:



(I)

wherein

Ring A is aryl or heteroaryl;

W^1 is N or C(H)

R^1 is $–L^1-L^2-E$;

R^2 is hydrogen, $-CX^2_3$, $–CHX^2_2$, $–CH_2X^2$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl;

R^3 is independently halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^4_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, 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;

z3 is an integer from 0 to 4;

L^1 is a bond, $-S(O)_2-$, $-S(O)_2-Ph-$, $-NR^6-$, -O-, -S-, -C(O)-, $-C(O)NR^6-$, $-NR^6C(O)-$, $-NR^6C(O)NH-$, $-NHC(O)NR^6-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$,

$-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, 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;

L^2 is a bond, $-S(O)_2-$, $-S(O)_2$-Ph-, $-NR^7-$, -O-, -S-, -C(O)-, $-C(O)NR^7-$, $-NR^7C(O)-$, $-NR^7C(O)NH-$, $-NHC(O)NR^7-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7D}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-C(O)R^{7C}$, $-C(O)-OR^{7C}$, $-C(O)NR^{7A}R^{7B}$, $-OR^{7D}$, $-NR^{7A}SO_2R^{7D}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7A}C(O)OR^{7C}$, $-NR^{7A}OR^{7C}$, 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^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9D}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-C(O)R^{9C}$, $-C(O)-OR^{9C}$, $-C(O)NR^{9A}R^{9B}$, $-OR^{9D}$, $-NR^{9A}SO_2R^{9D}$, $-NR^{9A}C(O)R^{9C}$, $-NR^{9A}C(O)OR^{9C}$, $-NR^{9A}OR^{9C}$, 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;

E is an electrophilic moiety;

each R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{9A}, R^{9B}, R^{9C}, and R^{9D} is independently hydrogen, $-CX_3$, -CN, -COOH, $-CONH_2$, $-CHX_2$, $-CH_2X$, 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^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded

to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} 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^3, X^6, X^7,and X^9 is independently –F, -Cl, -Br, or –I;

n3, n6, n7, and n9 are independently an integer from 0 to 4; and

m3, m6, m7, m9, v3, v6, v7, and v9, are independently an integer from 1 to 2.

FIG. 1A

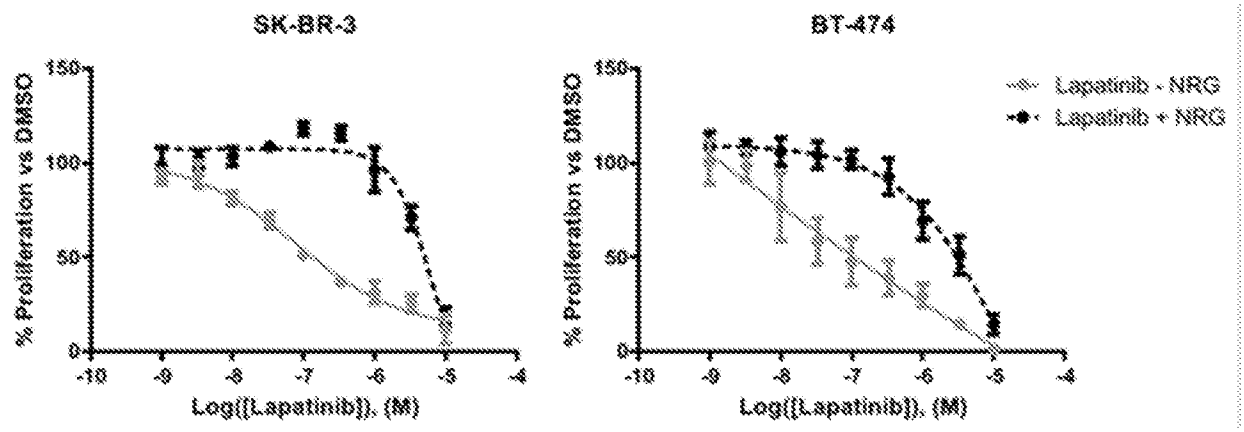


FIG. 1B

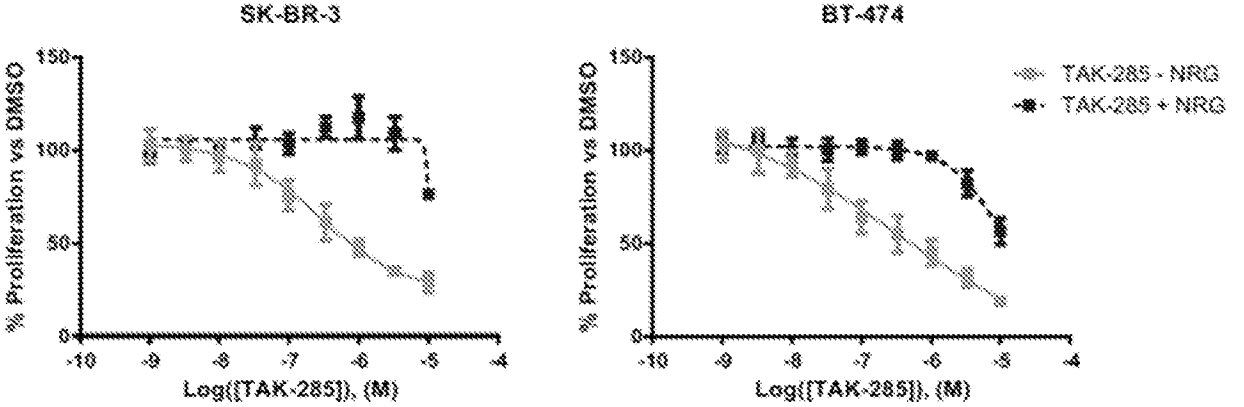


FIG. 1C

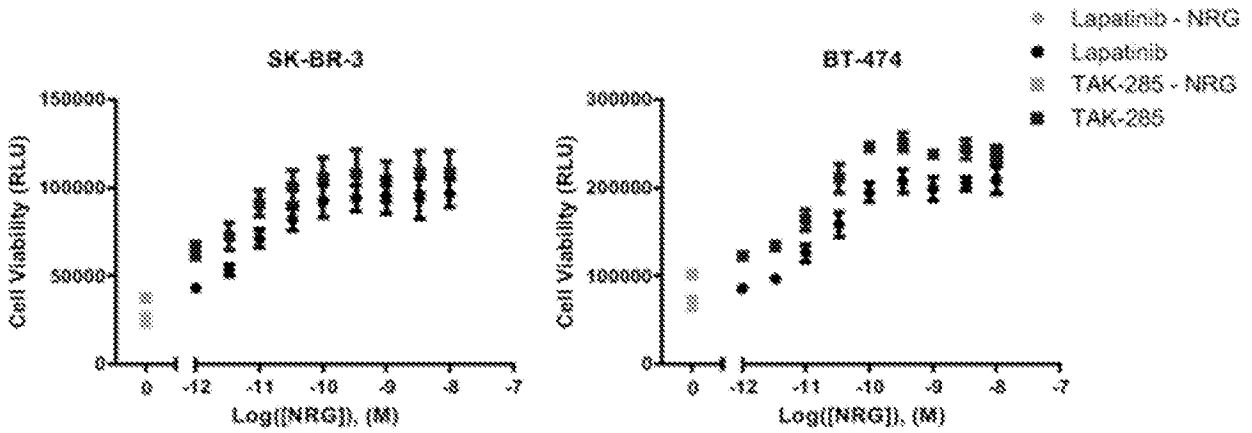


FIG. 1D

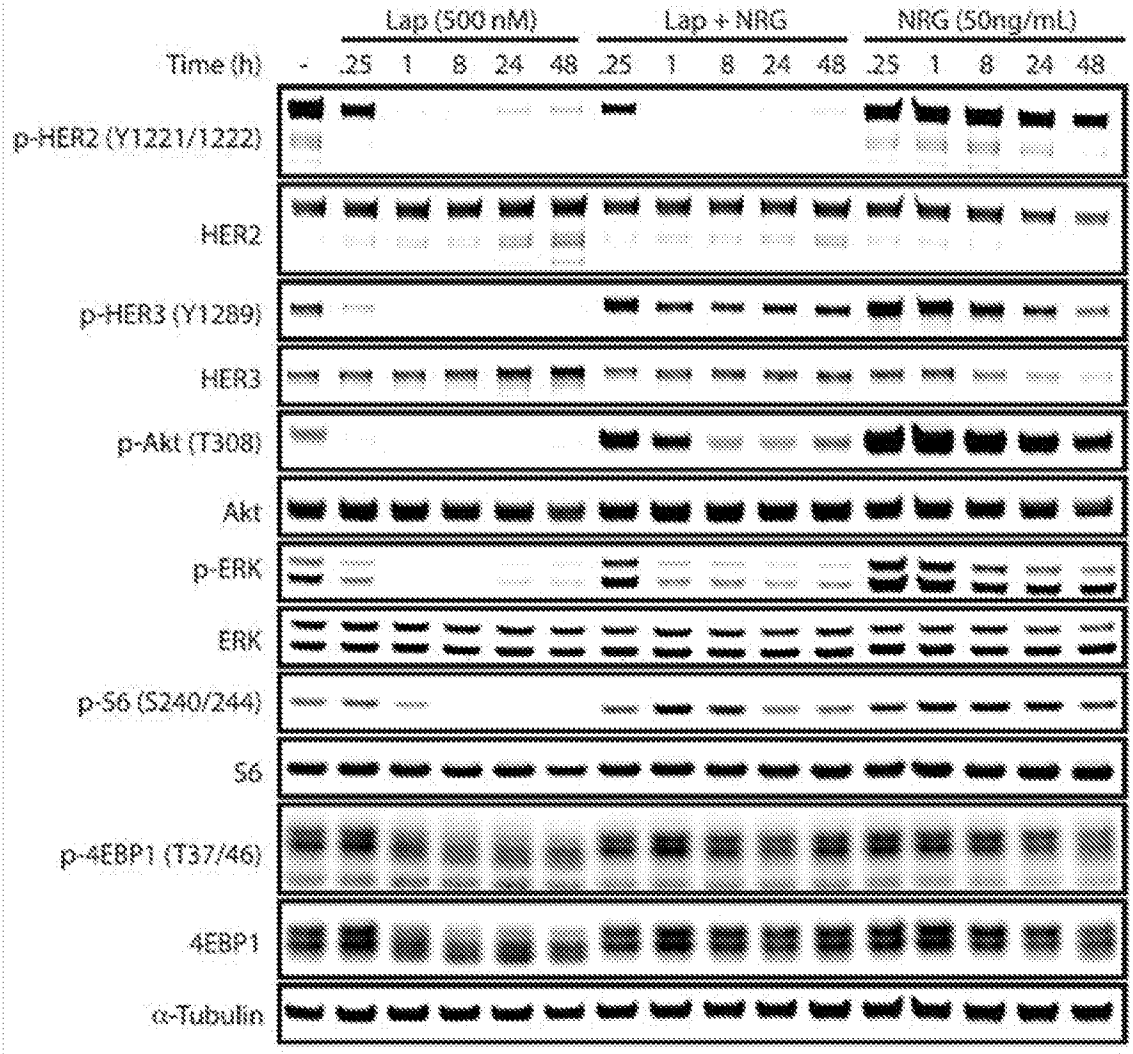

Lap (500 nM)
Lap + NRG
NRG (50ng/mL)
Time (h)
- .25 1 8 24 48 .25 1 8 24 48 .25 1 8 24 48
p-HER2 (Y1221/1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK
ERK
p-S6 (S240/244)
S6
p-4EBP1 (T37/46)
4EBP1
α-Tubulin

FIG. 1E

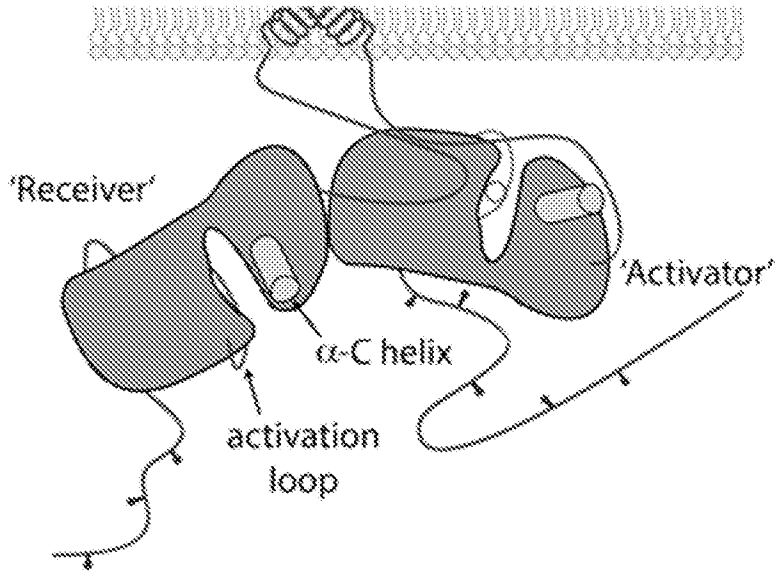

'Receiver'
'Activator'
α-C helix
activation loop

FIG. 2A

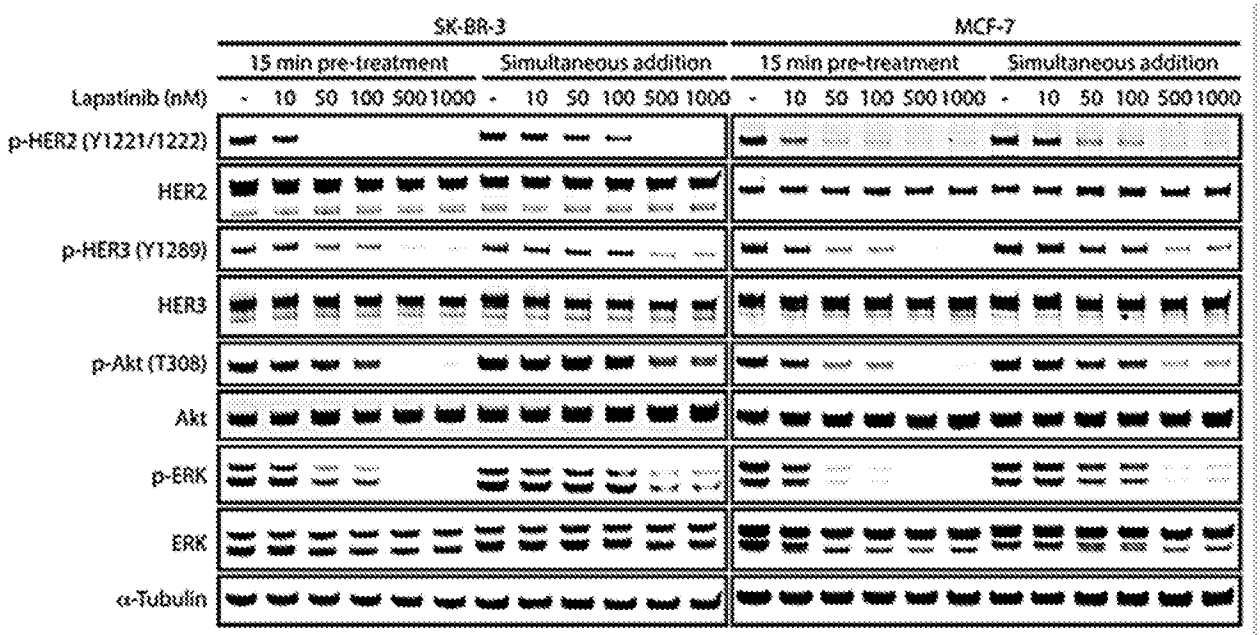

SK-BR-3
MCF-7
15 min pre-treatment
Simultaneous addition
15 min pre-treatment
Simultaneous addition
Lapatinib (nM)
- 10 50 100 500 1000
- 10 50 100 500 1000
- 10 50 100 500 1000
- 10 50 100 500 1000
p-HER2 (Y1221/1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK
ERK
α-Tubulin

FIG. 2B

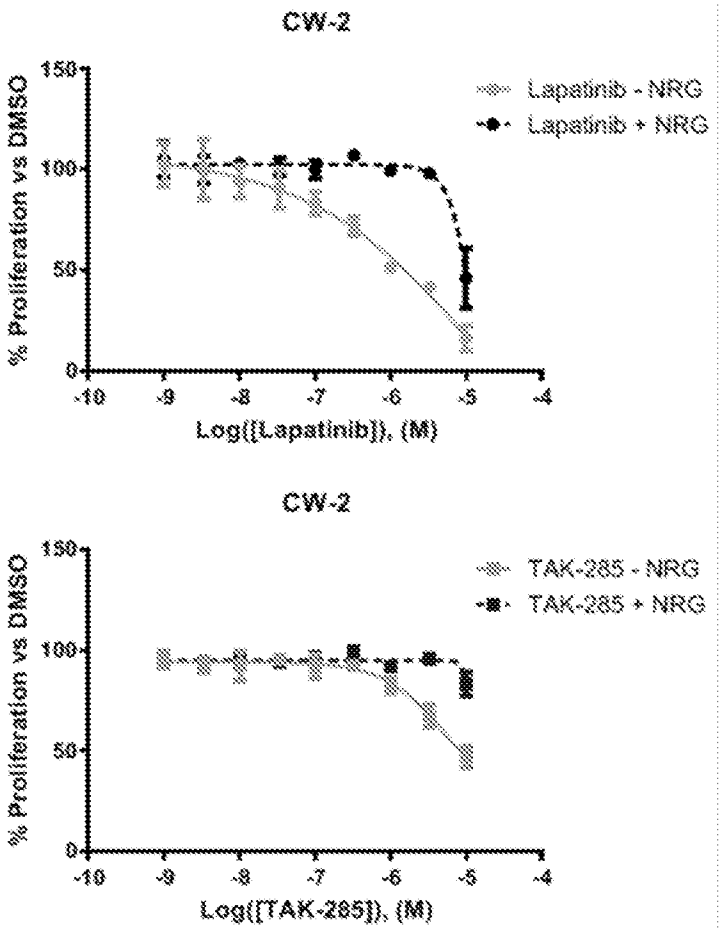

CW-2
% Proliferation vs DMSO
150
100
50
0
-10
-9
-8
-7
-6
-5
-4
Log([Lapatinib]), (M)
Lapatinib - NRG
Lapatinib + NRG
CW-2
% Proliferation vs DMSO
150
100
50
0
-10
-9
-8
-7
-6
-5
-4
Log([TAK-285]), (M)
TAK-285 - NRG
TAK-285 + NRG

FIG. 2C

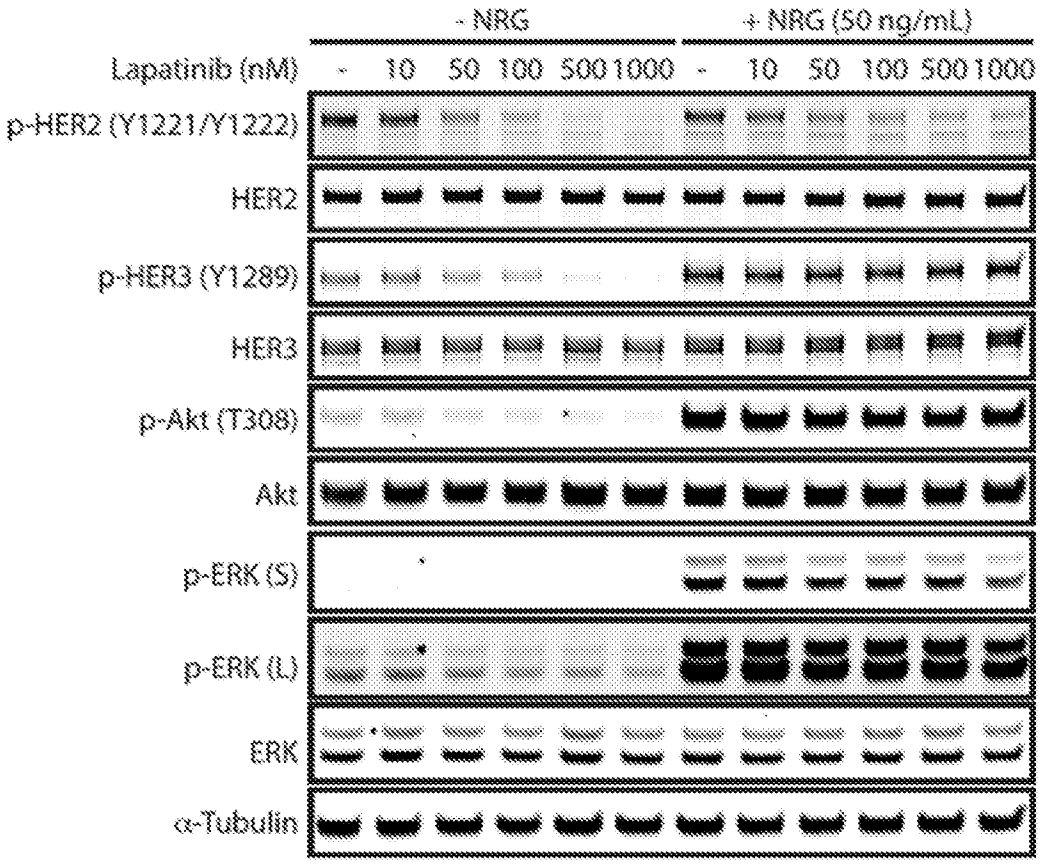

- NRG
+ NRG (50 ng/mL)
Lapatinib (nM) - 10 50 100 500 1000 - 10 50 100 500 1000
p-HER2 (Y1221/Y1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK (S)
p-ERK (L)
ERK
α-Tubulin

FIG. 2D

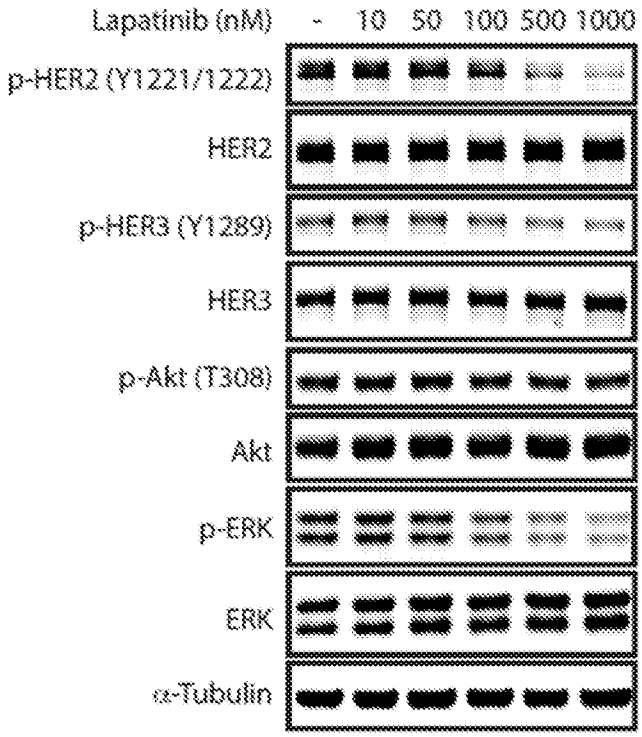

Lapatinib (nM) - 10 50 100 500 1000
p-HER2 (Y1221/1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK
ERK
α-Tubulin

FIG. 3A

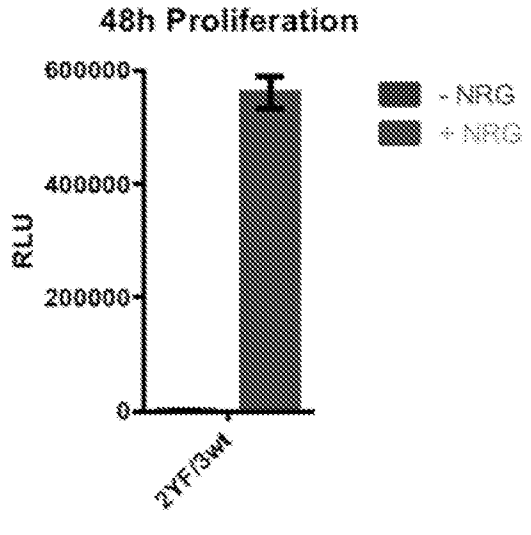


FIG. 3B

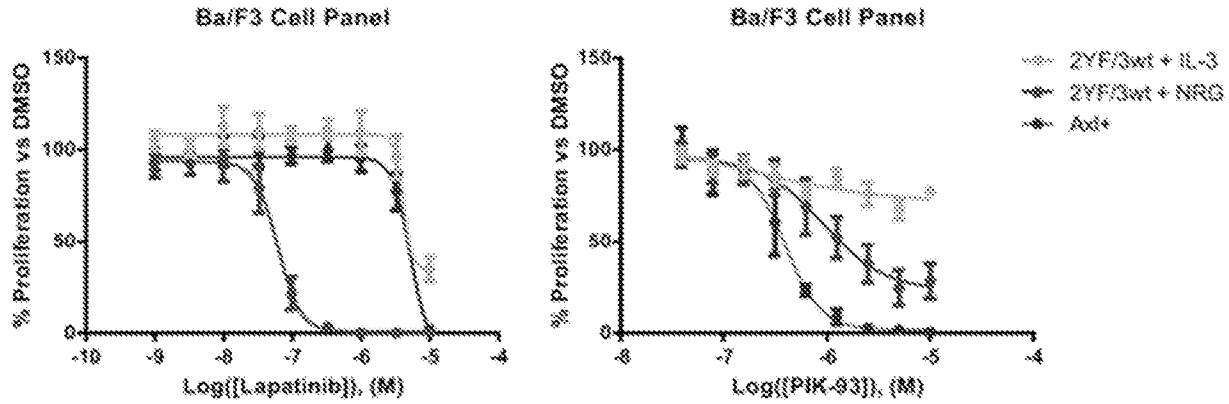
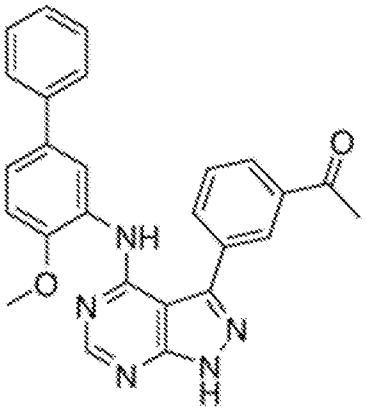


FIG. 3C



185

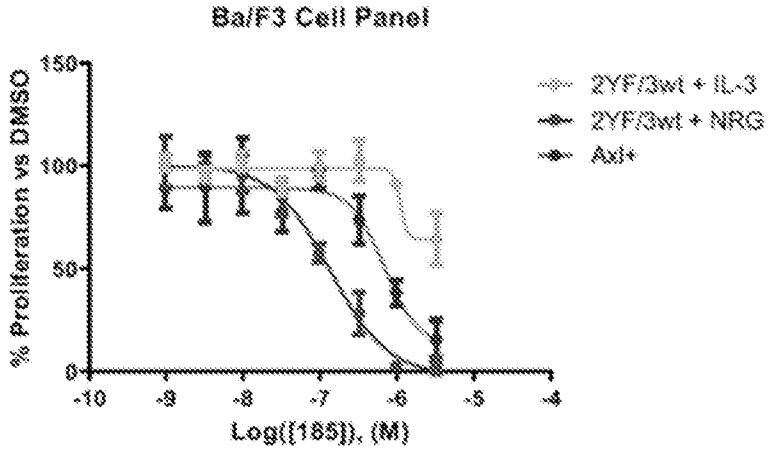


FIG. 3D

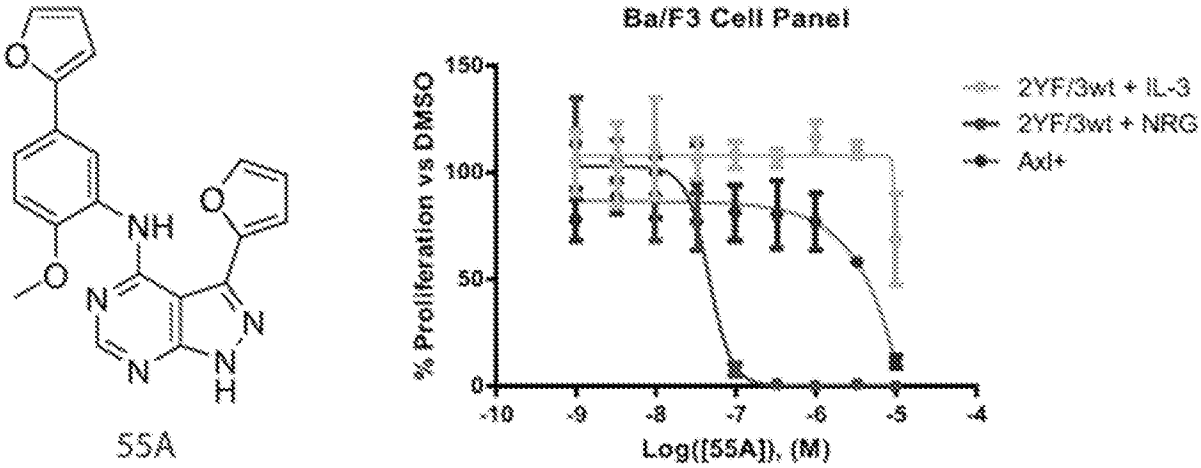


FIG. 4A

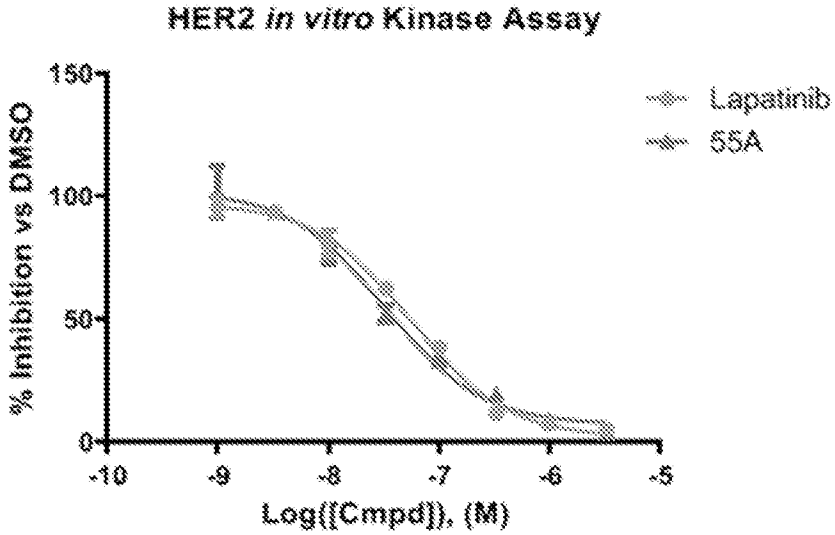


FIG. 4B

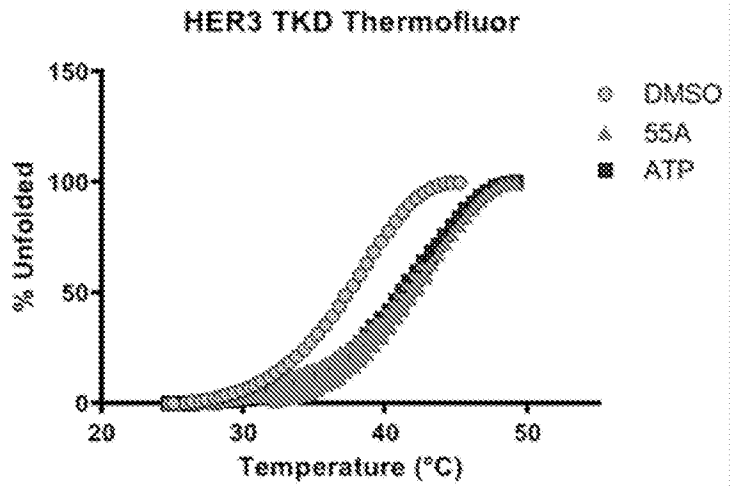


FIG. 4C

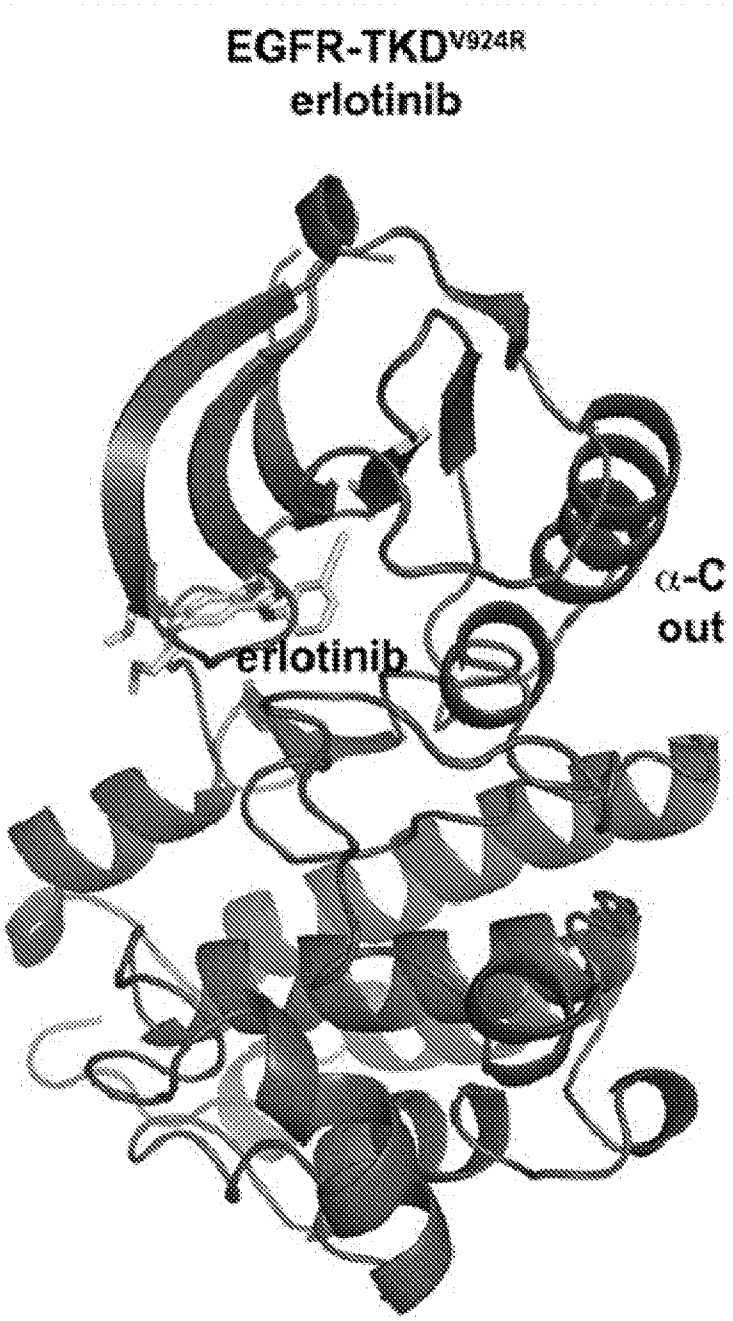


FIG. 4D

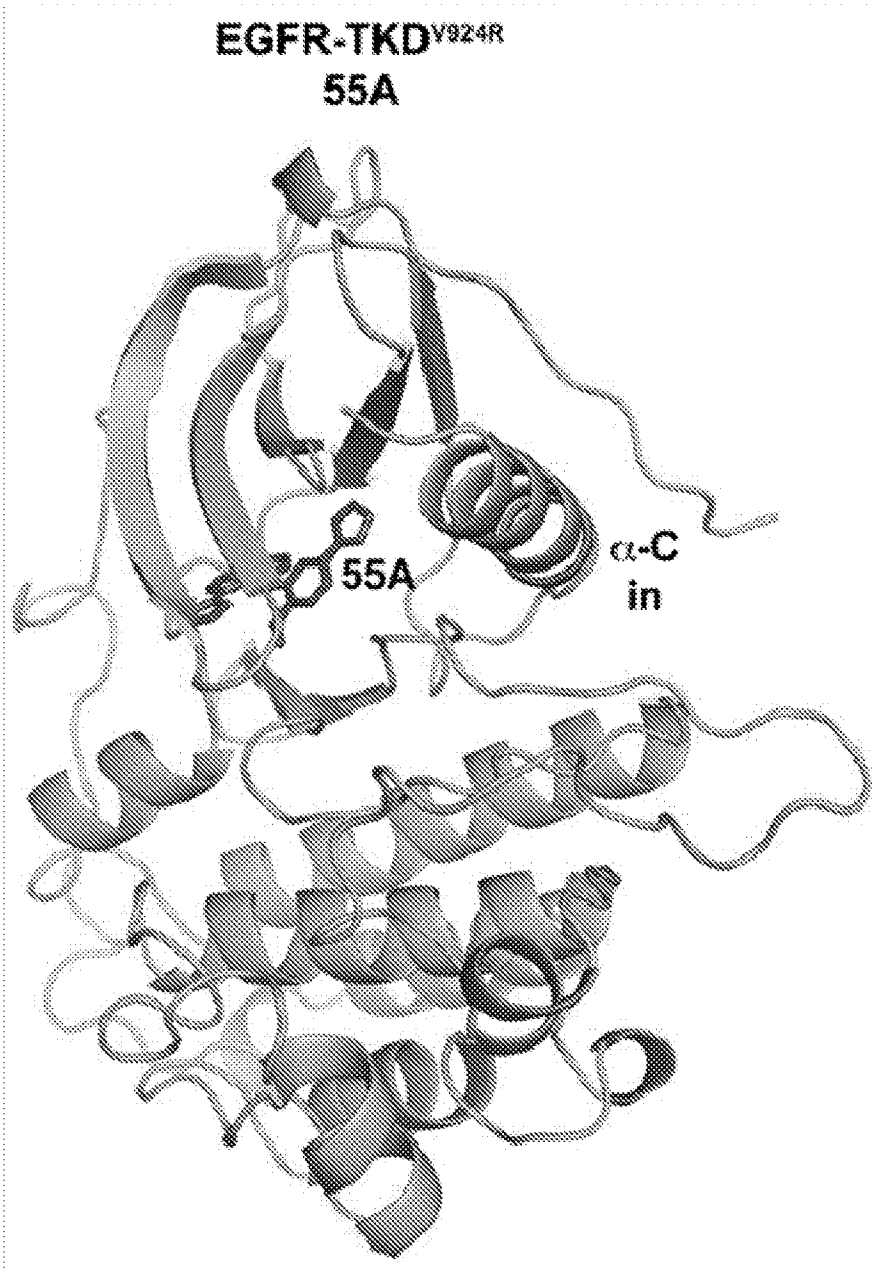


FIG. 4E

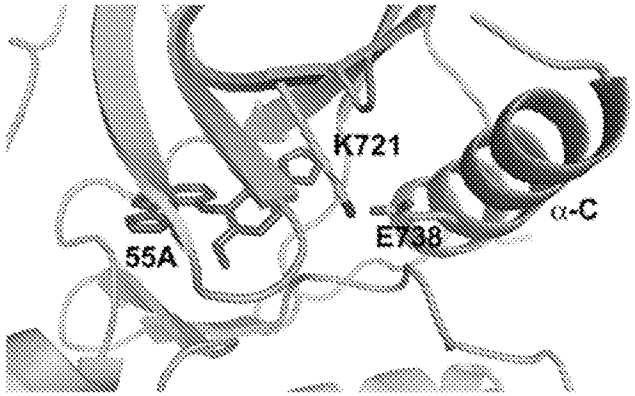


FIG. 4F

	IC_{50} of Gatekeeper Mutant Ba/F3 Cells Lines (nM ± SEM)			
	HER2YF/HER3wt	HER2YF/HER3TM	HER2YFTM/HER3wt	HER2YFTM/HER3TM
Lapatinib	32.4 ± 12.1	27.8 ± 3.9	>10,000	>10,000
Gefitinib	195.8 ± 25.7	125 ± 37.2	>10,000	>10,000
55A	20.0 ±4.5	18.6 ± 4.19	3,237 ± 291	3526 ± 563

FIG. 5A

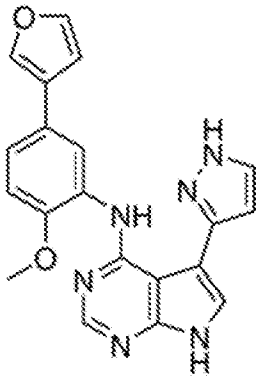


FIG. 5B

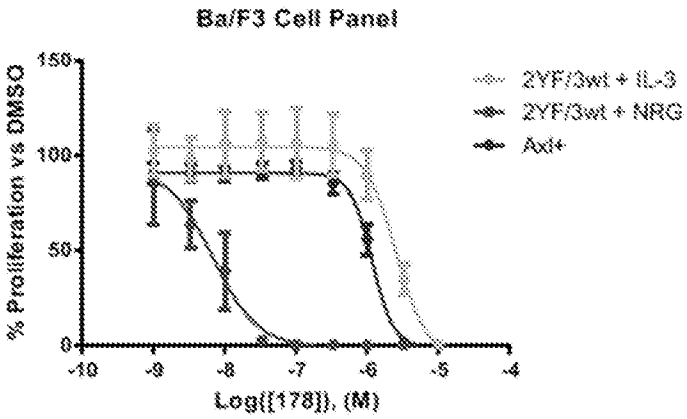


FIG. 5C

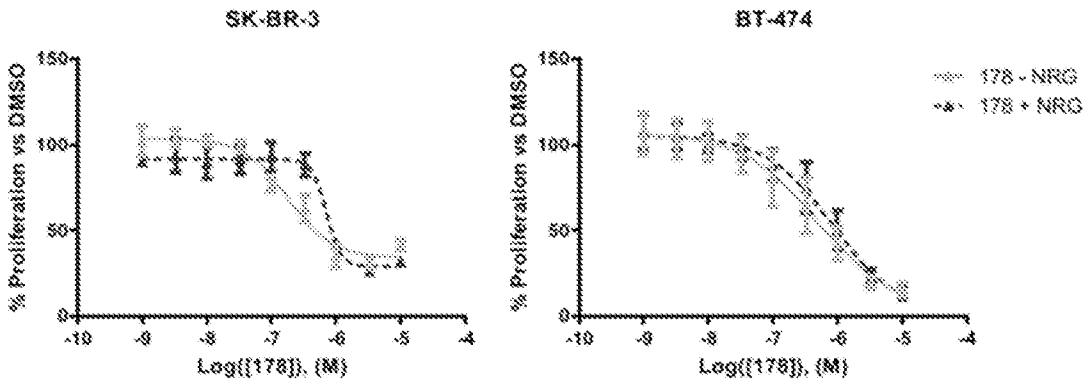


FIG. 5D

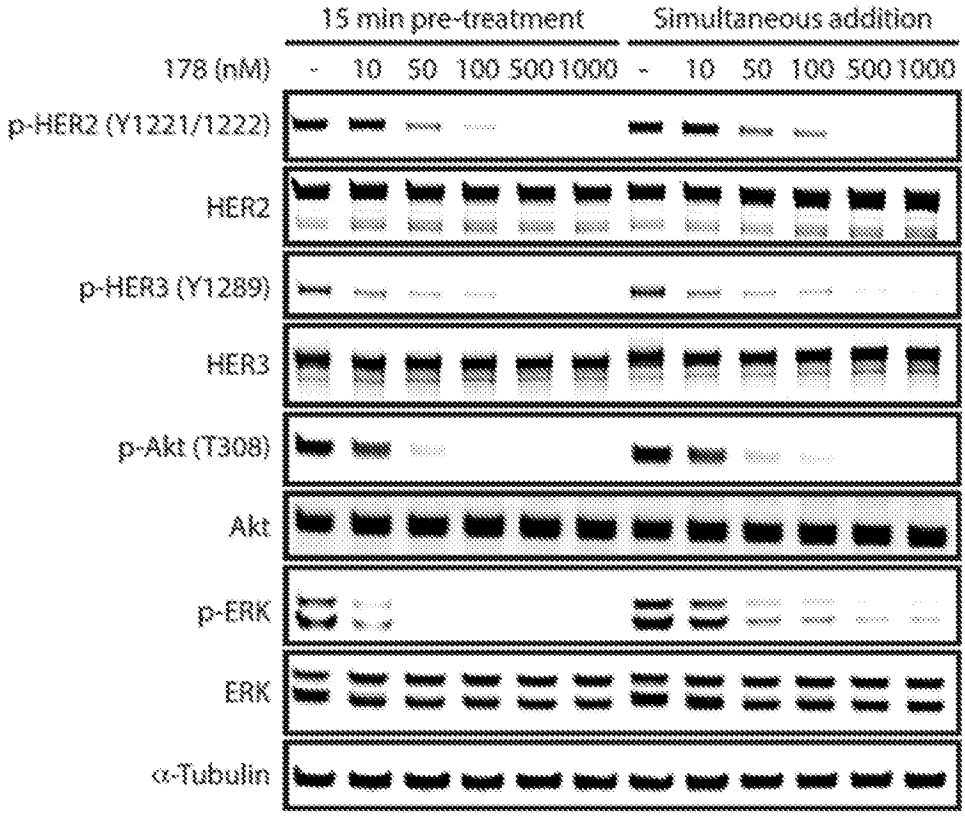

15 min pre-treatment
Simultaneous addition
178 (nM)
- 10 50 100 500 1000 - 10 50 100 500 1000
p-HER2 (Y1221/1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK
ERK
α-Tubulin

FIG. 6A

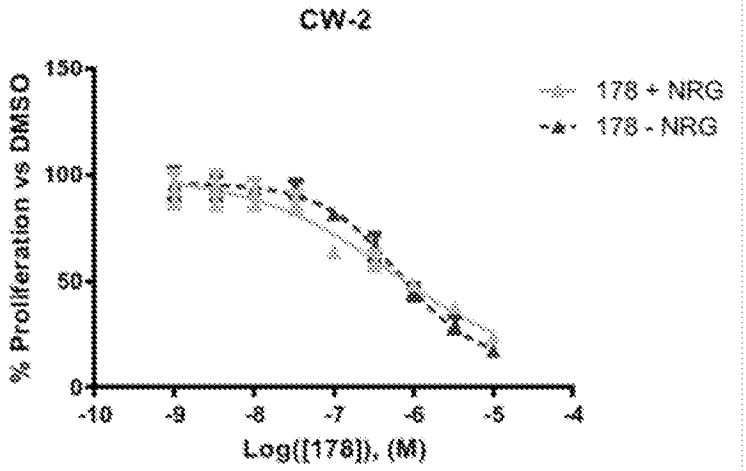

CW-2
178 + NRG
178 - NRG
% Proliferation vs DMSO
150
100
50
0
-10
-9
-8
-7
-6
-5
-4
Log([178]), (M)

FIG. 6B

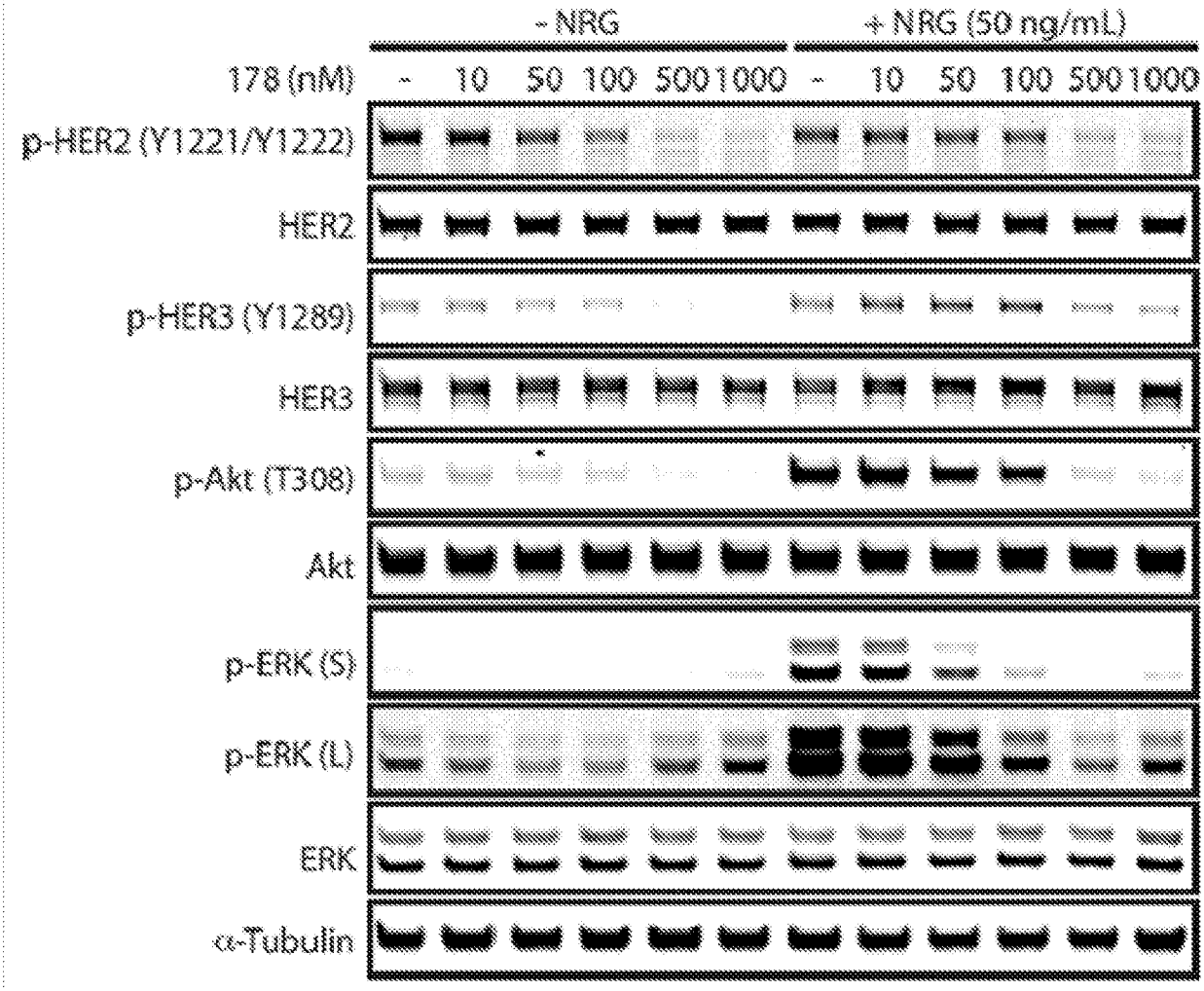

- NRG
+ NRG (50 ng/mL)
178 (nM)
- 10 50 100 500 1000 - 10 50 100 500 1000
p-HER2 (Y1221/Y1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK (S)
p-ERK (L)
ERK
α-Tubulin

FIG. 6C

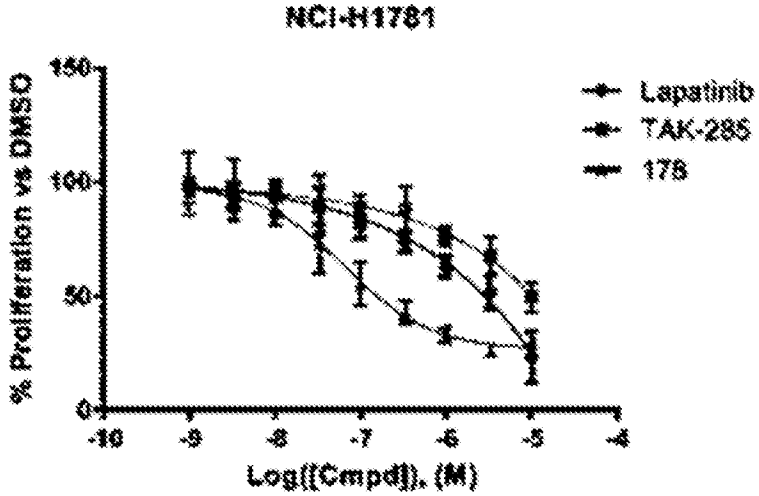

NCI-H1781
% Proliferation vs DMSO
150
100
50
0
-10
-9
-8
-7
-6
-5
-4
Log([Cmpd]), (M)
Lapatinib
TAK-285
178

FIG. 6D

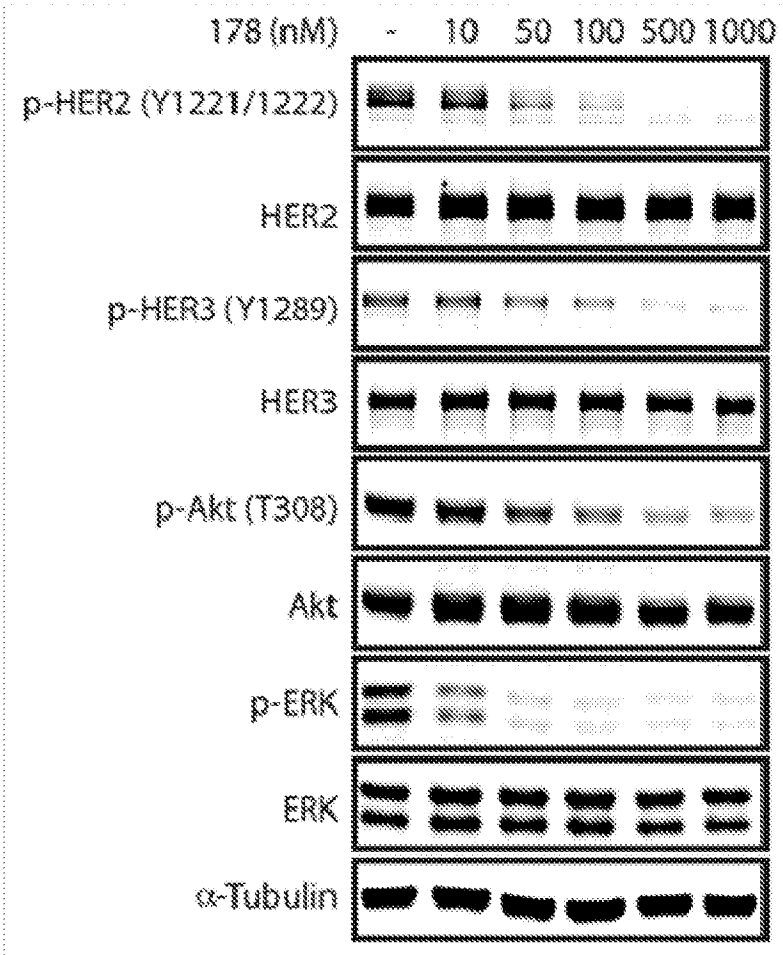

178 (nM) - 10 50 100 500 1000
p-HER2 (Y1221/1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK
ERK
α-Tubulin

FIG. 6E

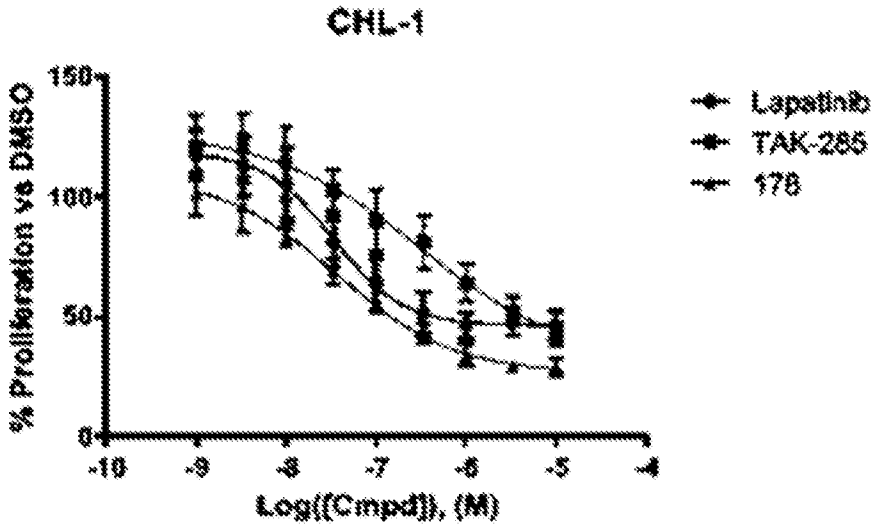

CHL-1
% Proliferation vs DMSO
150
100
50
0
-10
-9
-8
-7
-6
-5
-4
Log([Cmpd]), (M)
Lapatinib
TAK-285
178

FIG. 6F

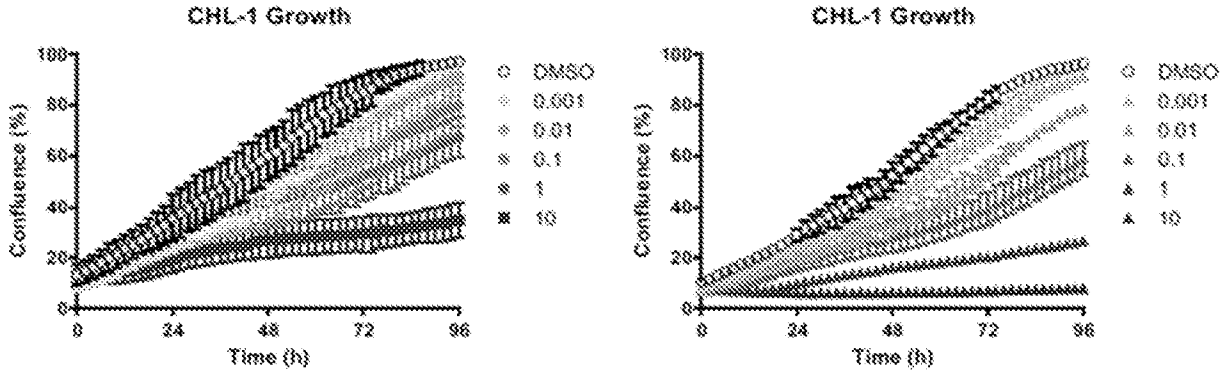

CHL-1 Growth
Confluence (%)
Time (h)
DMSO
0.001
0.01
0.1
1
10
CHL-1 Growth
Confluence (%)
Time (h)
DMSO
0.001
0.01
0.1
1
10

FIG. 6G

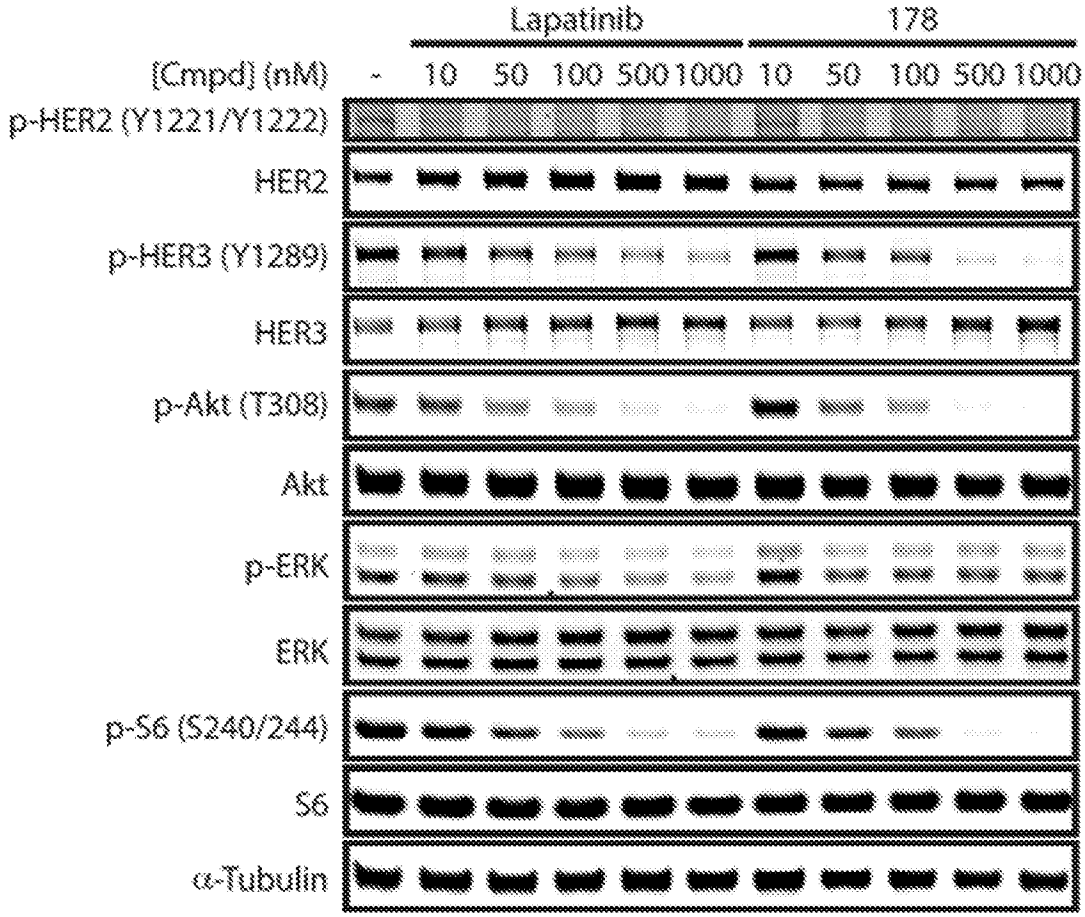

Lapatinib
178
(Cmpd) (nM)
-
10
50
100
500
1000
10
50
100
500
1000
p-HER2 (Y1221/Y1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK
ERK
p-S6 (S240/244)
S6
α-Tubulin

FIG. 7A

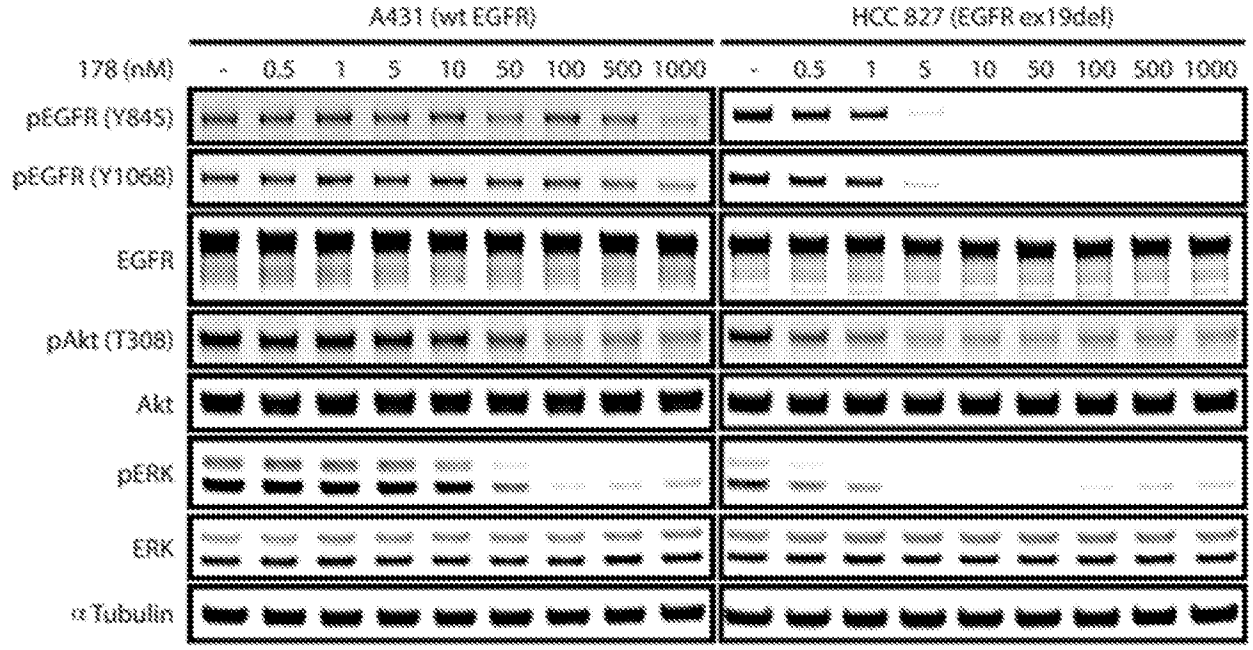

A431 (wt EGFR)
HCC 827 (EGFR ex19del)
178 (nM)
- 0.5 1 5 10 50 100 500 1000
- 0.5 1 5 10 50 100 500 1000
pEGFR (Y845)
pEGFR (Y1068)
EGFR
pAkt (T308)
Akt
pERK
ERK
α-Tubulin

FIG. 7B

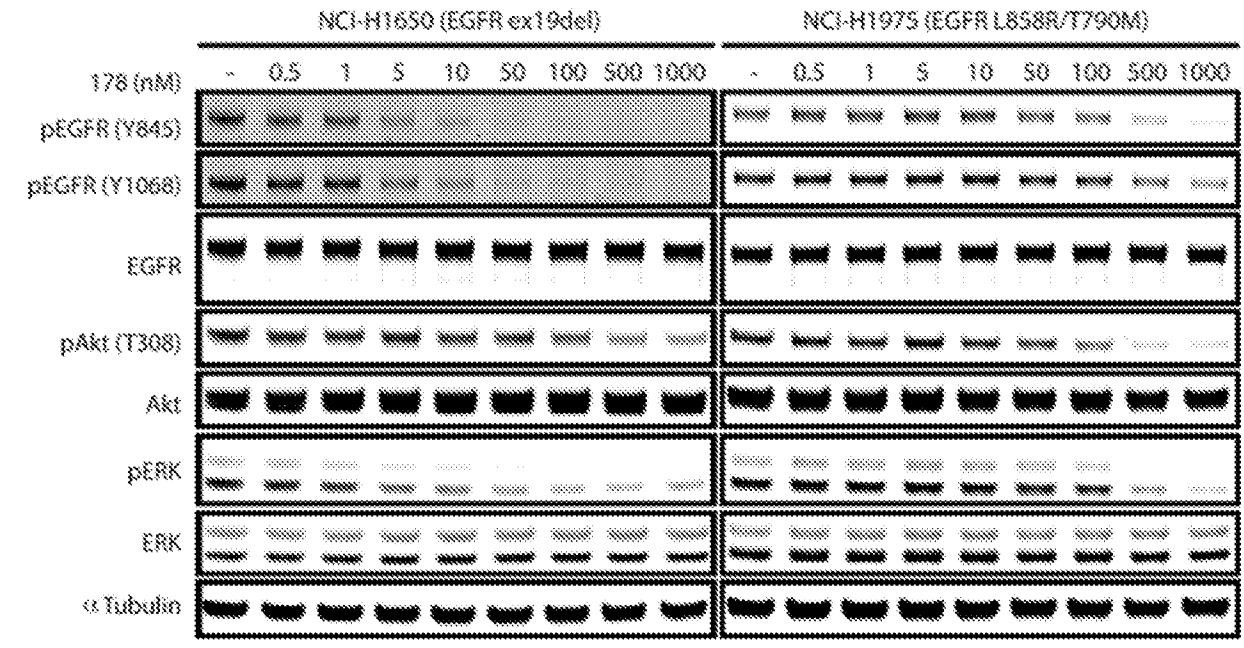

NCI-H1650 (EGFR ex19del)
NCI-H1975 (EGFR L858R/T790M)
178 (nM)
- 0.5 1 5 10 50 100 500 1000
- 0.5 1 5 10 50 100 500 1000
pEGFR (Y845)
pEGFR (Y1068)
EGFR
pAkt (T308)
Akt
pERK
ERK
α-Tubulin

FIG. 7C

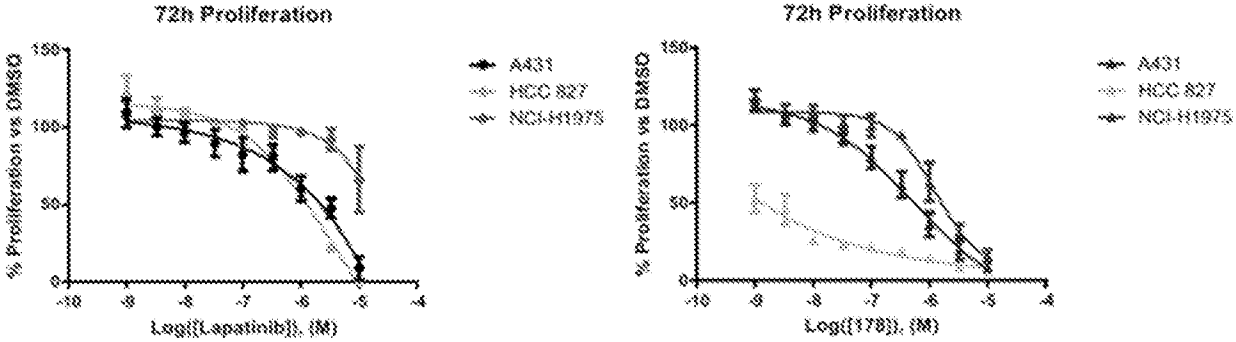

72h Proliferation
% Proliferation vs DMSO
Log([Lapatinib]), (M)
A431
HCC 827
NCI-H1975
72h Proliferation
% Proliferation vs DMSO
Log([178]), (M)
A431
HCC 827
NCI-H1975

FIG. 8

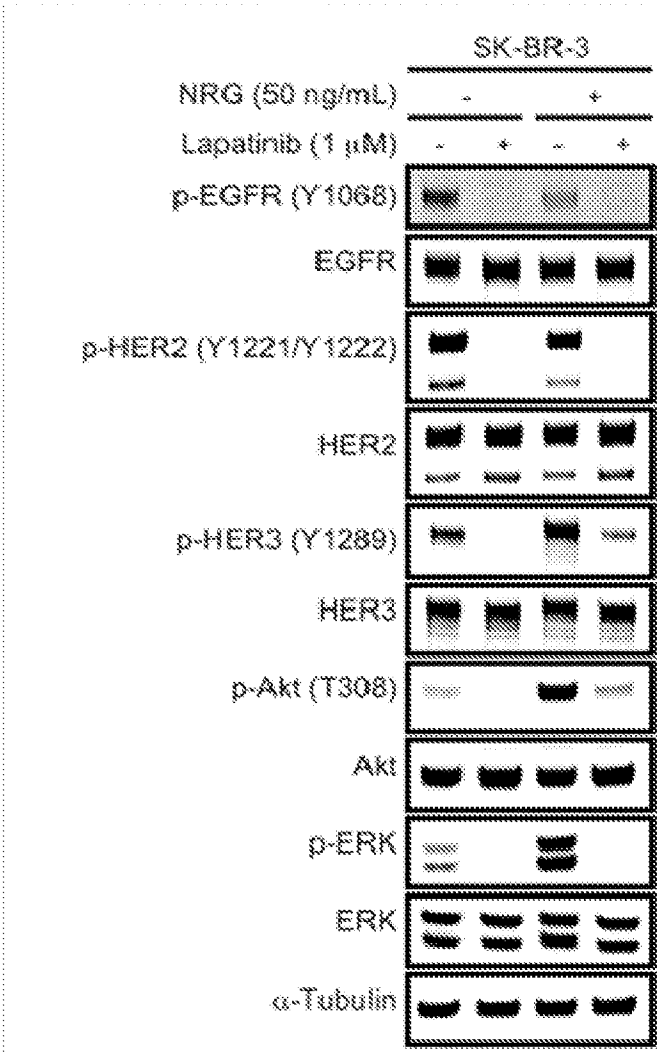

SK-BR-3
NRG (50 ng/mL)
Lapatinib (1 μM)
p-EGFR (Y1068)
EGFR
p-HER2 (Y1221/Y1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK
ERK
α-Tubulin

FIG. 9

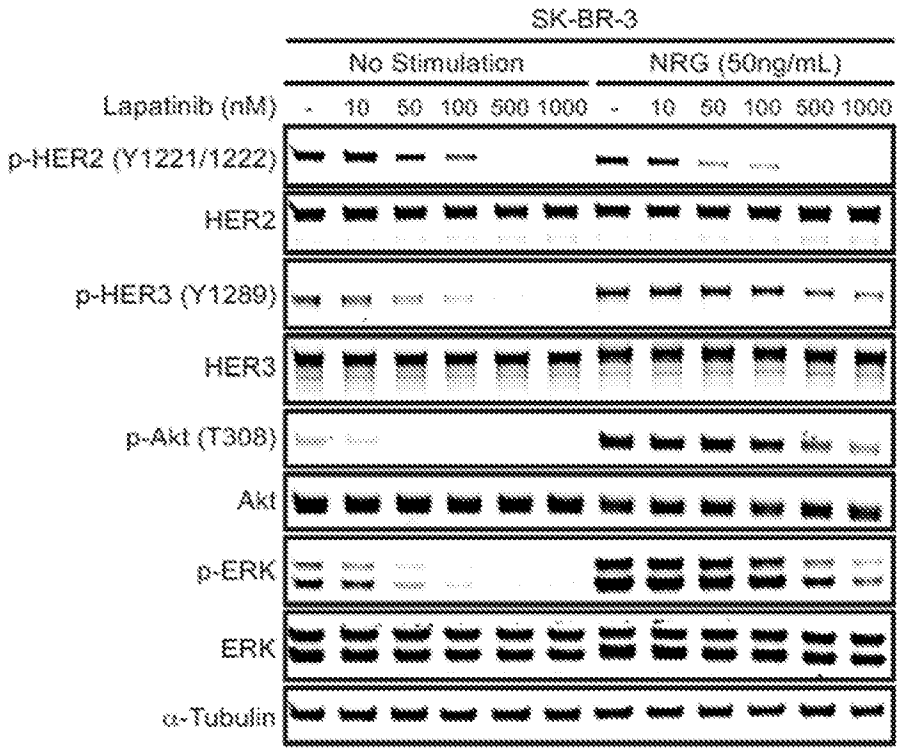


FIG. 10

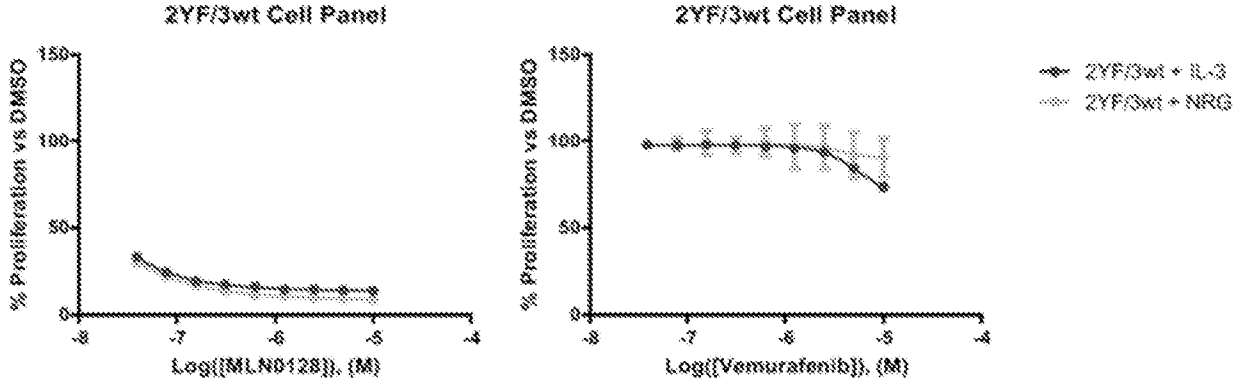


FIG. 11

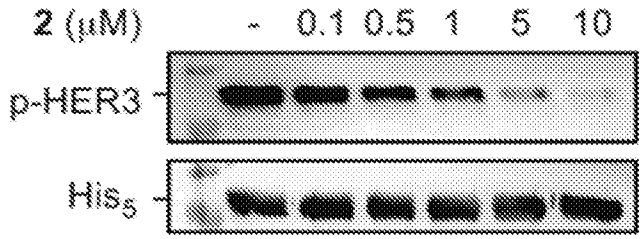


FIG. 12A

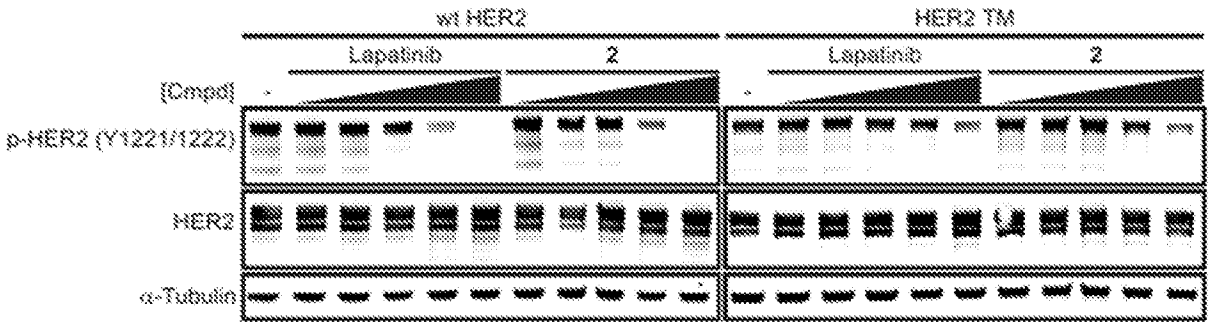


FIG. 12B

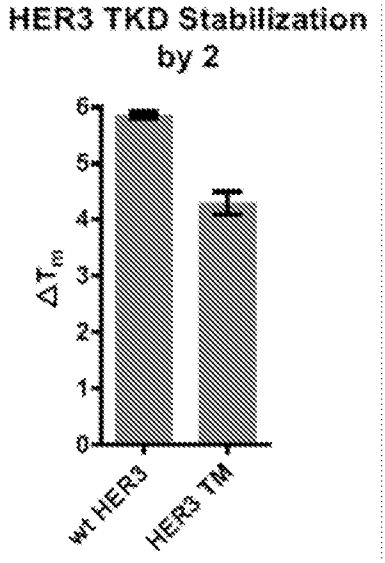


FIG. 13

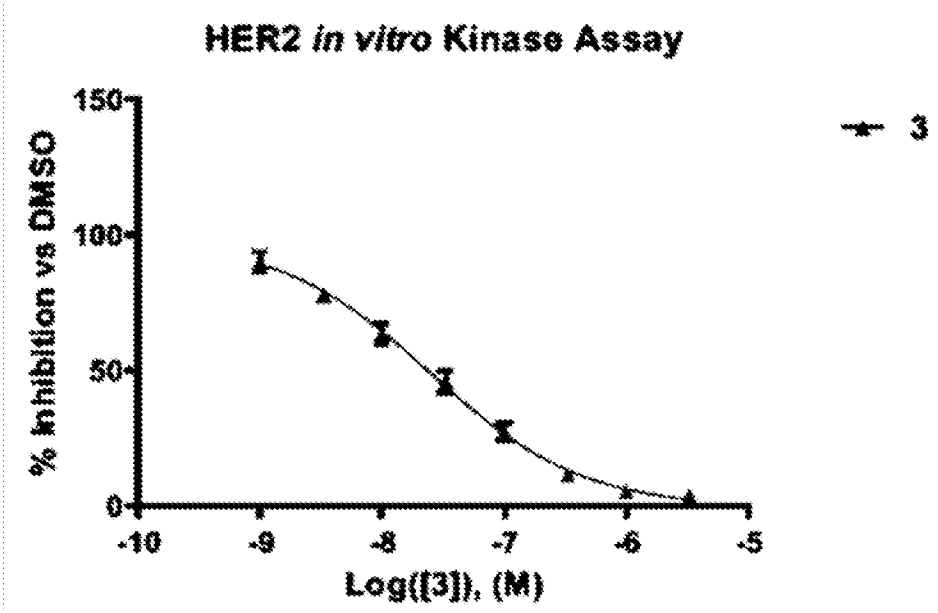


FIG. 14

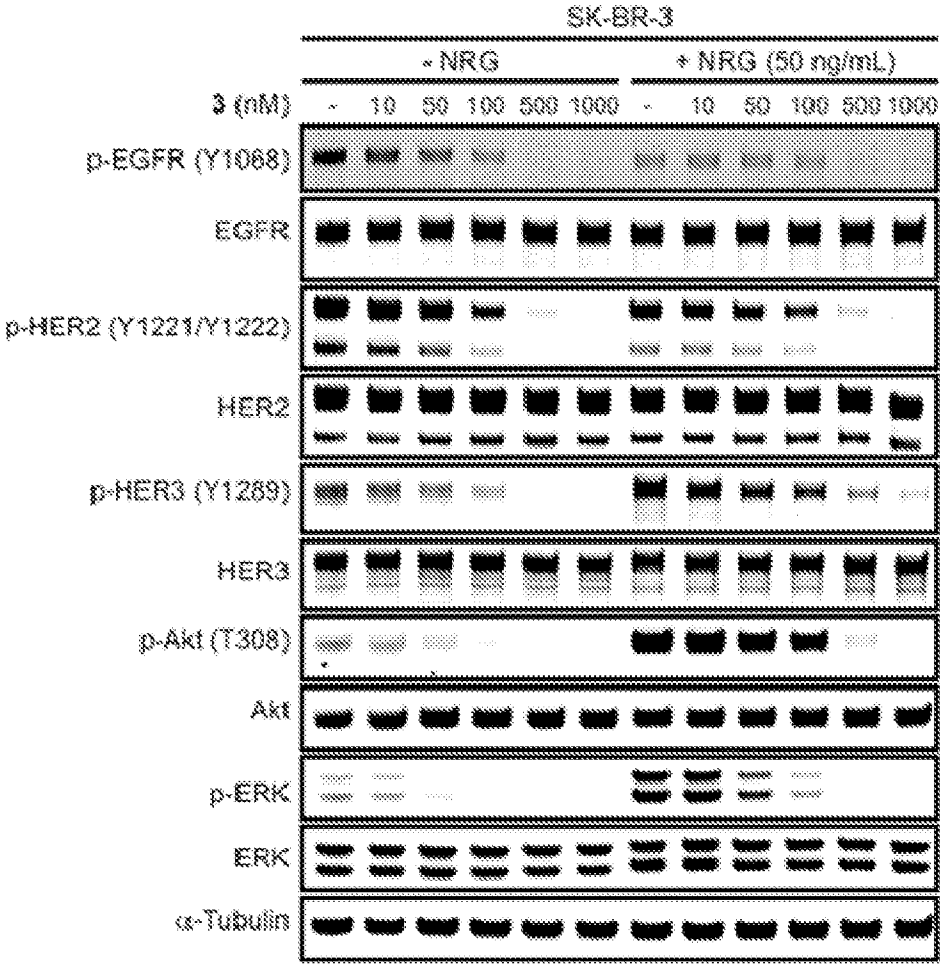


FIG. 15A

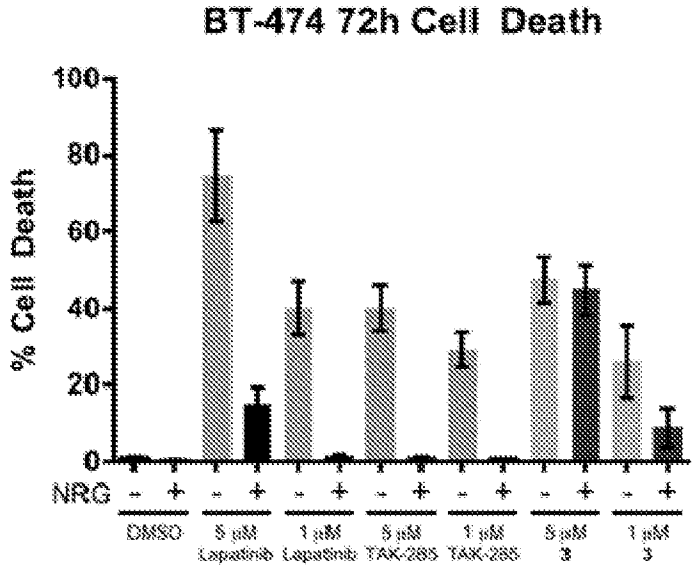


FIG. 15B

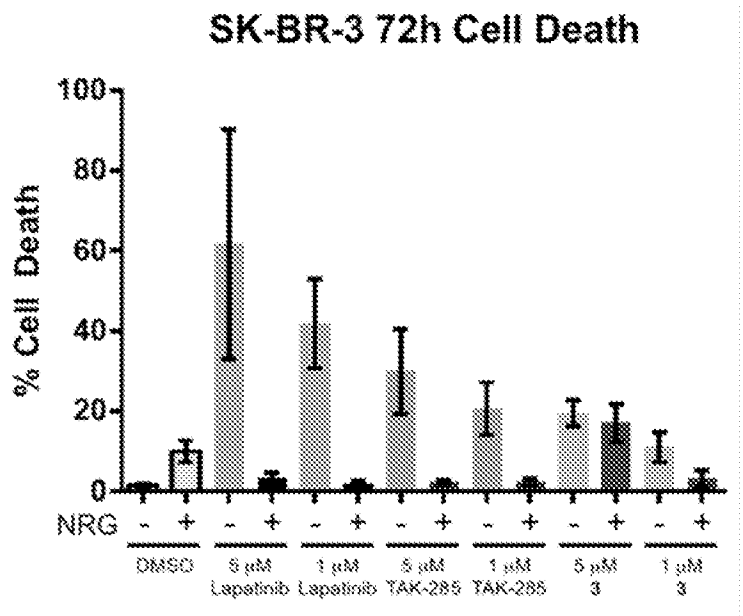


FIG. 15C

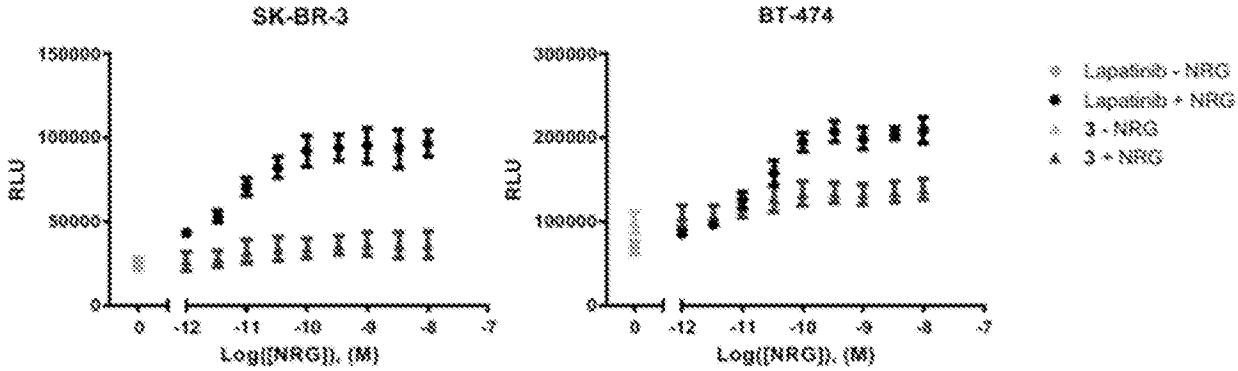


FIG. 16

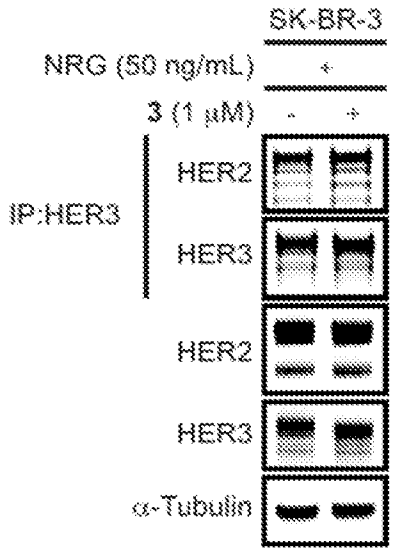


FIG. 17

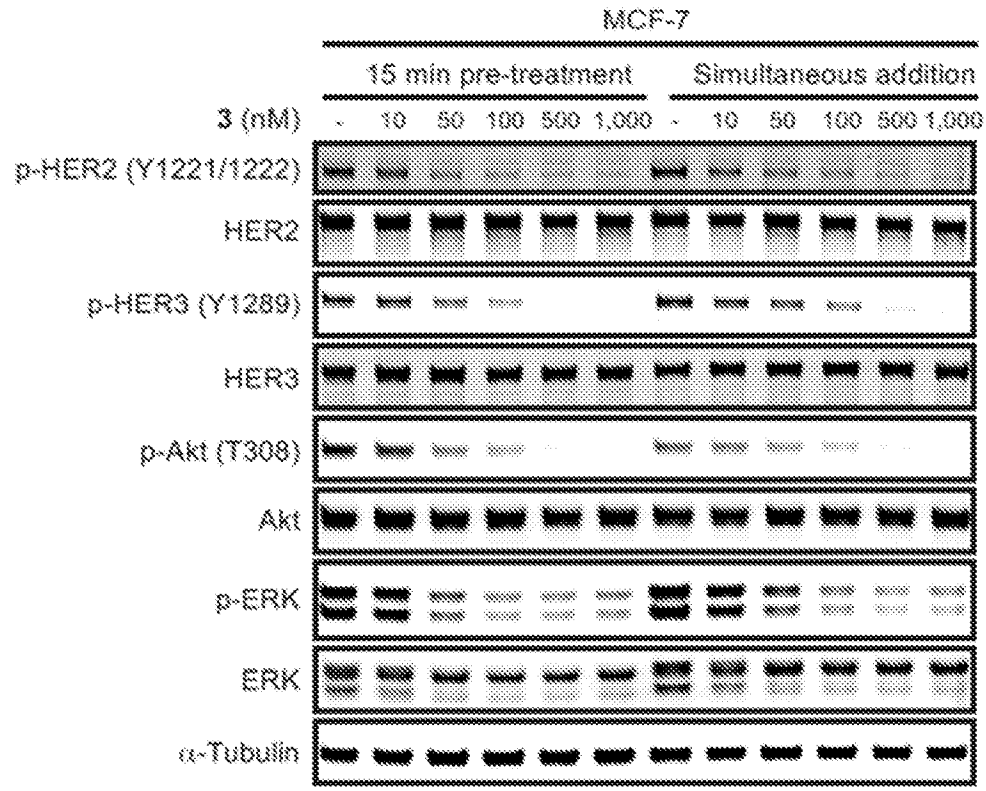

MCF-7
15 min pre-treatment
Simultaneous addition
3 (nM)
- 10 50 100 500 1,000 - 10 50 100 500 1,000
p-HER2 (Y1221/1222)
HER2
p-HER3 (Y1289)
HER3
p-Akt (T308)
Akt
p-ERK
ERK
α-Tubulin

FIG. 18

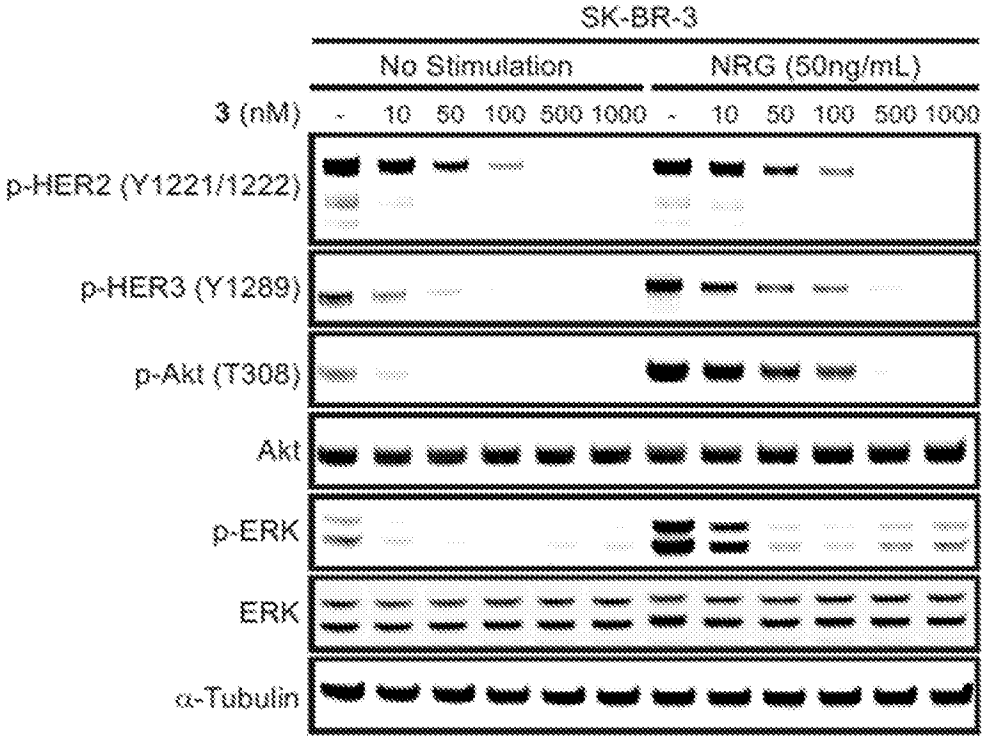

SK-BR-3
No Stimulation
NRG (50ng/mL)
3 (nM)
- 10 50 100 500 1000 - 10 50 100 500 1000
p-HER2 (Y1221/1222)
p-HER3 (Y1289)
p-Akt (T308)
Akt
p-ERK
ERK
α-Tubulin

FIG. 19A

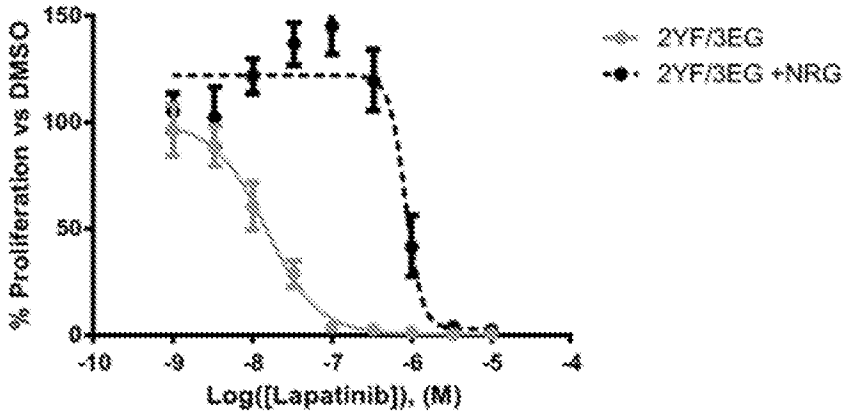


FIG. 19B

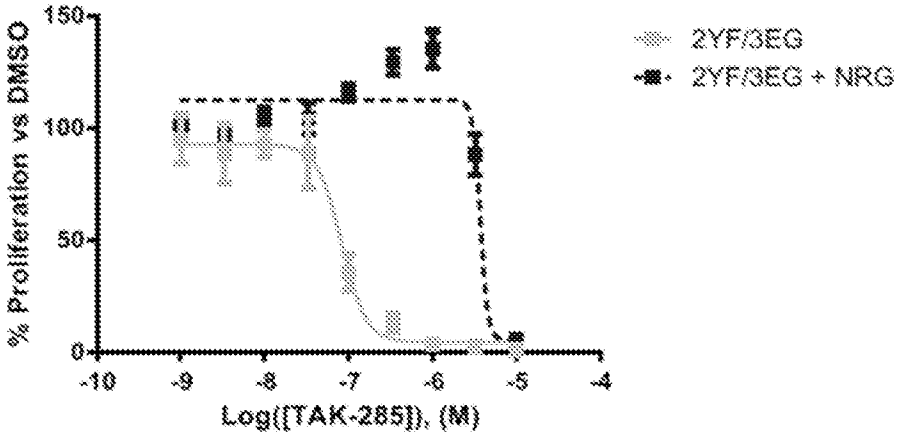


FIG. 19C

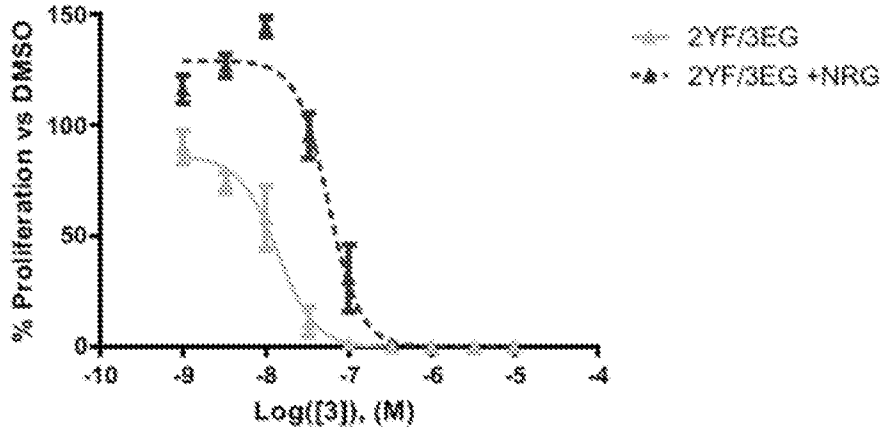


FIG. 19D

	2YF/3EG	2YF/3EG + NRG	NRG Fold Rescue
Lapatinib	15.7 ± 5.4	860.5 ± 99.6	55.0
TAK-285	97.7 ± 17.8	3,841.3 ± 319.7	39.3
3	14 ± 4.0	58 ± 13.5	4.1

FIG. 20A

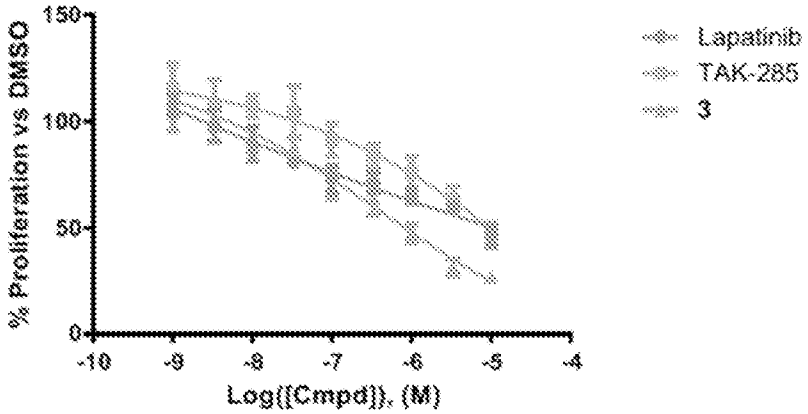


FIG. 20B

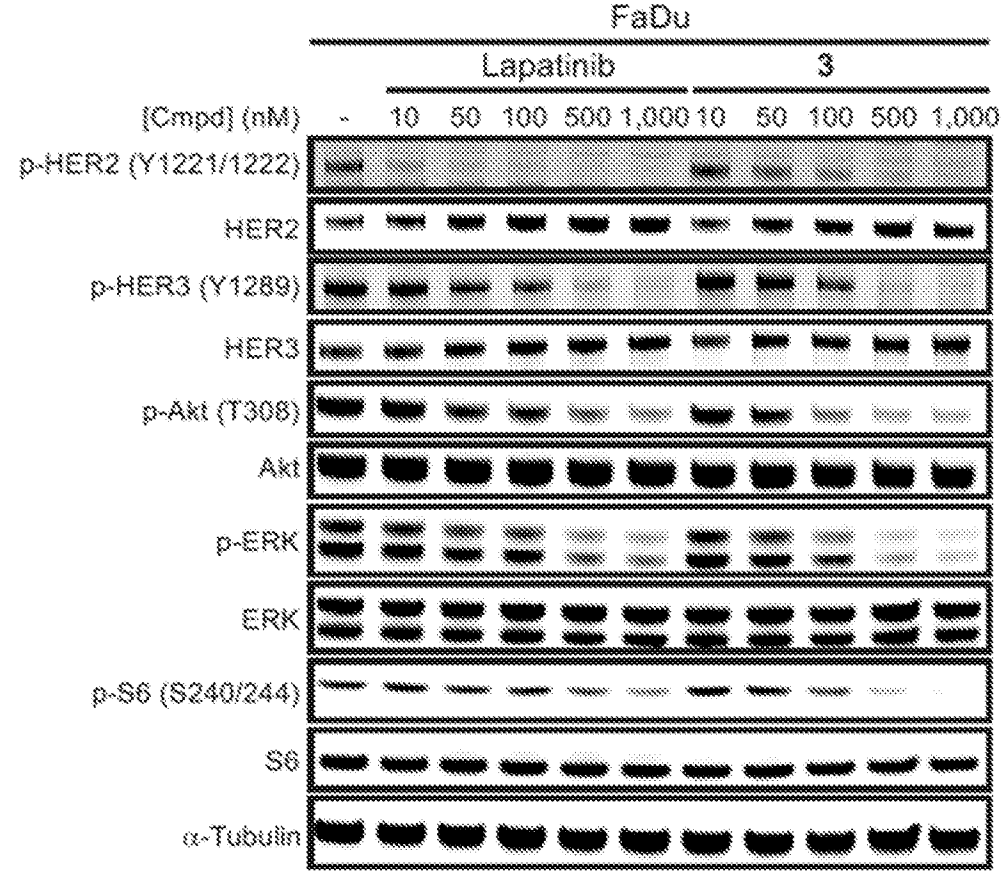
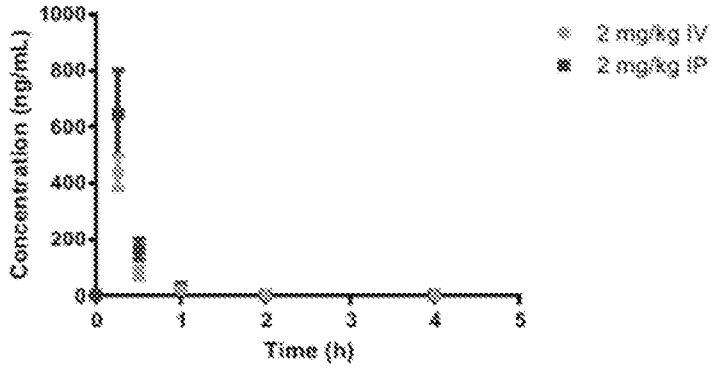


FIG. 21



PK parameters of **3** in CD-1 mice following a single IV and IP dose

Administration Route	Dose (mg/kg)	Cmax (ng/mL)	Tmax (h)	AUC(0-24) (ng/mL*h)	T-HALF (h)	CL (L/h/kg)	Vd (L/Kg)	F%
IV	2	438	0.25	157	0.3	12.8	6.0	
IP	2	648	0.25	259	0.3	N/A	N/A	165%

FIG. 22A

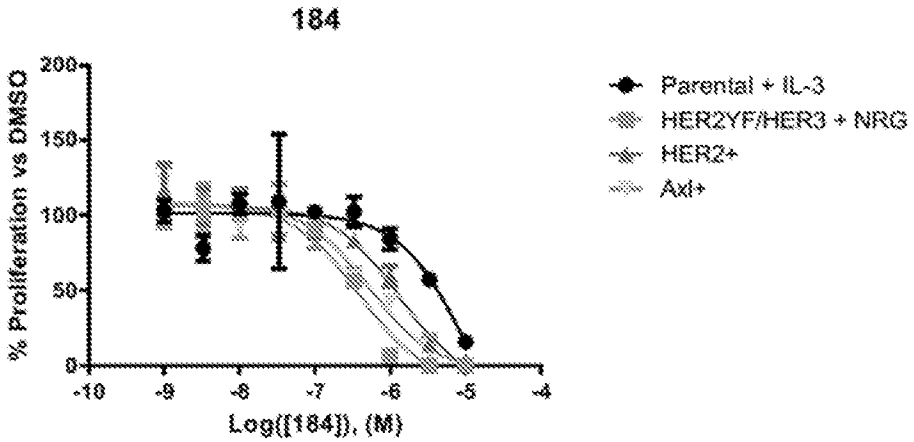


FIG. 22B

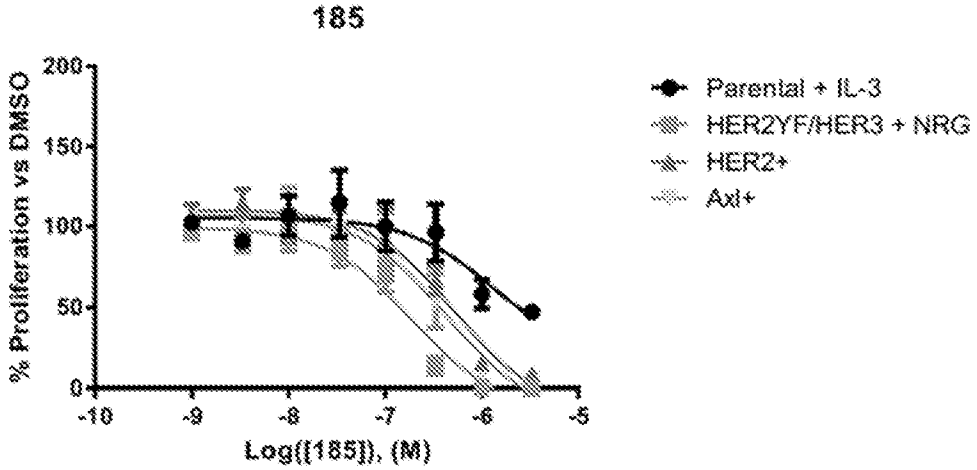


FIG. 22C

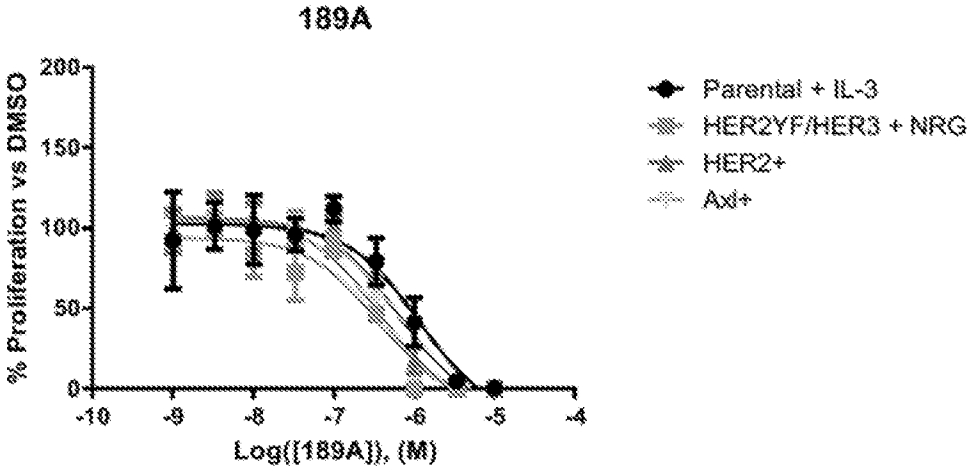


FIG. 22D

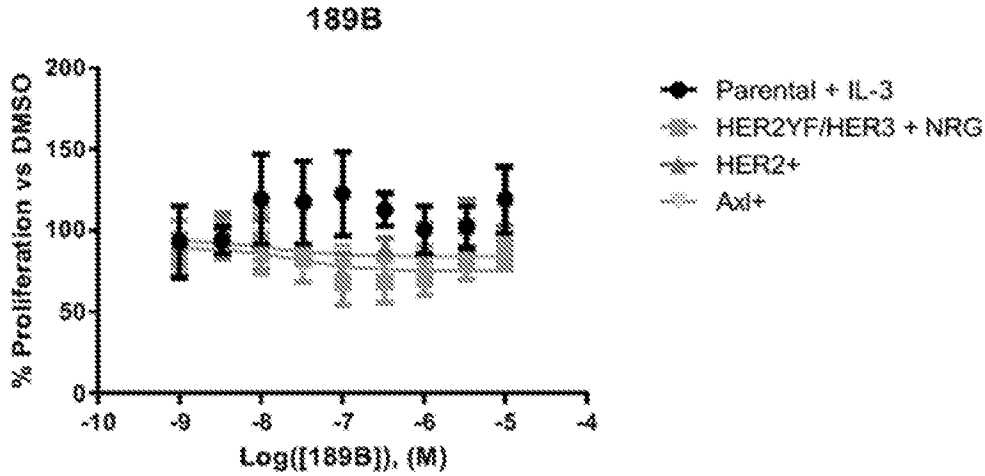


FIG. 22E

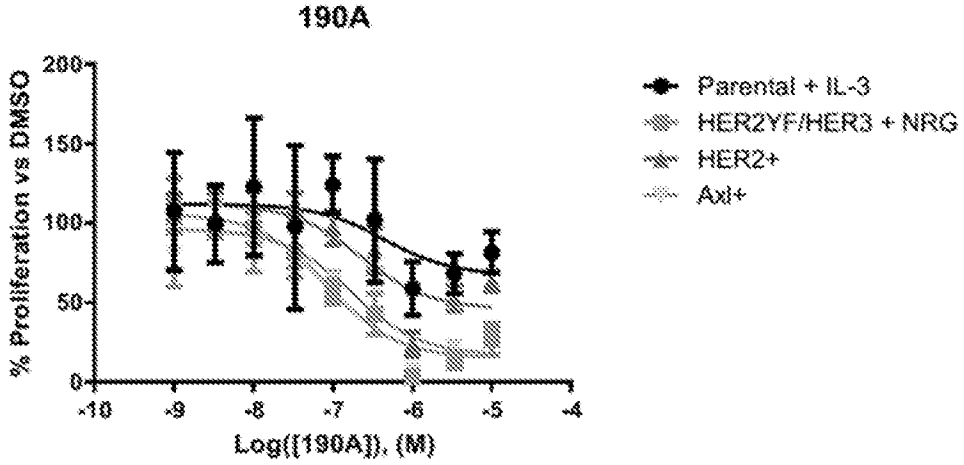


FIG. 22F

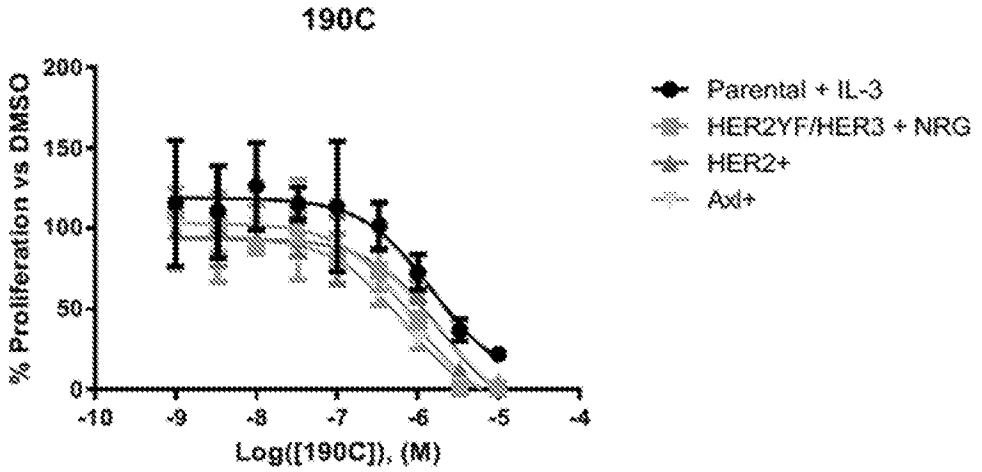


FIG. 22G

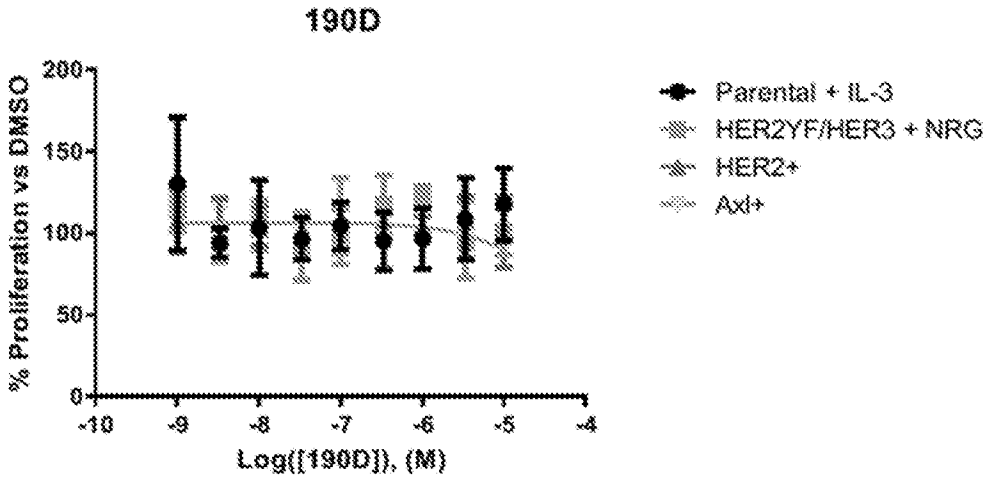


FIG. 22H

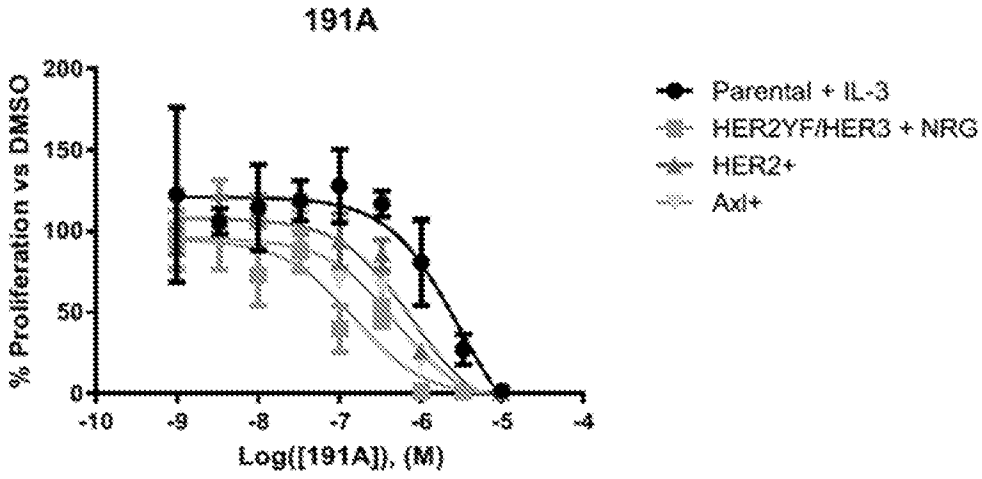


FIG. 23A

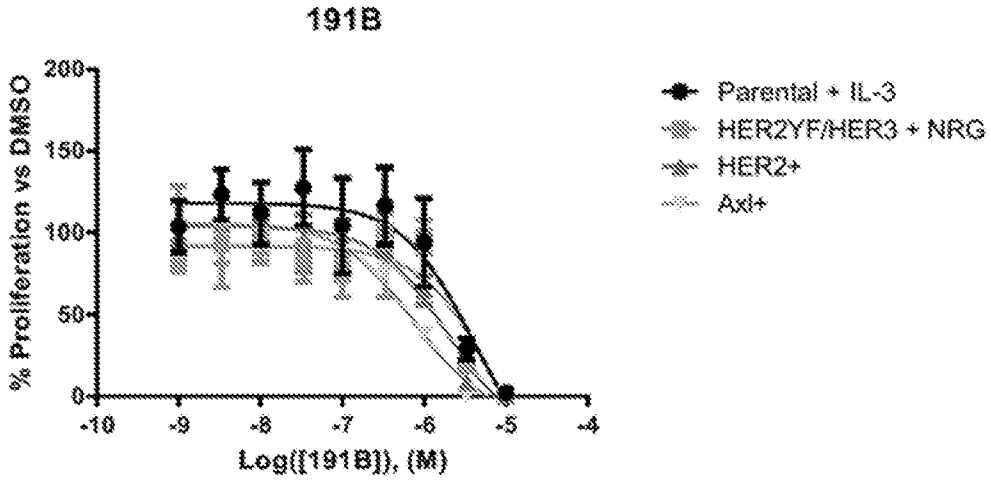


FIG. 23B

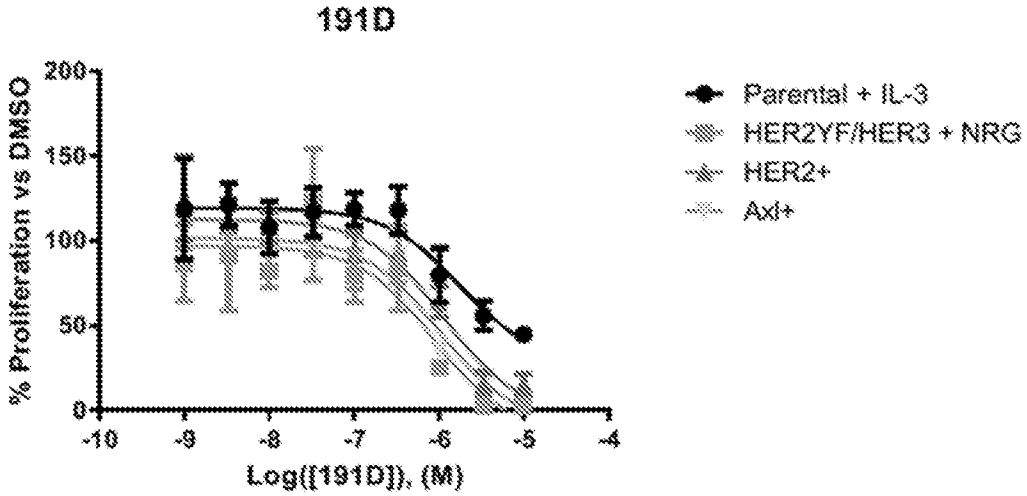


FIG. 23C

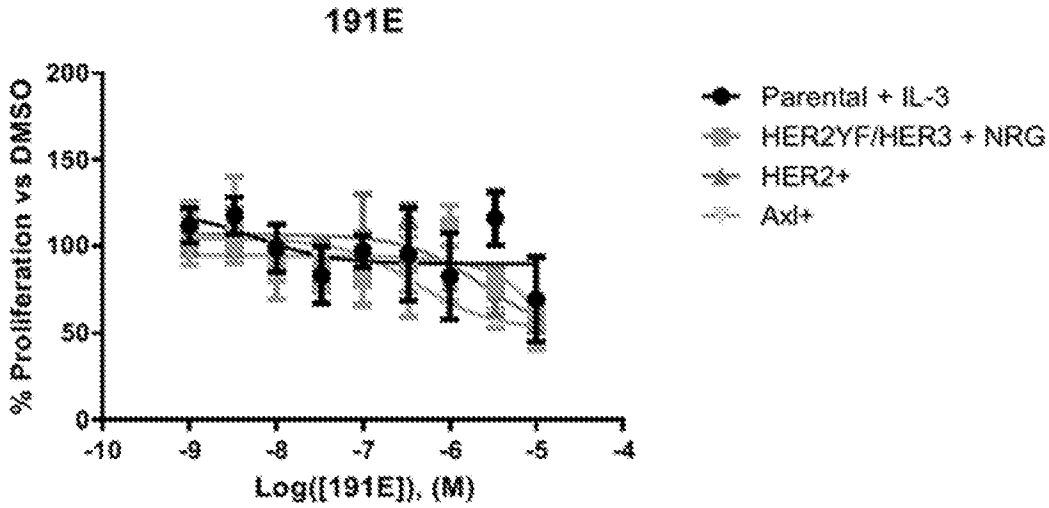


FIG. 23D

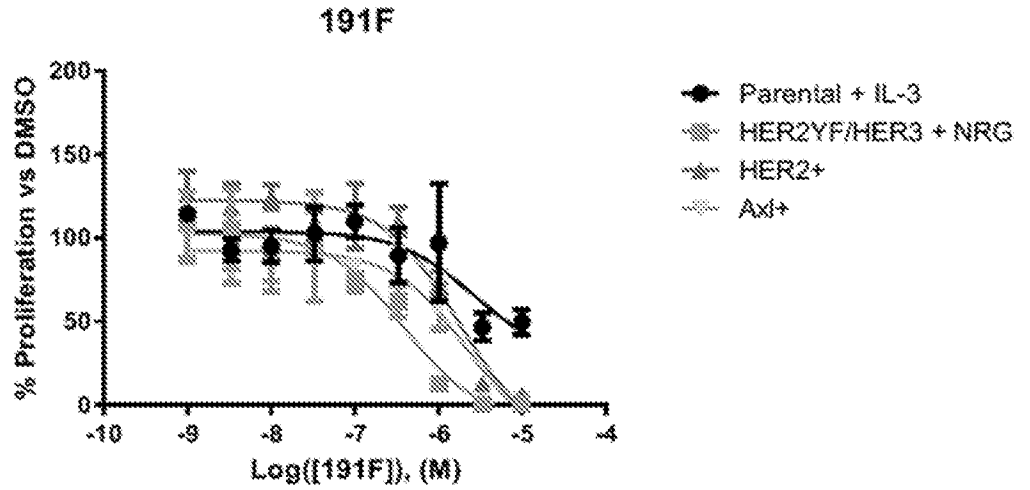


FIG. 23E

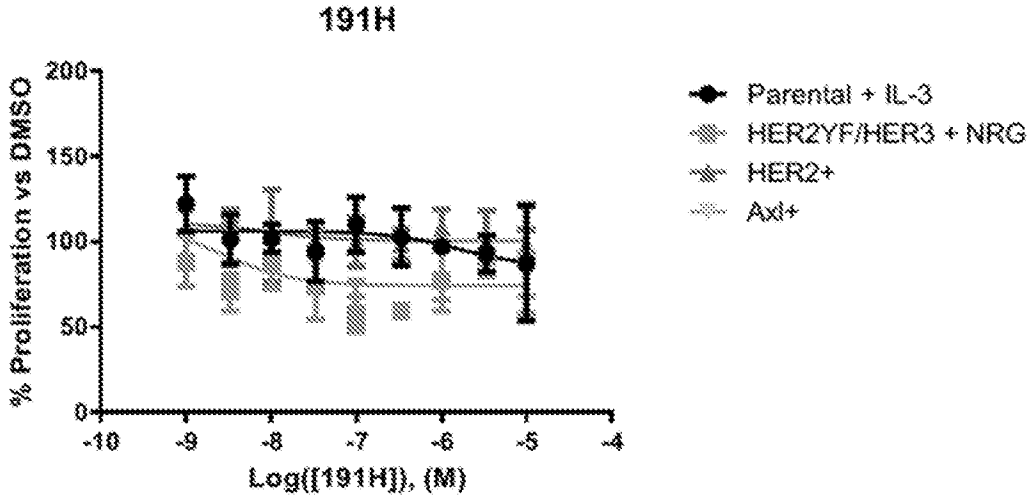


FIG. 23F

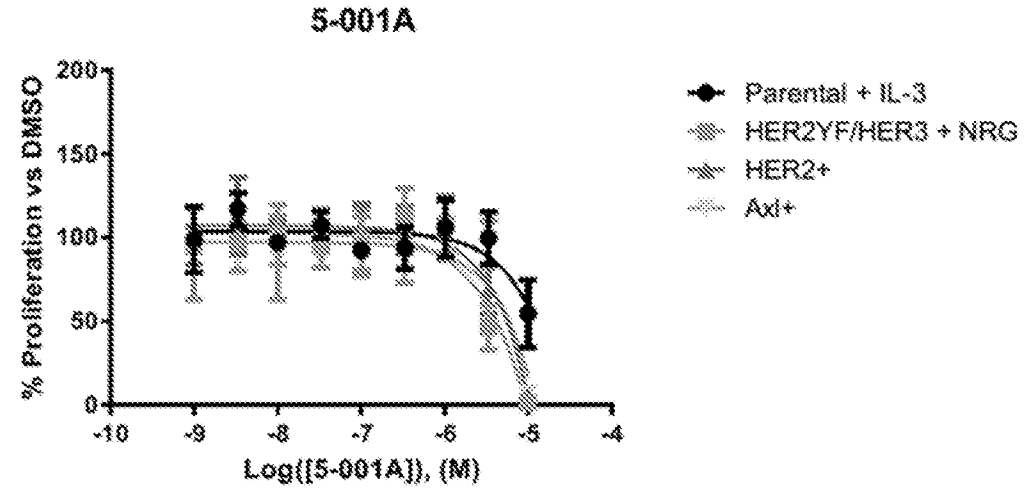


FIG. 23G

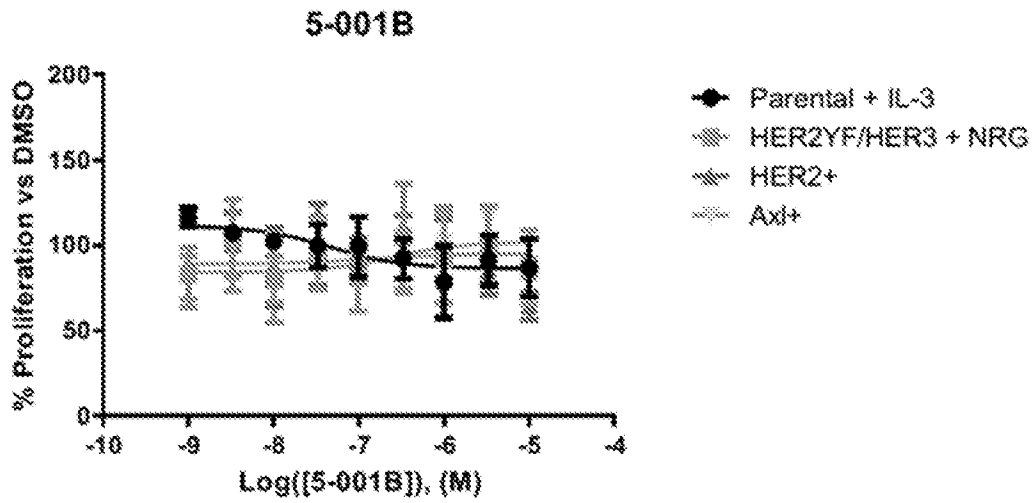


FIG. 23H

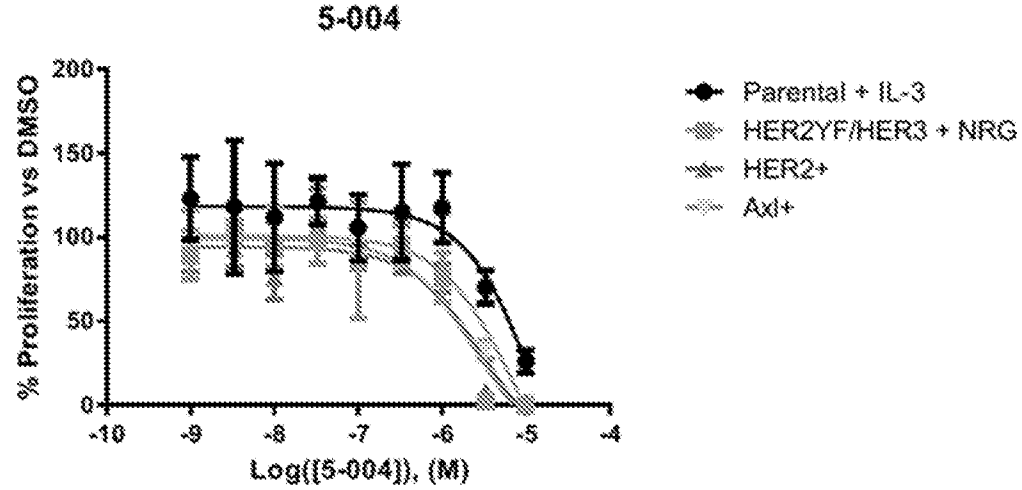


FIG. 24A

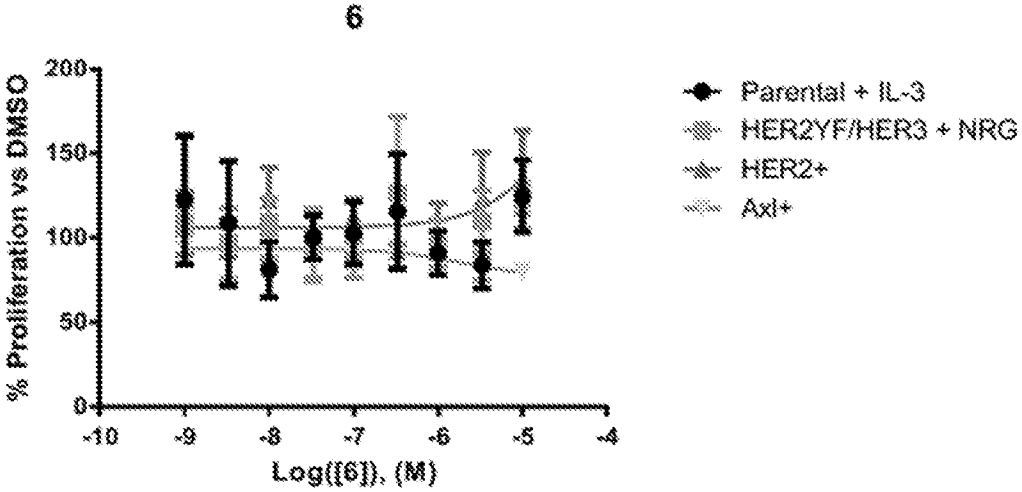


FIG. 24B

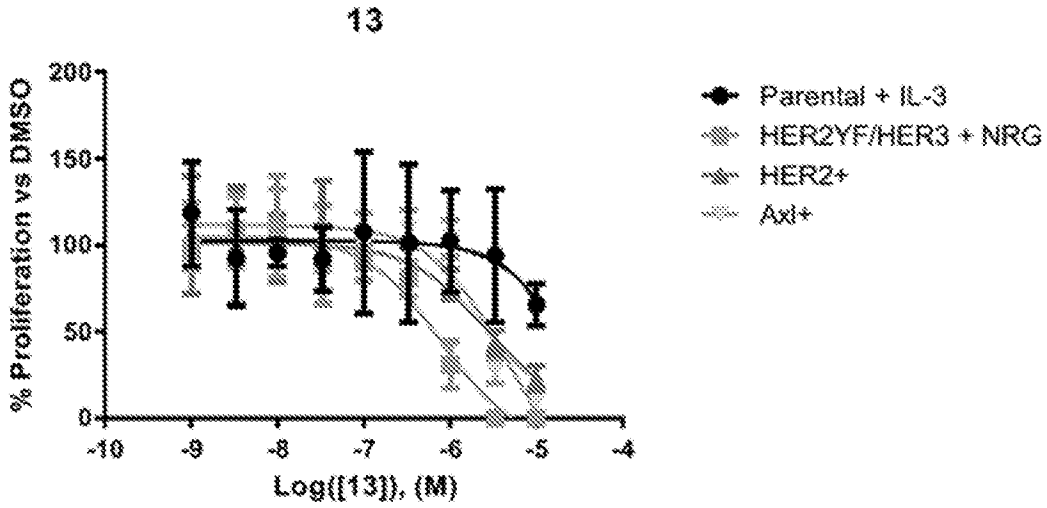


FIG. 24C

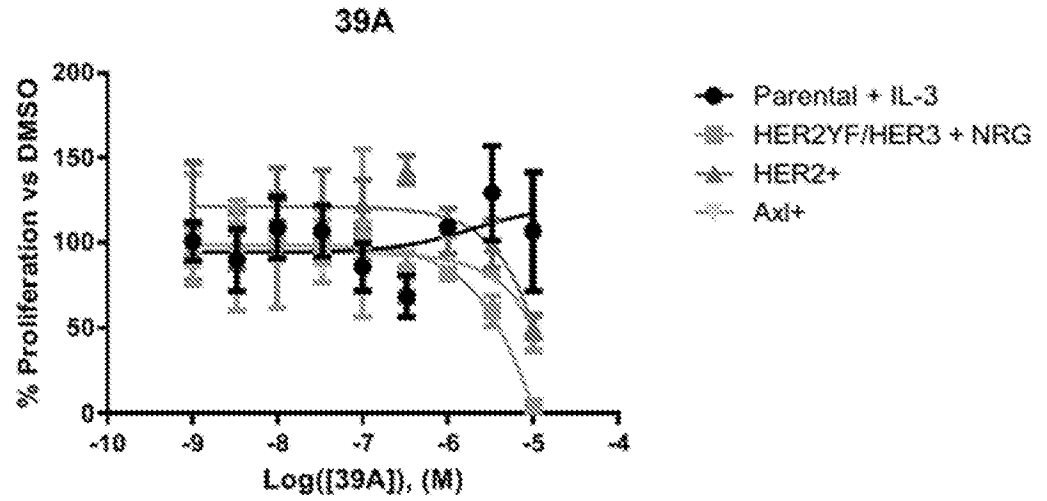


FIG. 24D

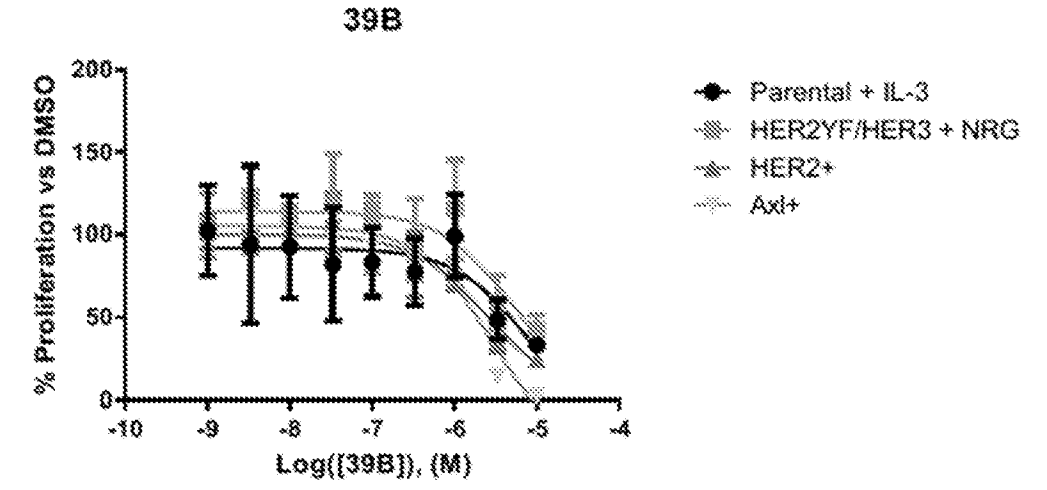


FIG. 24E

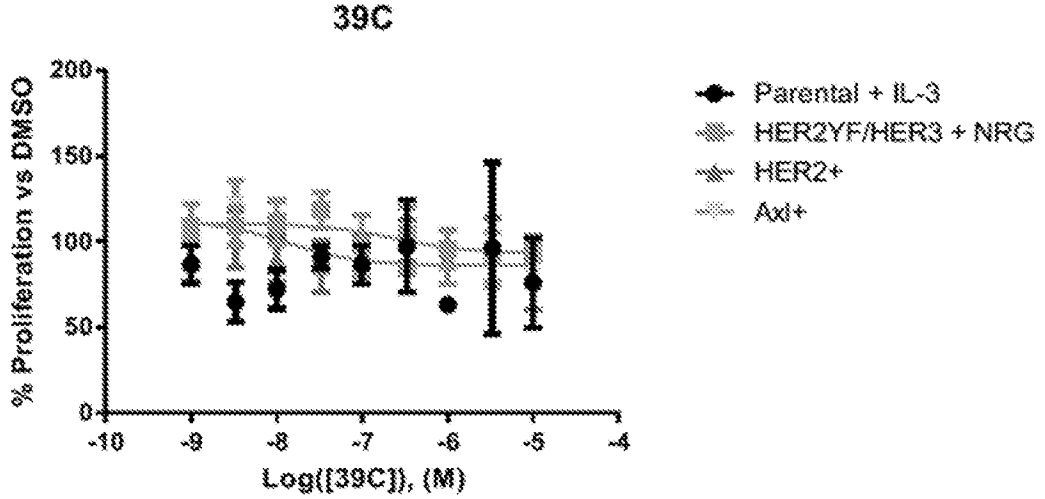


FIG. 24F

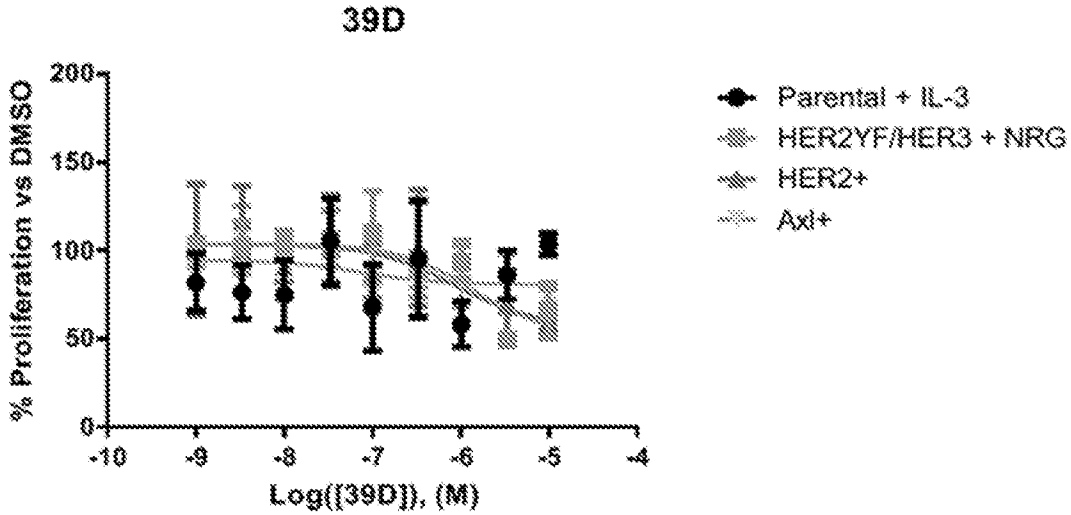


FIG. 24G

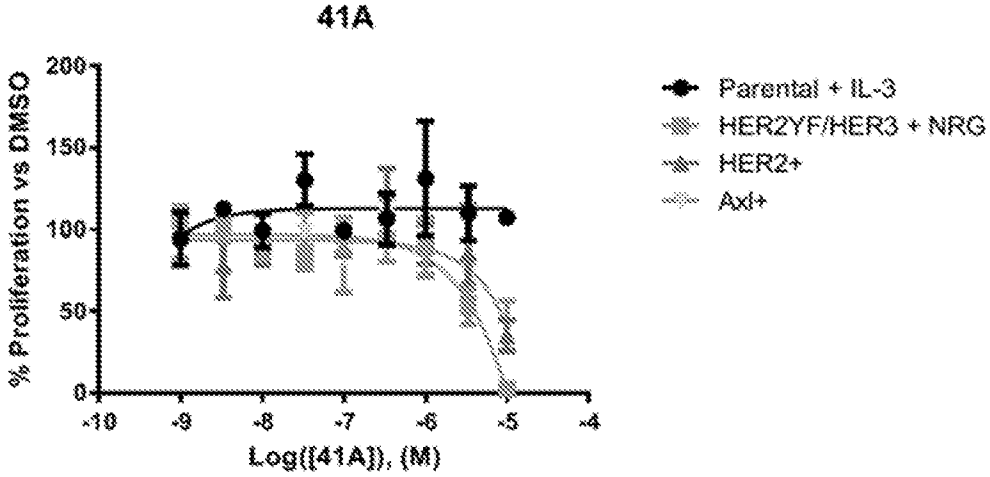


FIG. 24H

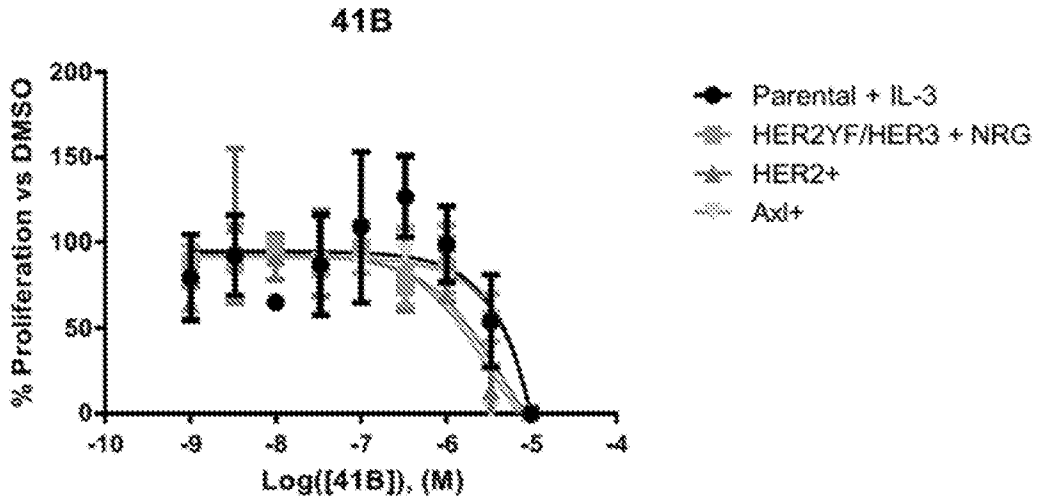


FIG. 25A

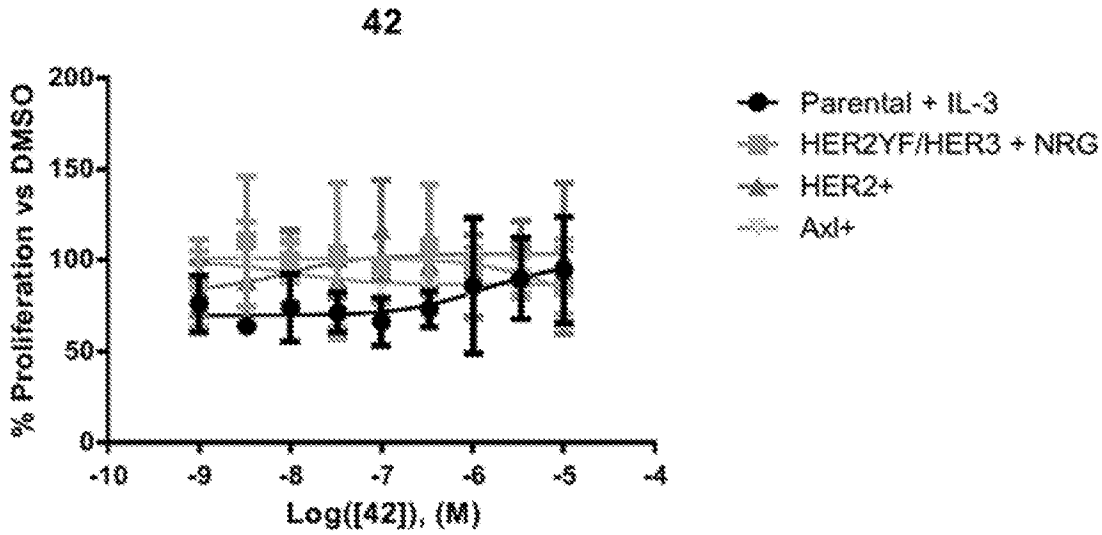


FIG. 25B

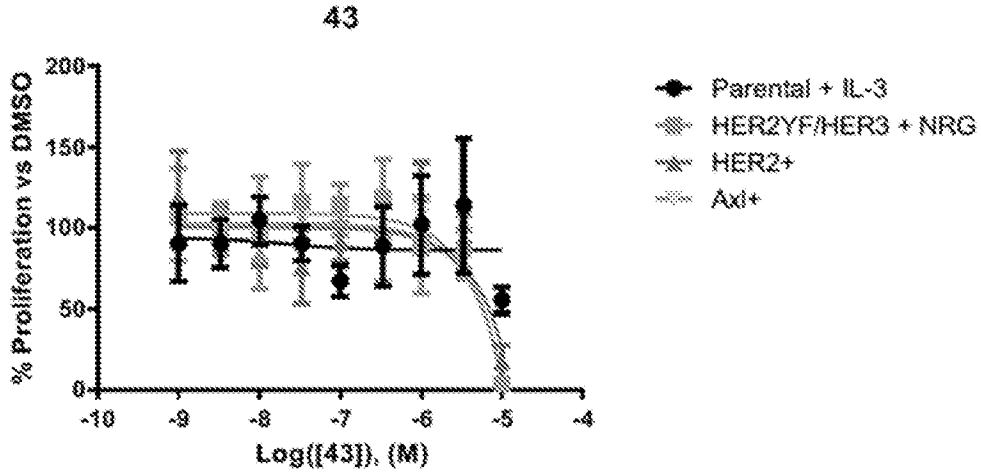


FIG. 25C

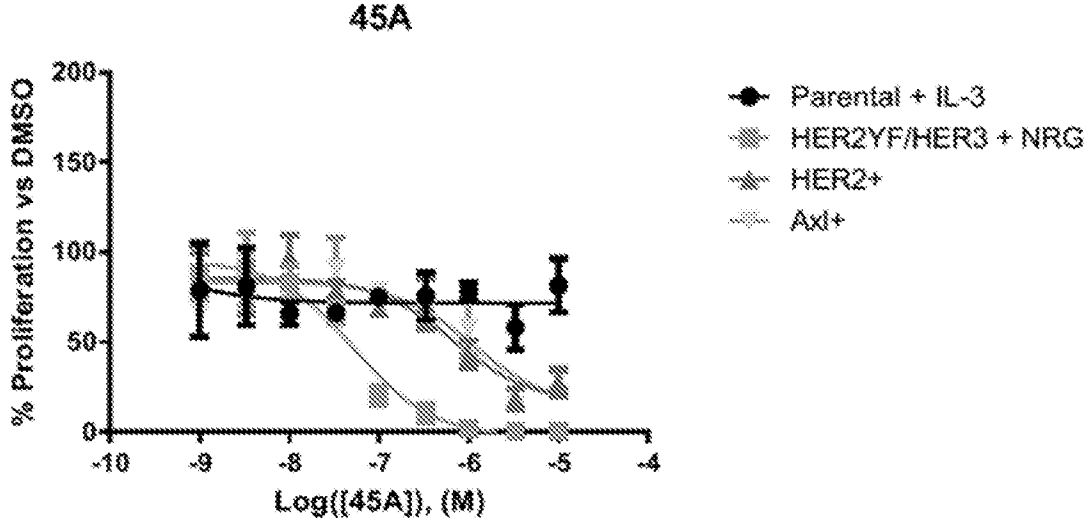


FIG. 25D

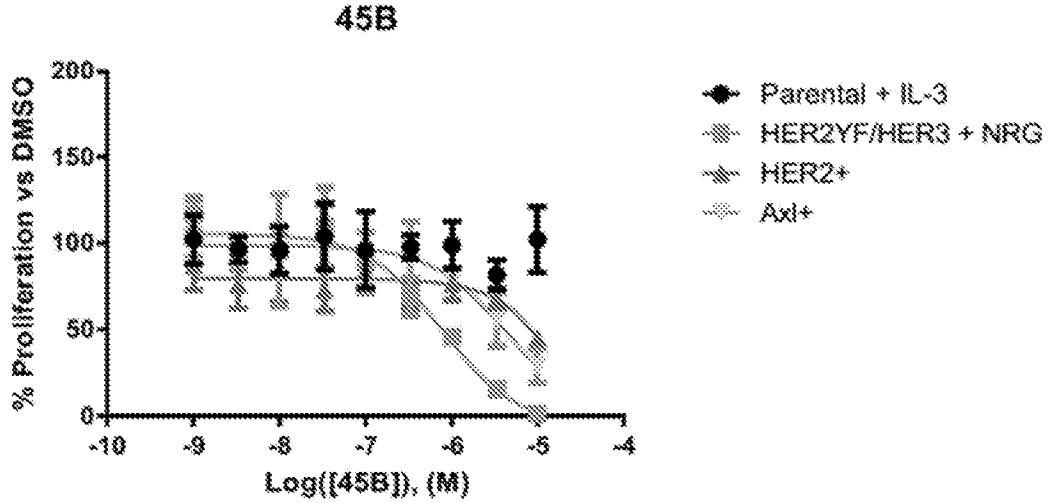


FIG. 25E

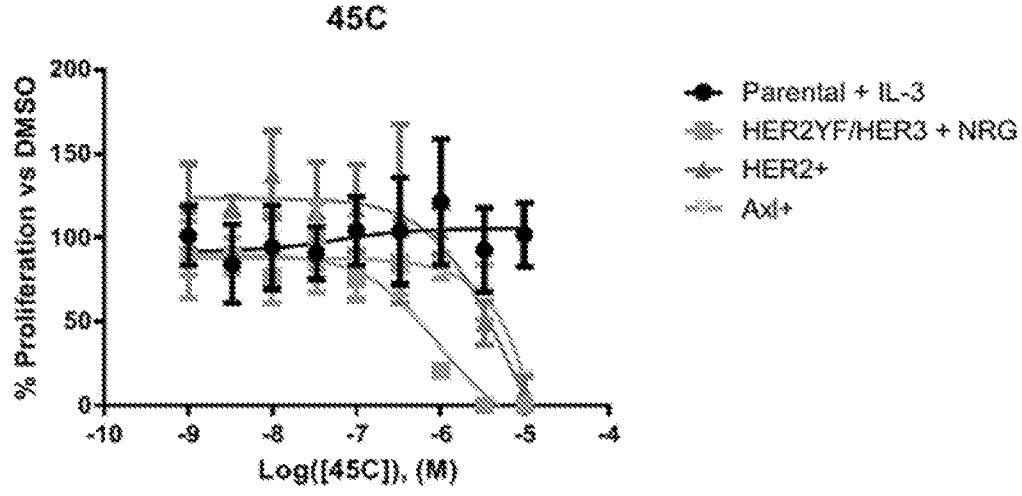


FIG. 25F

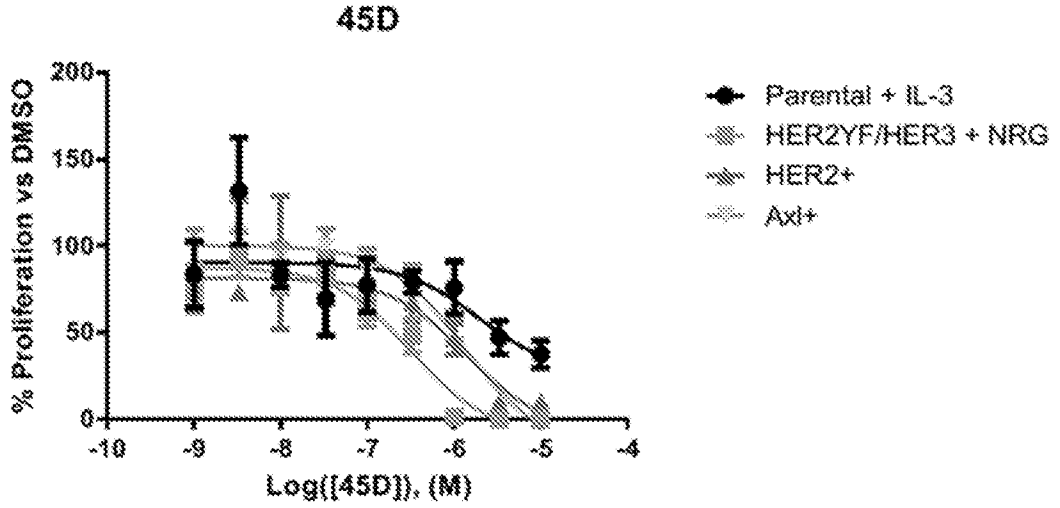


FIG. 25G

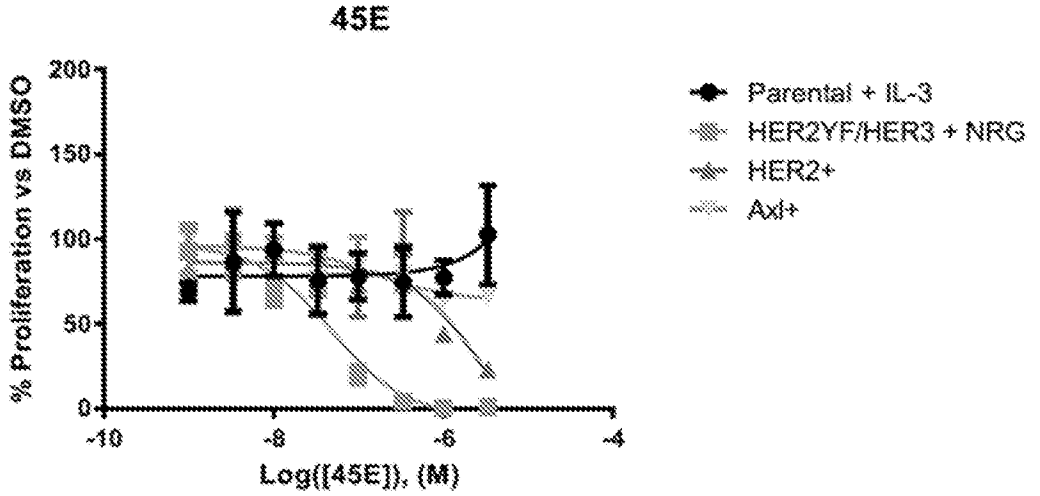


FIG. 25H

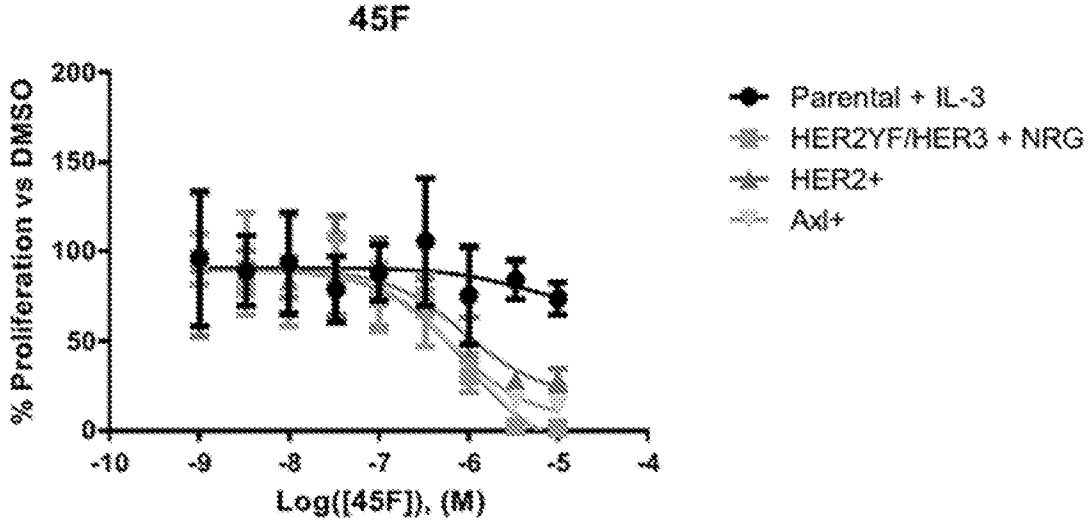


FIG. 26A

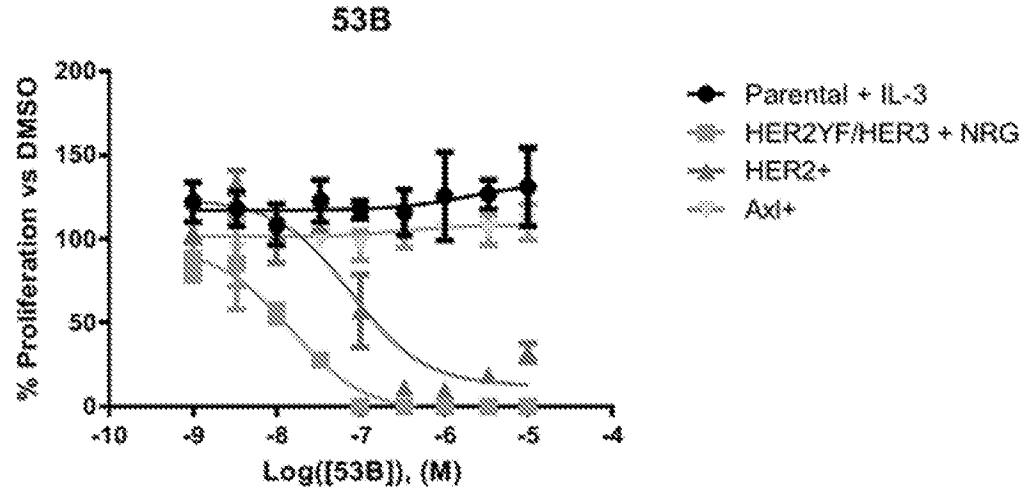


FIG. 26B

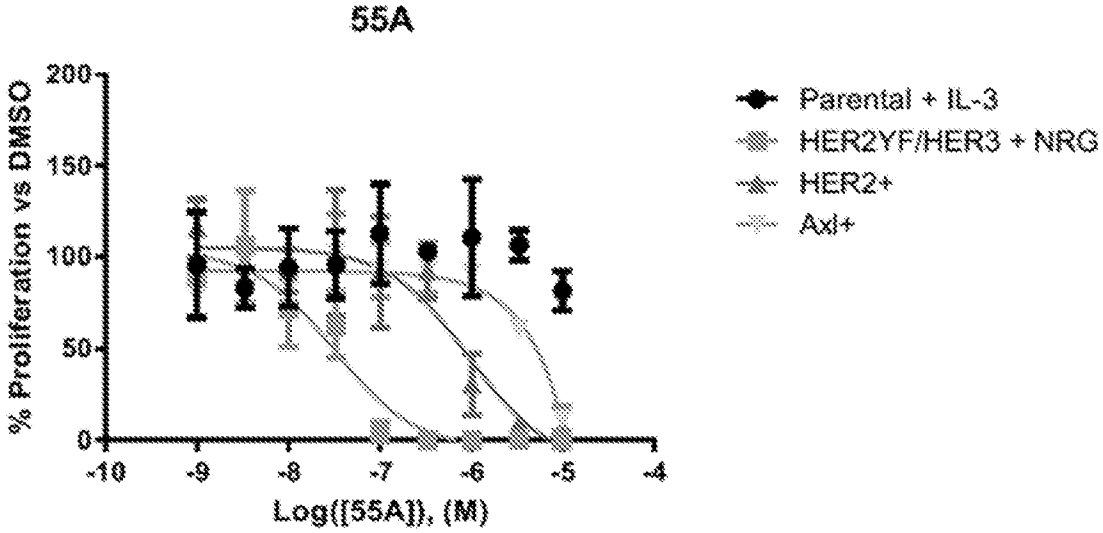


FIG. 26C

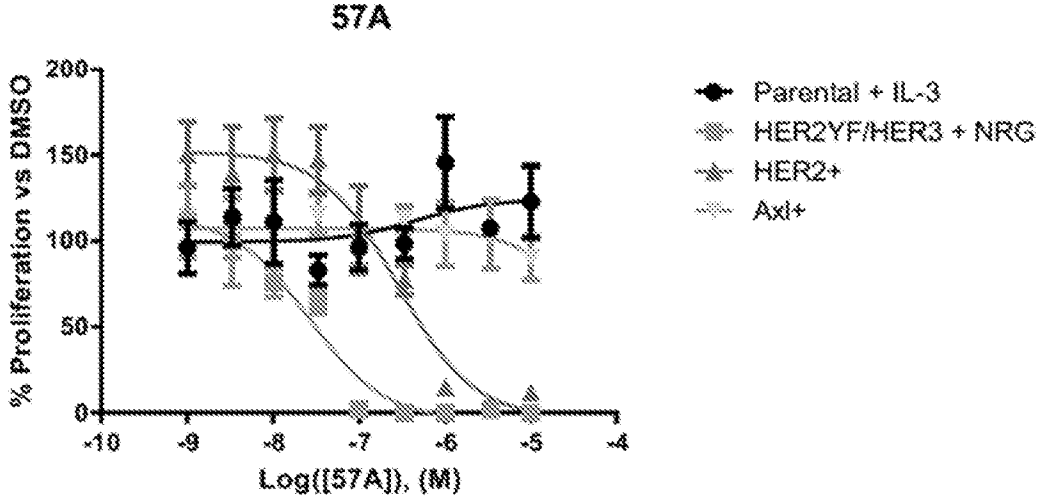


FIG. 26D

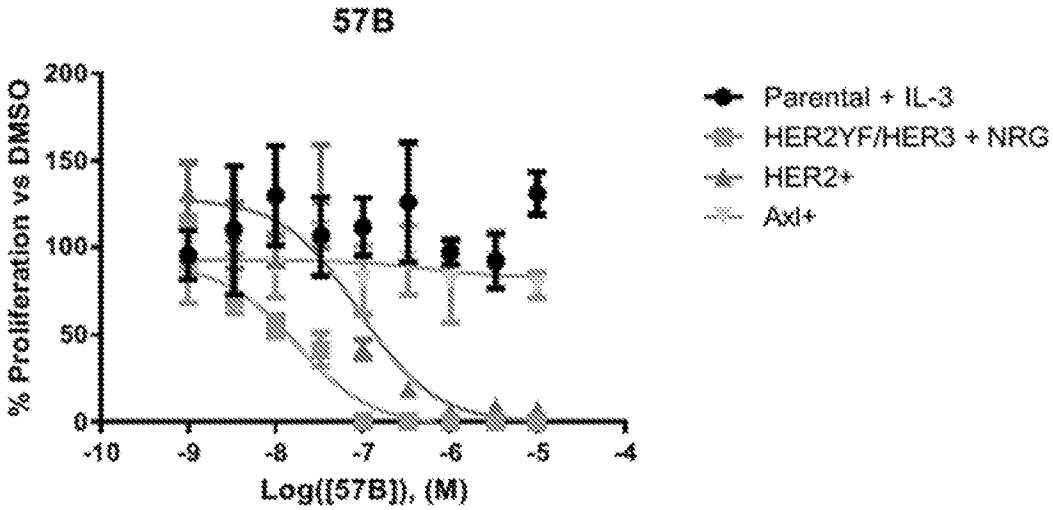


FIG. 27A

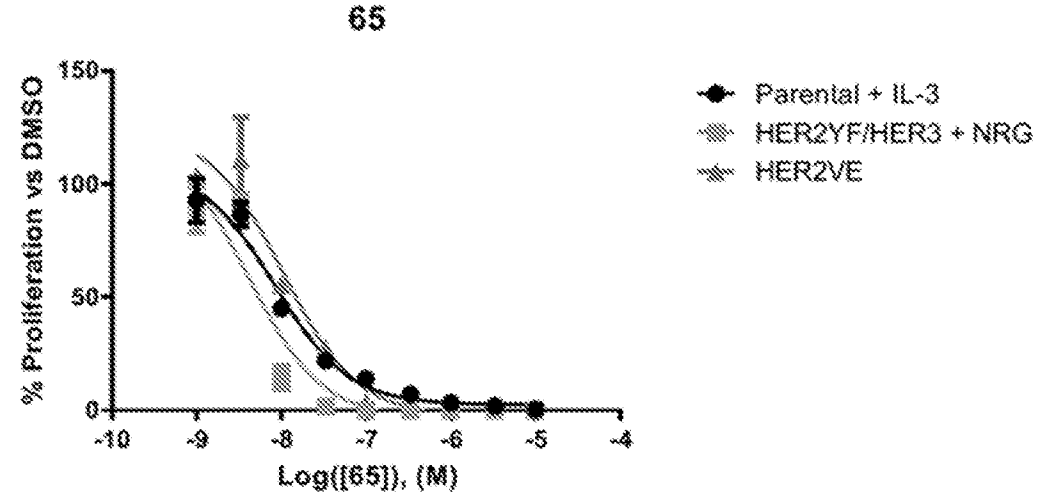


FIG. 27B

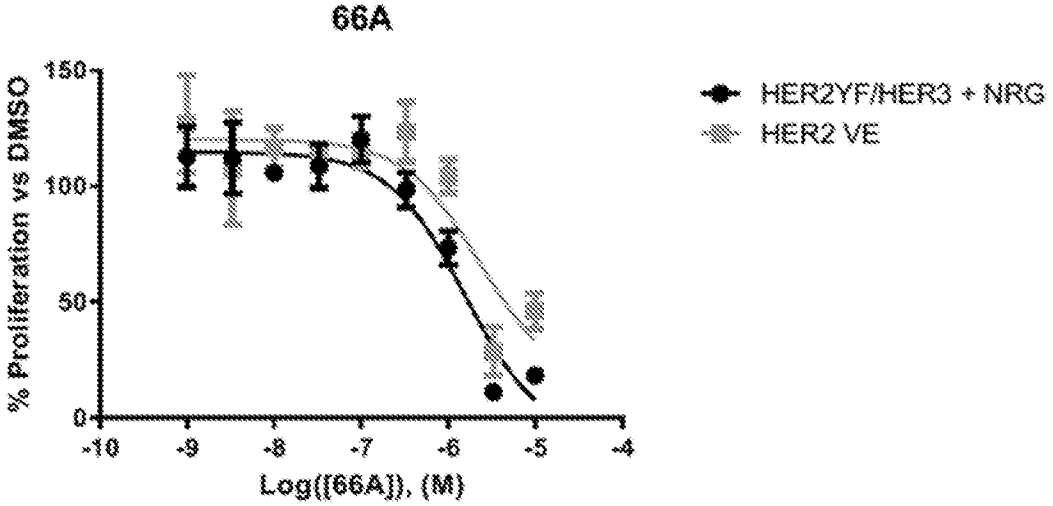


FIG. 27C

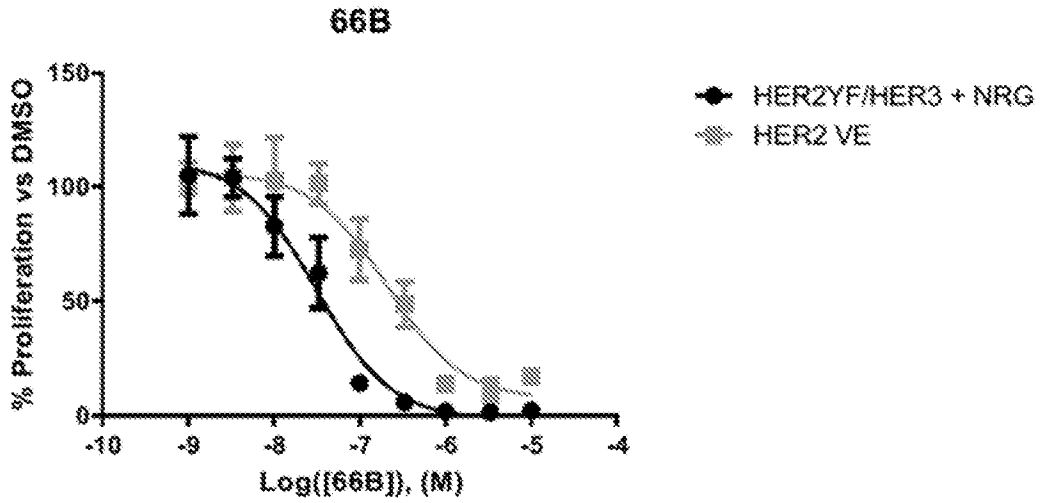


FIG. 27D

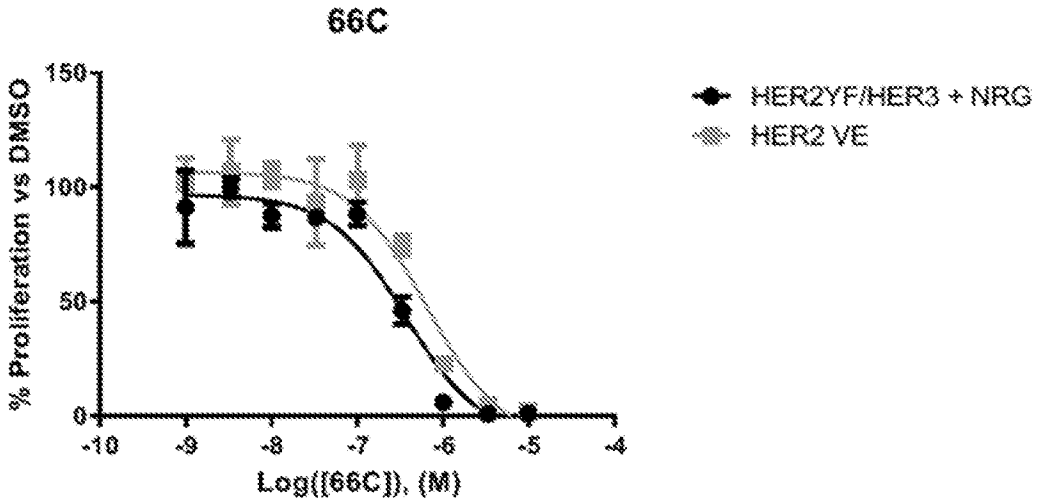


FIG. 28A

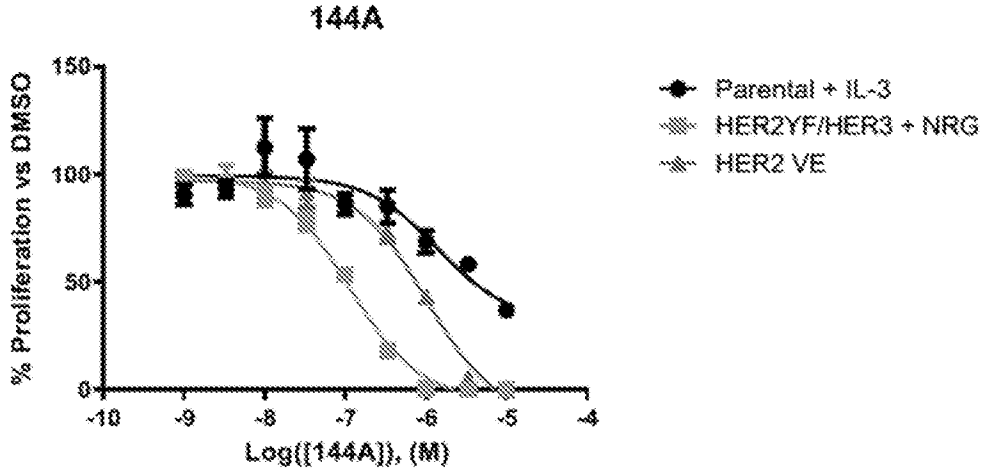


FIG. 28B

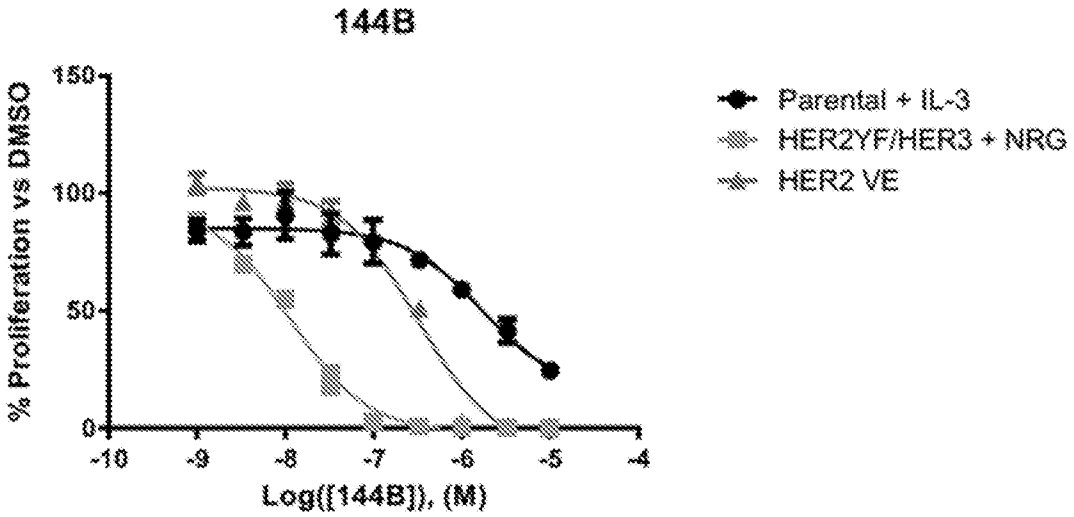


FIG. 28C

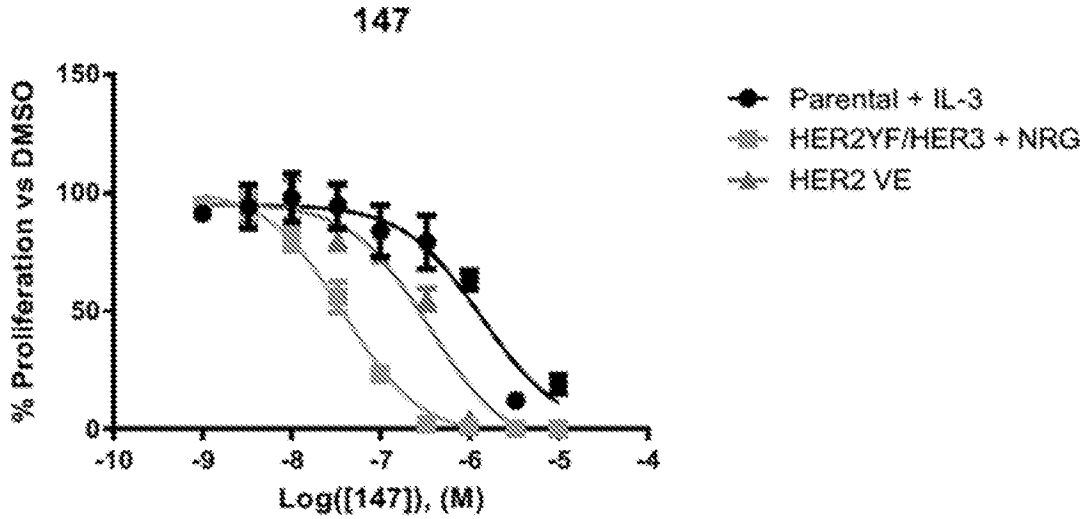


FIG. 28D

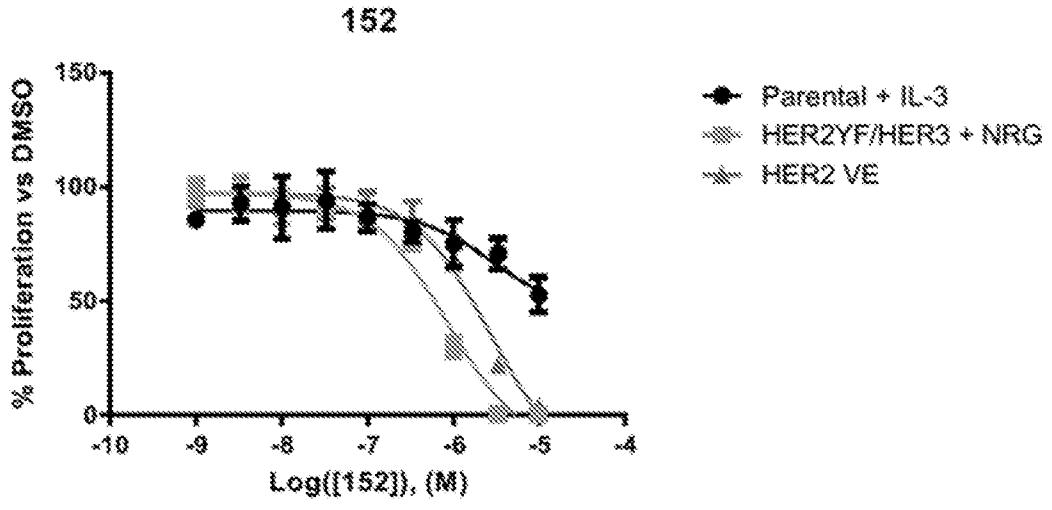


FIG. 28E

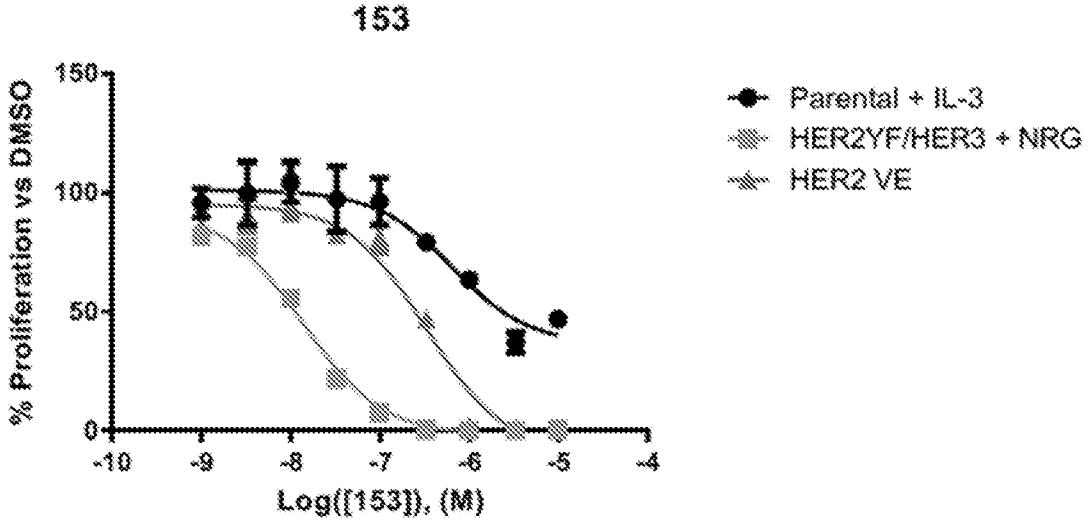


FIG. 28F

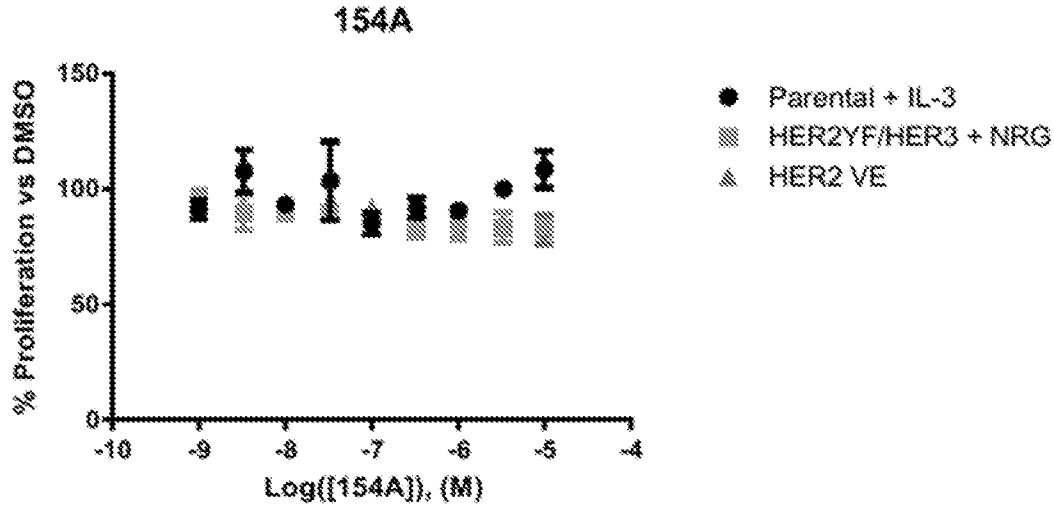


FIG. 28G

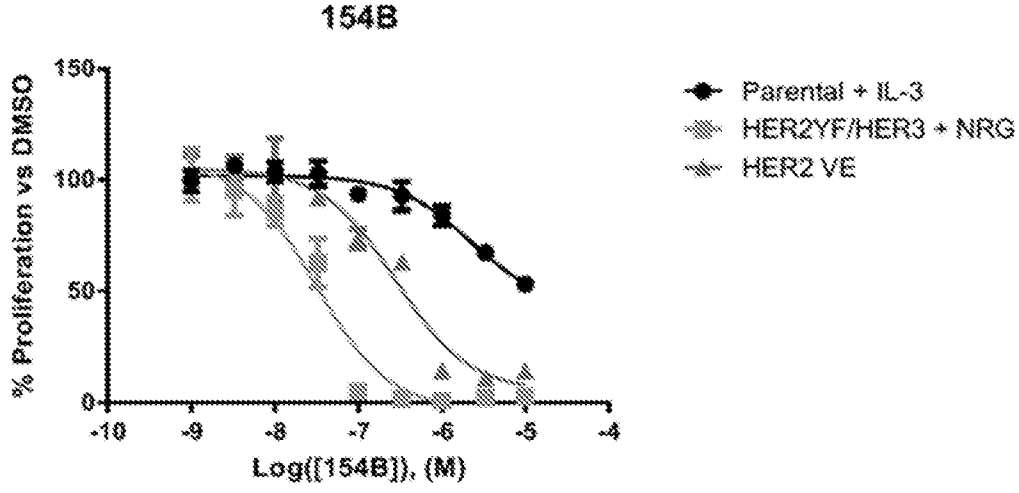


FIG. 28H

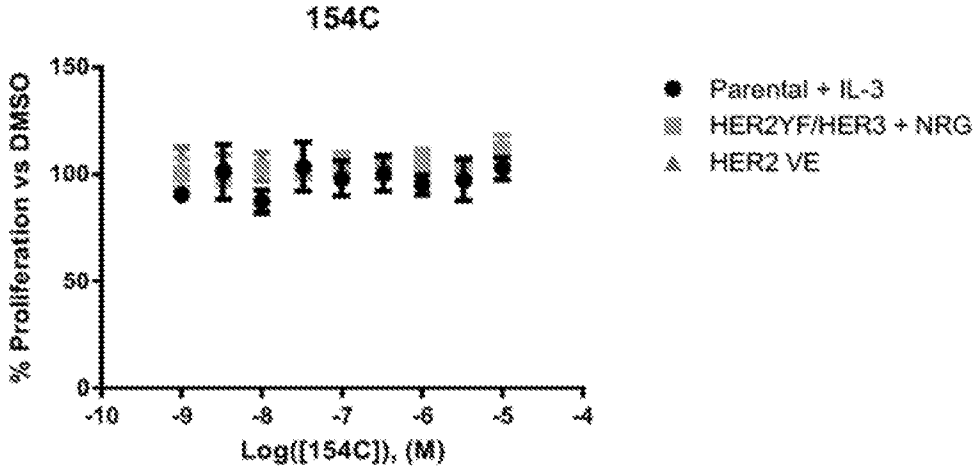


FIG. 29A

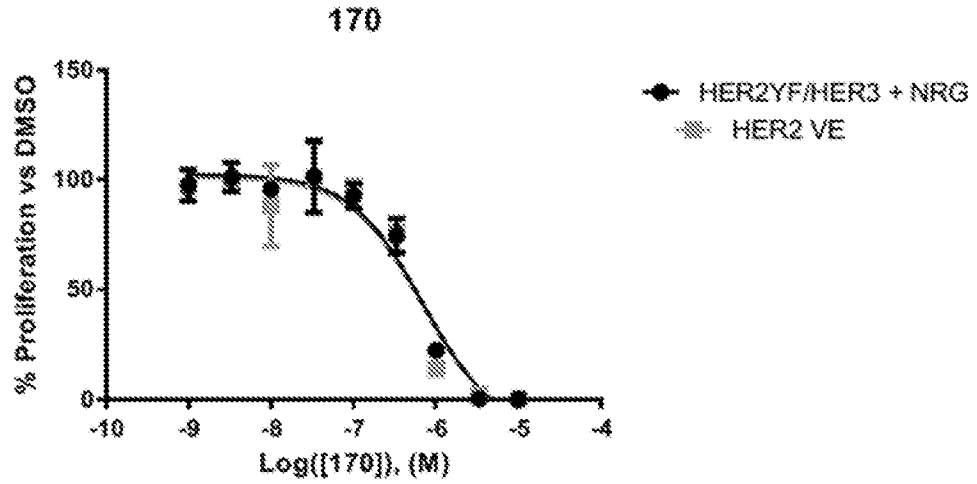


FIG. 29B

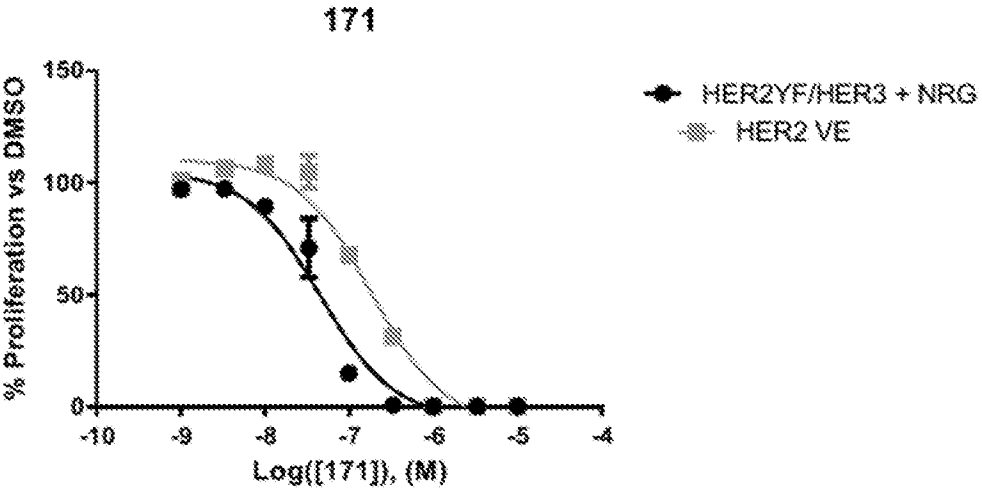


FIG. 29C

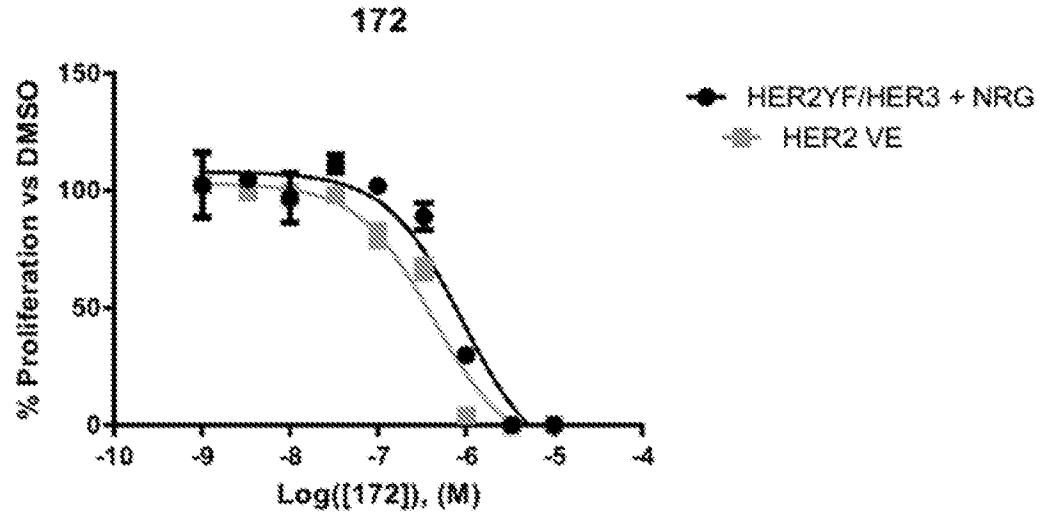


FIG. 29D

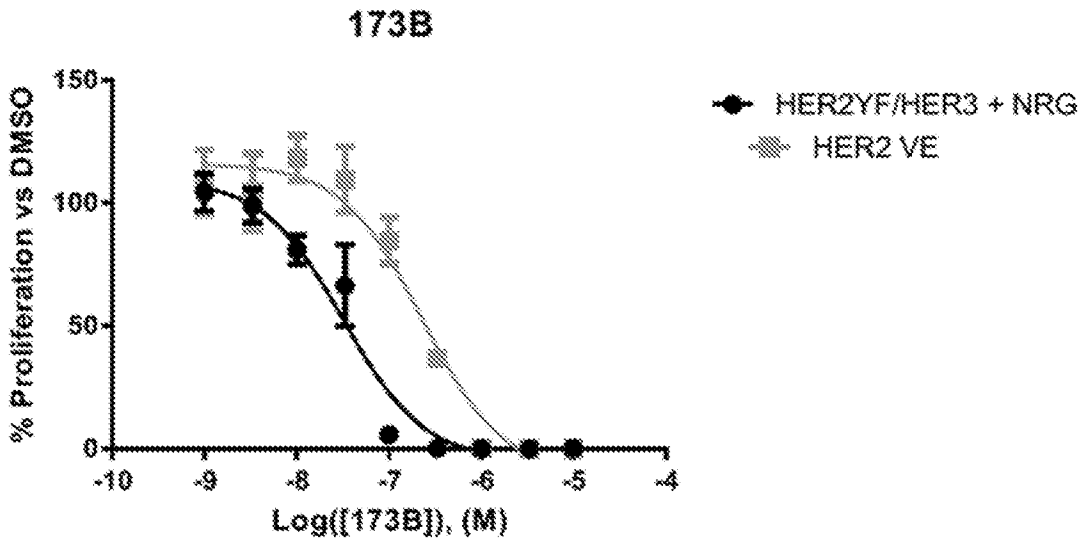


FIG. 30A

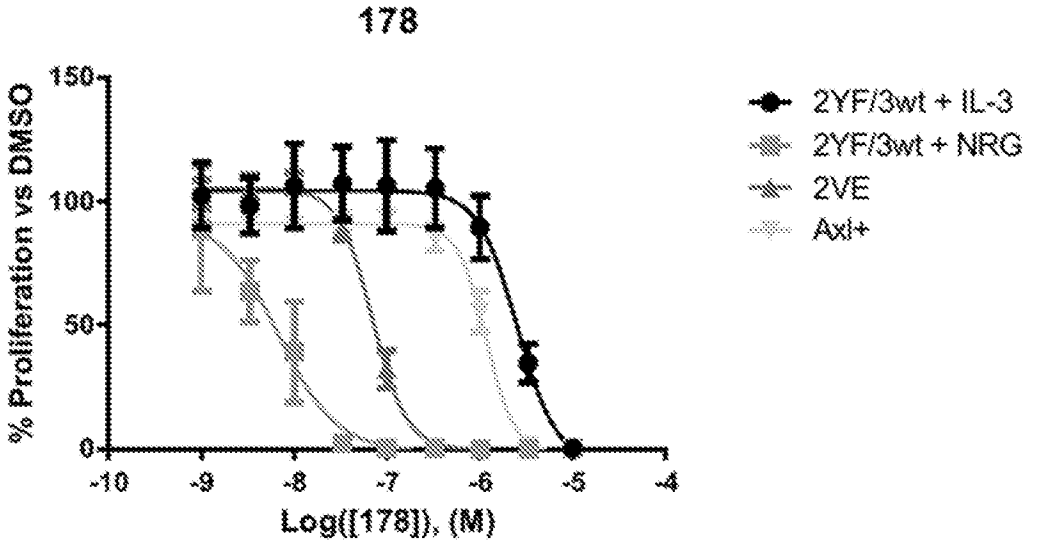


FIG. 30B

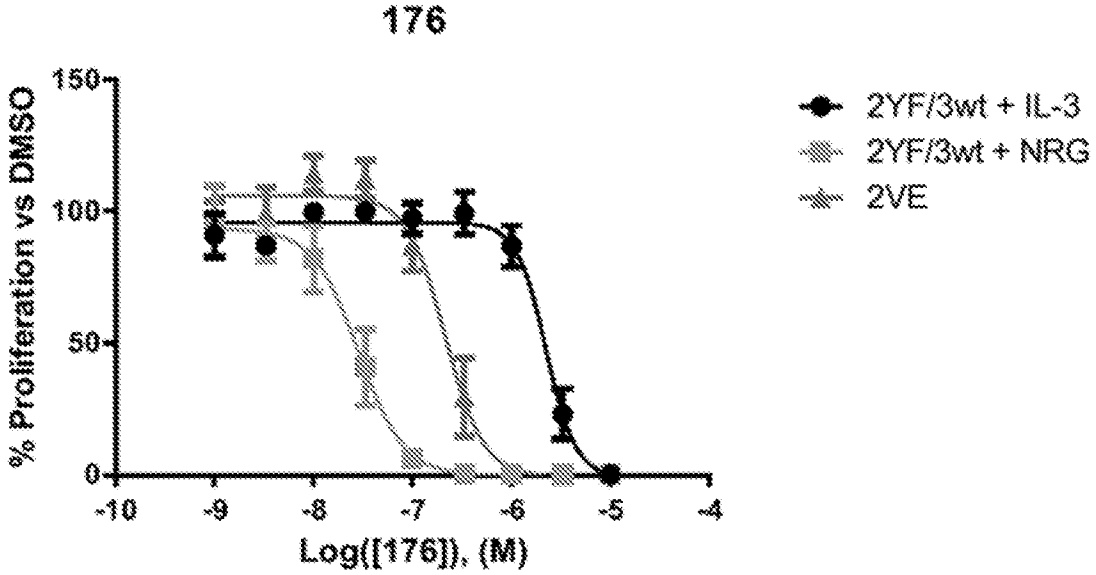


FIG. 31A

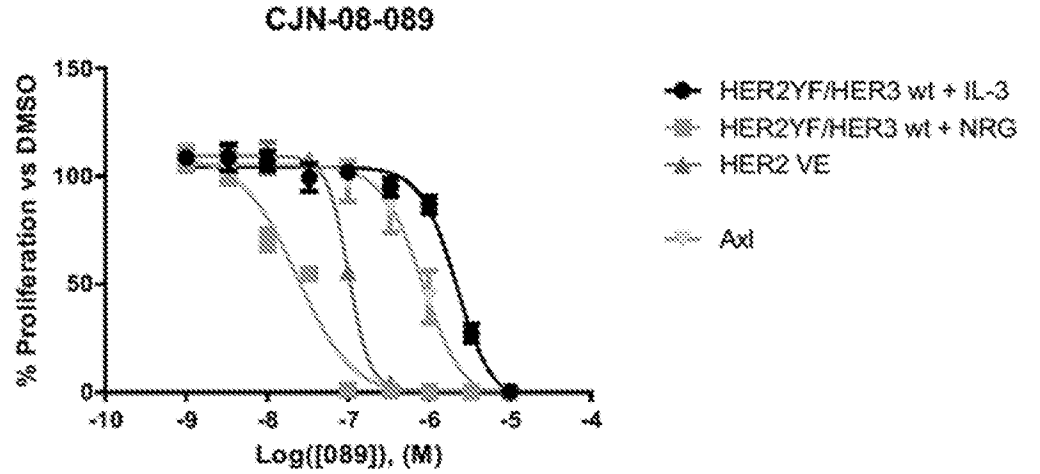


FIG. 31B

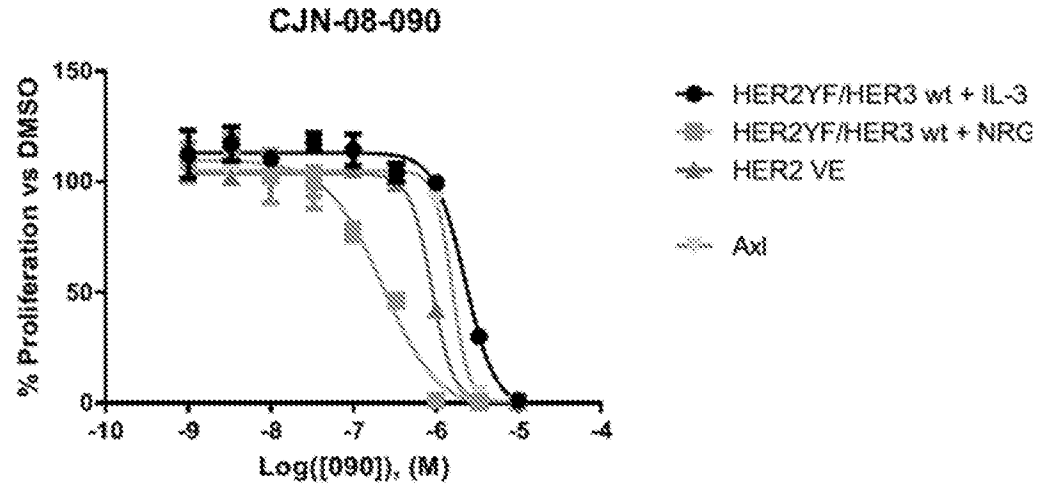


FIG. 31C

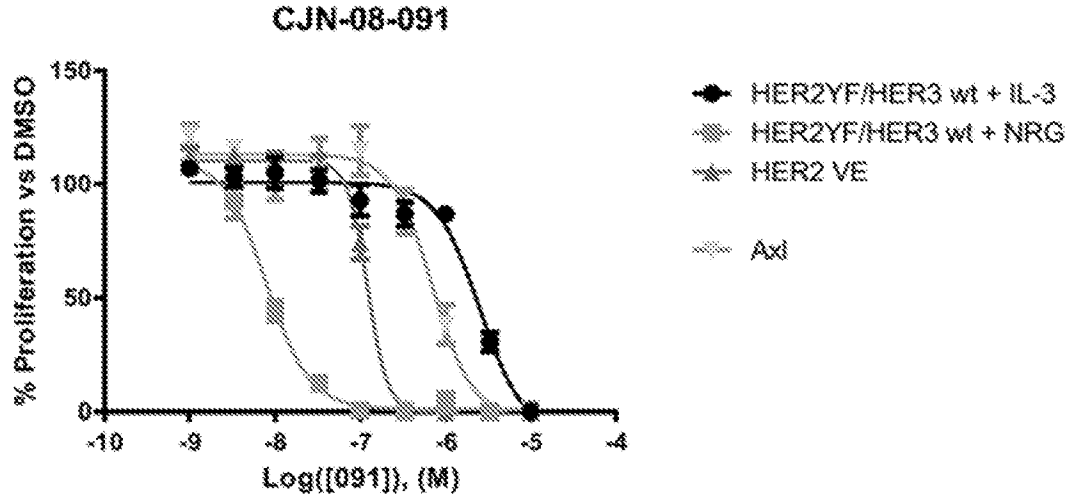


FIG. 31D

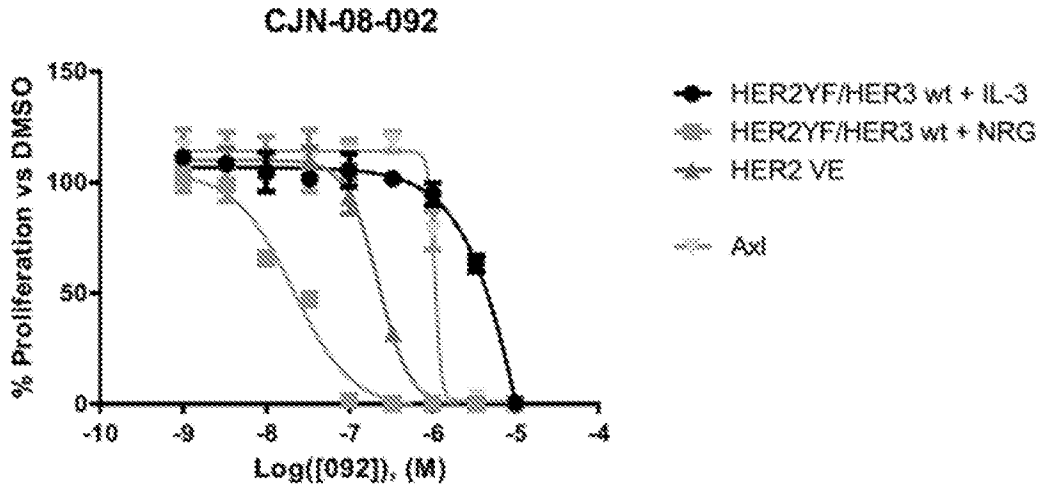


FIG. 32A

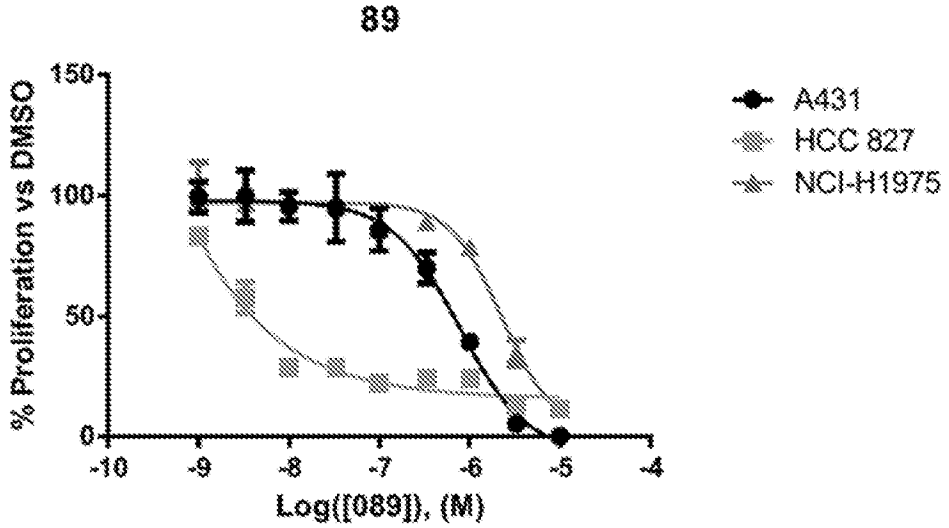


FIG. 32B

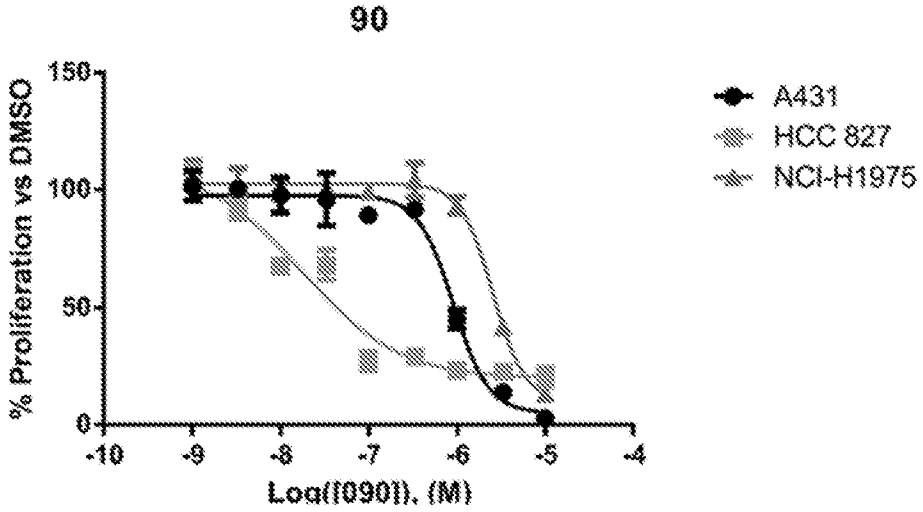


FIG. 32C

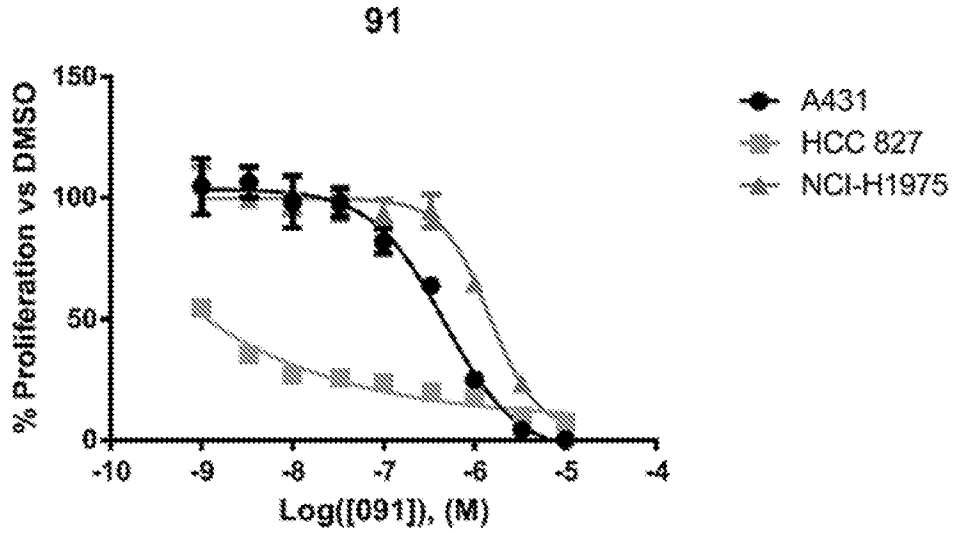


FIG. 32D

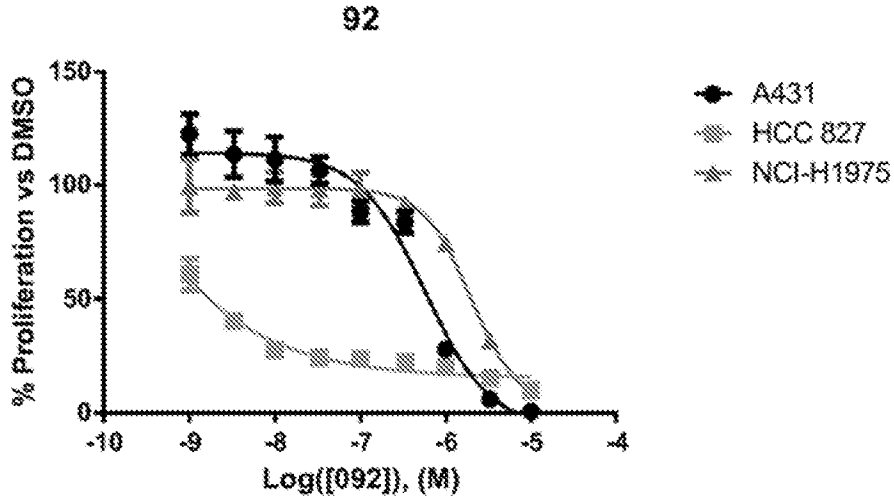


FIG. 33A

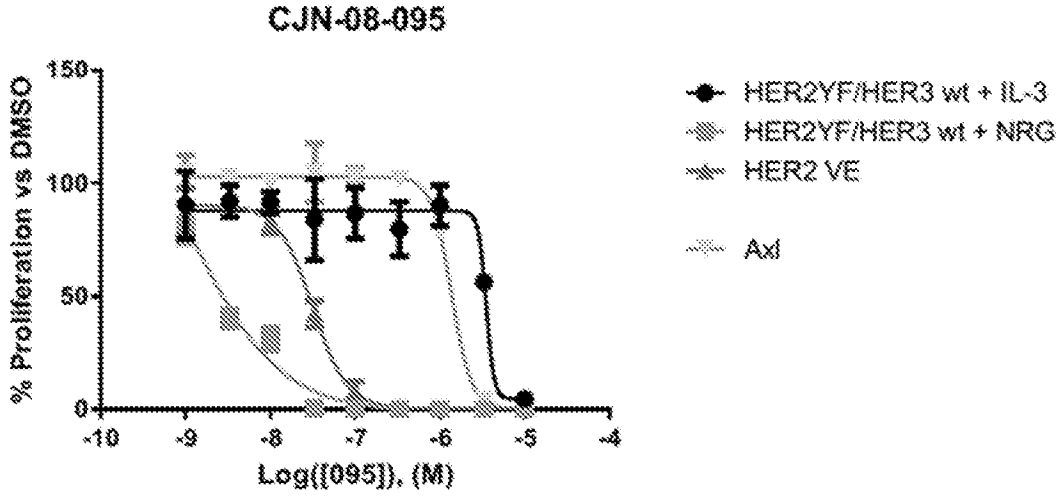


FIG. 33B

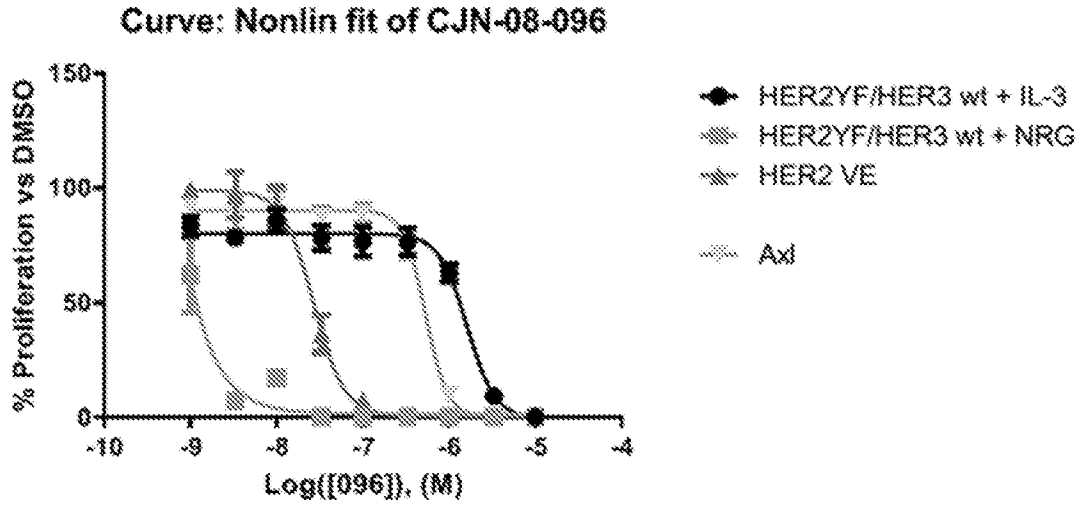


FIG. 33C

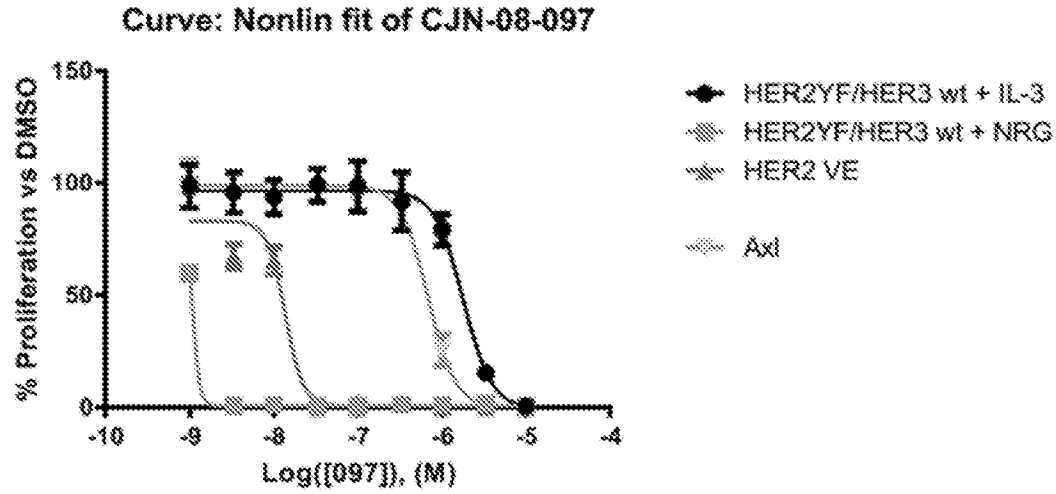


FIG. 34A

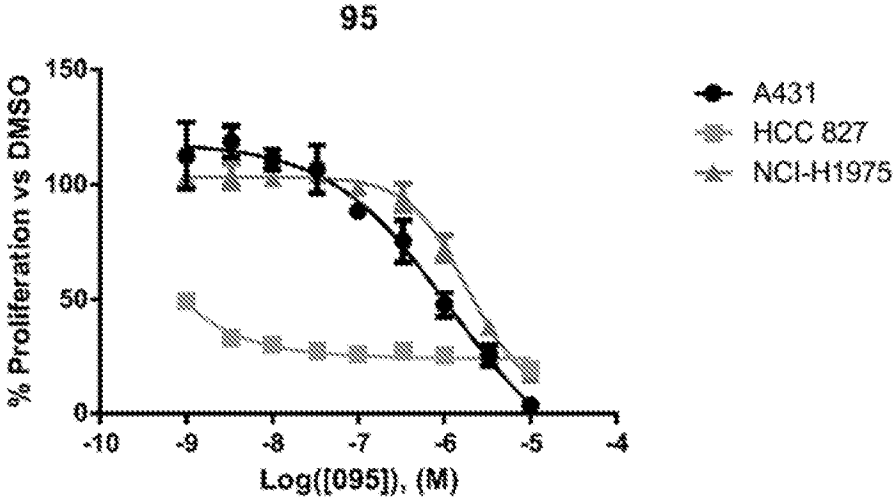


FIG. 34B

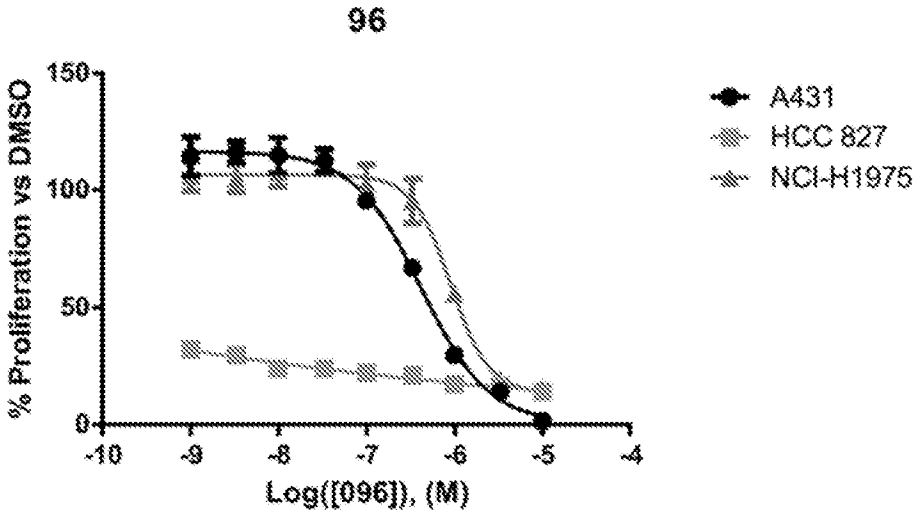


FIG. 34C

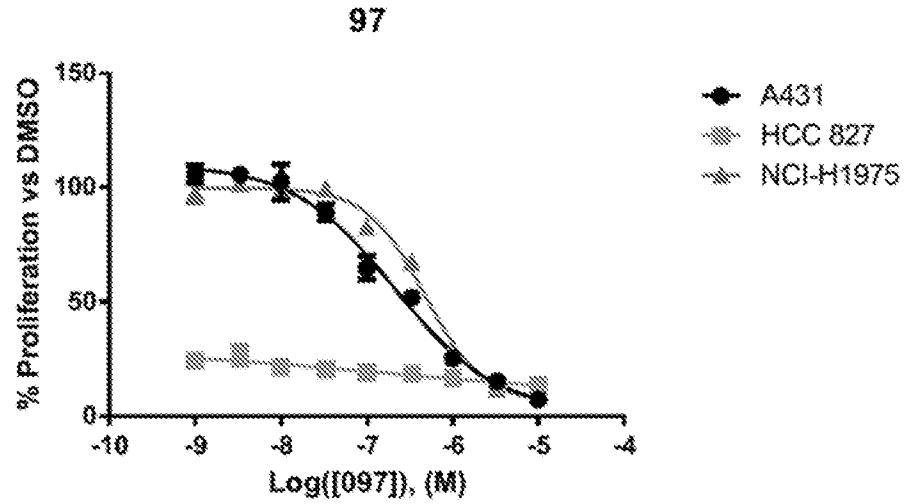


FIG. 35A

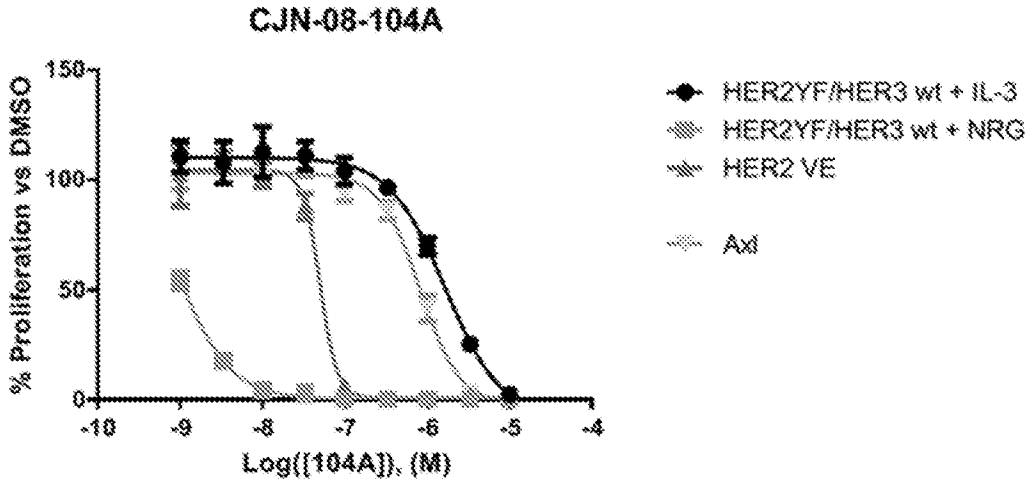


FIG. 35B

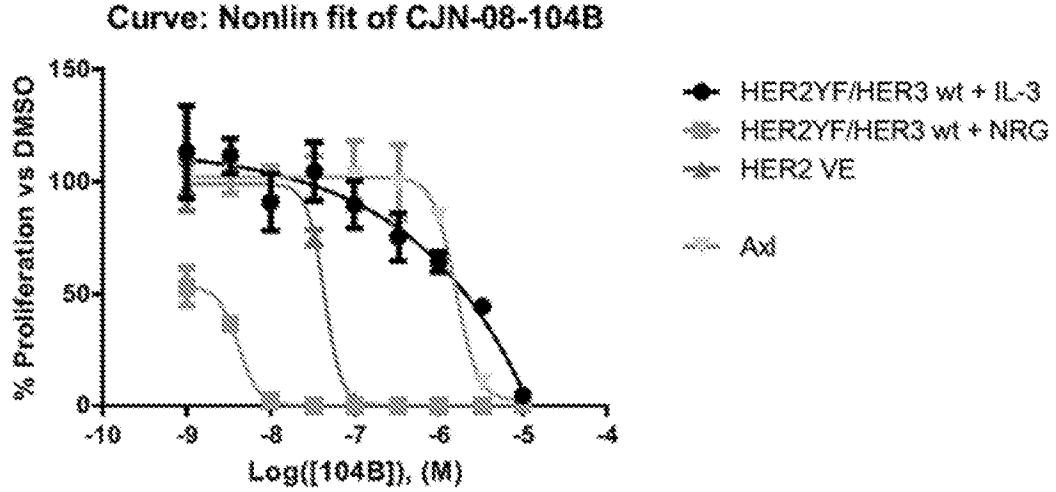


FIG. 36A

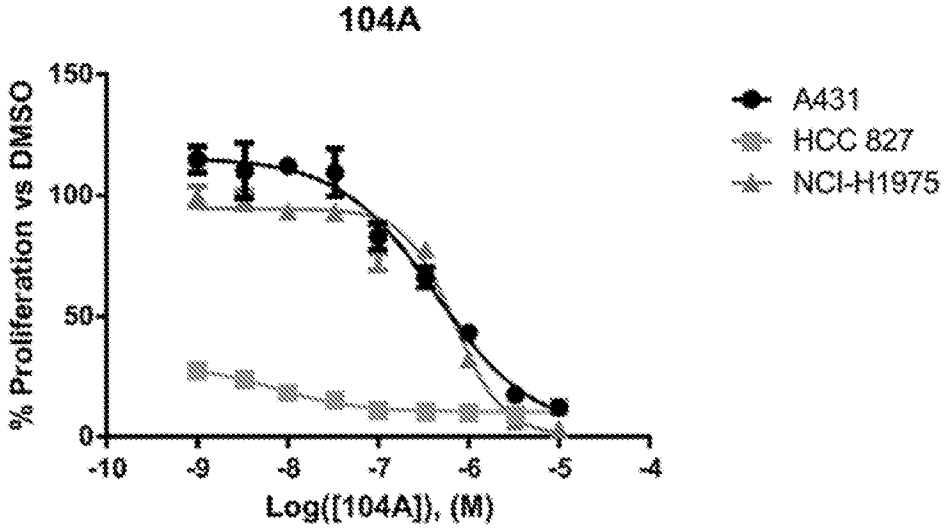


FIG. 36B

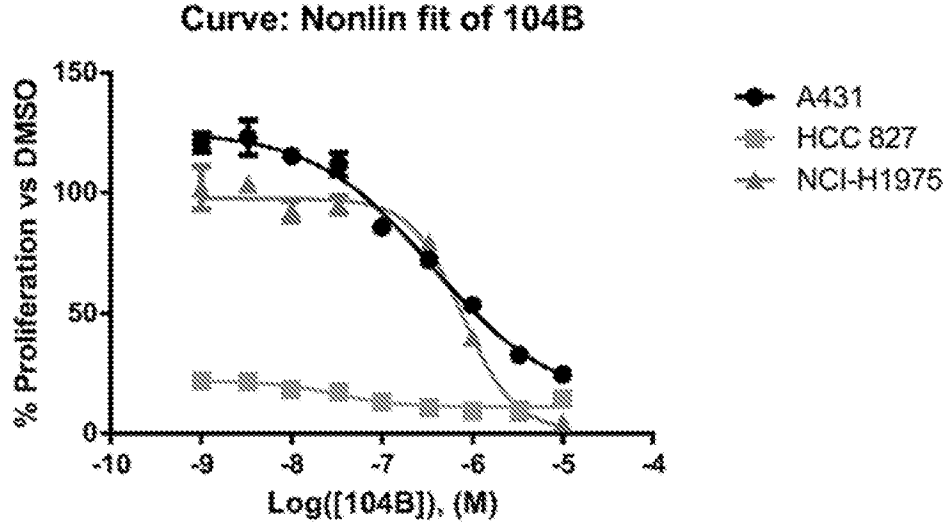


FIG. 37

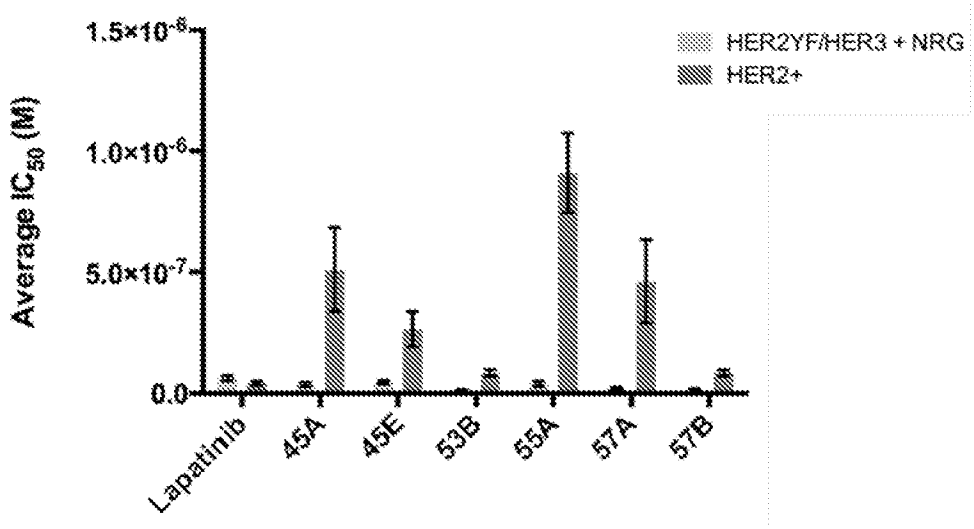


FIG. 38A

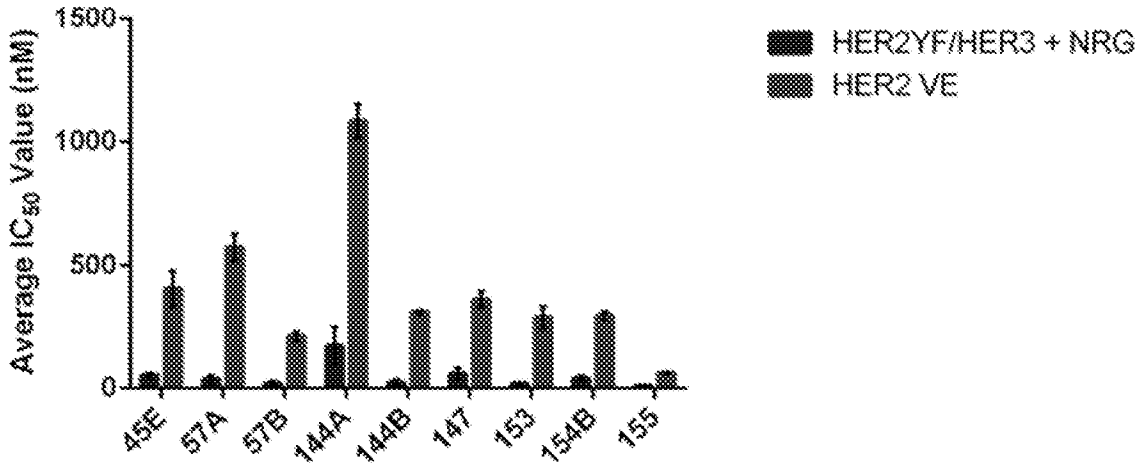


FIG. 38B

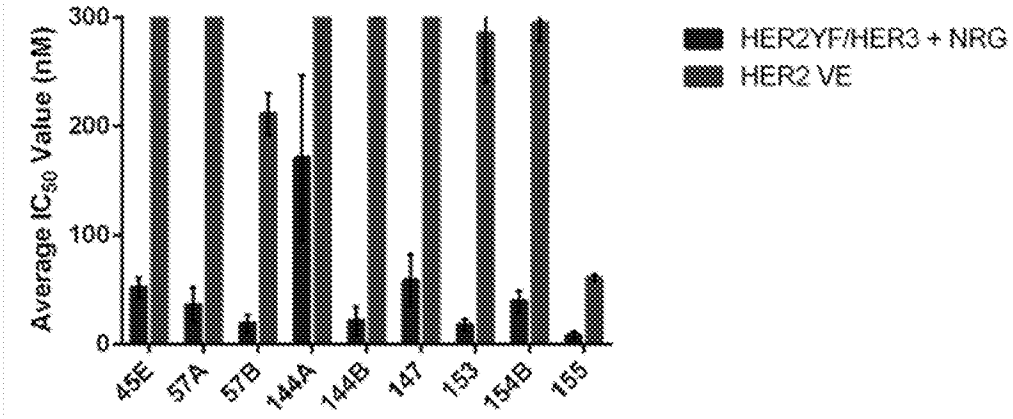


FIG. 39

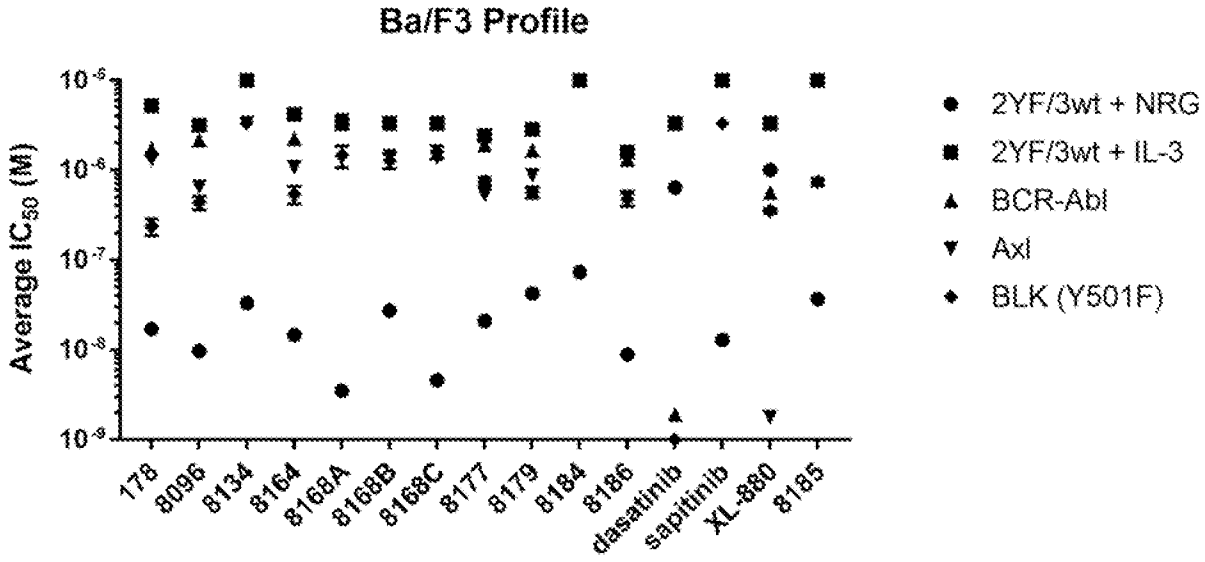
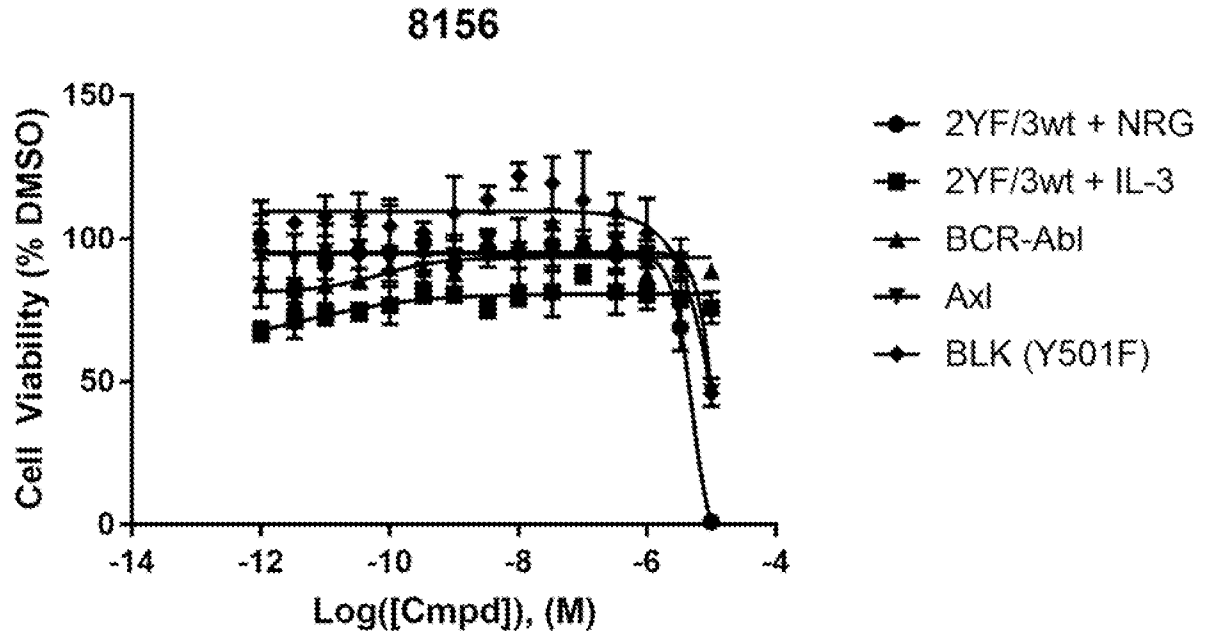

Ba/F3 Profile
Average IC50 (M)
10-5
10-6
10-7
10-8
10-9
178
8096
8134
8164
8168A
8168B
8168C
8177
8179
8184
8186
dasatinib
sapitinib
XL-880
8185
2YF/3wt + NRG
2YF/3wt + IL-3
BCR-Abl
Axl
BLK (Y501F)

FIG. 40


8156
Cell Viability (% DMSO)
150
100
50
0
-14
-12
-10
-8
-6
-4
Log([Cmpd]), (M)
2YF/3wt + NRG
2YF/3wt + IL-3
BCR-Abl
Axl
BLK (Y501F)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/28437

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 519/00, A61K 31/495 (2017.01)
CPC - C07D 519/00, A61K 31/495, A61K 31/506, C07D 403/12

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)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	PubChem-CID-254758, Create Date: 26 March 2005 (26.03.2005), pg 4, Fig.	1,10 --- 45-46
Y	US 2015/0315191 A1 (YANG et al.) 5 November 2015 (0511.2015), entire document, especially: para [0002]; para [0006], structural formula I; para [0152]; para [0161].	45-46
A	US 2008/0108613 A1 (BARLAAM et al.) 8 May 2008 (08.05.2008), entire document.	1, 10, 45-46
A	PubChem-CID-59148297, Create Date: 20 August 2012 (20.08.2012), pg 4, Fig.	1, 10, 45-46

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2017	08 SEP 2017

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/28437

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--See attached extra sheet--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 10, 45-46

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/28437

--Box III - Lack of Unity--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

GROUP I+: Claims 1-46, directed to a compound having the formula (I). The compound of Formula (I) will be searched to the extent that it encompasses the first species of claim 1, wherein Ring A is aryl; W1 is N; R1 is hydrogen; R2 is hydrogen; R3 is independently halogen; z3 is 0; and R9 is hydrogen. It is believed that claims 1, 10 and 45-46 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. Applicant is invited to elect additional compounds of Formula (I), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein Ring A is aryl; W1 is N; R1 is -L1-L2-E; R2 is hydrogen; R3 is independently halogen; z3 is 0; and R9 is hydrogen (i.e. claims 1, 10, 20-22 and 24-46).

GROUP II: claims 47-97, directed to a method of treating a disease by modulating HER2 or EGFR with a compound of formula (I).

GROUP III: claims 98-99, directed to a protein of HER2 or EGFR with covalent bond to a compound of formula (I).

The inventions listed as Groups I+, II, and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

Group I+ includes the technical feature of a unique compound of Formula (I), which is not required by any other invention of Group I+.

Groups I+ and II do not require a protein of HER2 or EGFR with covalent bond to a compound of formula (I), as required by Group III.

Groups I+ and III do not require a method of treating a disease by modulating HER2 or EGFR with a compound of formula (I), as required by Group II.

Shared Common Features

The only feature shared by Groups I+, II, and III that would otherwise unify the groups is a compound of formula (I). However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by the document entitled PubChem-CID-59148297 (hereinafter 'PubChem-297'). PubChem-297 teaches a compound of formula (I) wherein Ring A is aryl; W1 is N; R1 is hydrogen; R2 is hydrogen; R3 is-C(O)NR3AR3B; R3A and R3B are H; z3 is 1; and R9 is halogen (pg 4, Fig).

As the technical features were known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups. Groups I+, II, and III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.