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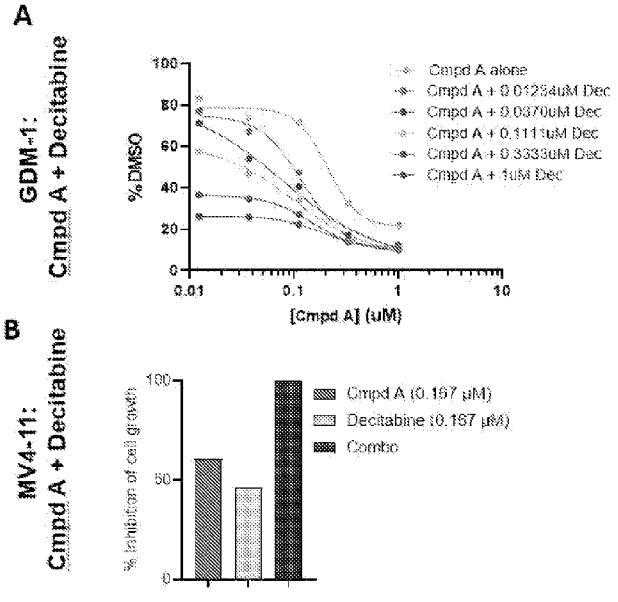

Figure 3

(57) Abstract: The present disclosure describes methods of treating a subject suffering from cancer using a combination therapy comprising (i) administering to the subject a therapeutically-effective amount of a compound that blocks SUMOylation in the subject; and (ii) administering to the subject a therapeutically-effective amount of an anti-cancer agent that functions through a pathway other than SUMOylation.

[Continued on next page]

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COMBINATION THERAPY FOR TREATMENT OF CANCER

BACKGROUND

[001] SUMOylation is a reversible post-translational modification by small ubiquitin-like modifier (SUMO). SUMOylation controls many cellular functions and plays a critical role in the regulation of genome integrity, cell cycle progression, and the immune response. Three different enzyme components are involved in the SUMOylation cascade including a SUMO-activating enzyme E1 (SUMO E1 or SAE1/UBA2), an E2 enzyme (ubiquitin-conjugating enzyme 9 (UBC9)), and a limited set of E3 ligases. The process of SUMOylation starts when SUMO E1 activates SUMO through ATP hydrolysis and forms a thioester conjugate with SUMO. Next, SUMO is transferred and forms a new thioester conjugate with E2. Finally, SUMO is attached to target proteins, a step catalyzed by an E3 ligase. Specific small molecule inhibitors of the SUMO E1 enzyme have recently been developed that allow for the exploration of pharmacological SUMOylation inhibitors as novel anticancer therapeutics. Inhibition of SUMOylation by small molecules impairs cancer cell proliferation and triggers antitumor immune responses by stimulating the interferon (IFN) response. An allosteric covalent mechanism to inhibit SUMO E1 has been characterized, lending rationale towards the development of other novel pharmacological agents to block SUMOylation.

[002] While many cancer therapeutics have shown efficacy as single agent treatments, combination therapies offer potentially superior outcomes due to synergistic effects.

SUMMARY

[003] Provided herein is a method of treating cancer in a subject in need thereof, the method comprising: (i) administering to the subject a therapeutically-effective amount of a compound that blocks SUMOylation in the subject; and (ii) administering to the subject a therapeutically-effective amount of an anti-cancer agent that functions through a pathway other than SUMOylation. In some embodiments, a compound of the disclosure comprises a substituted 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group, wherein the compound blocks SUMOylation. In some embodiments, the compound binds to Uba2. In some embodiments, the compound has an inhibitory effect on activating enzymes (E1) of SUMO.

[004] Disclosed herein is a method comprising: a) administering a therapeutically-effective amount of a compound to a subject in need thereof, wherein the compound blocks SUMOylation in the subject; and b) after the administering, observing that the administering increases an immune response in the subject against a cancer.

BRIEF DESCRIPTION OF THE FIGURES

[005] FIG. 1 Tumor Growth Curve in the Mice in Different Groups. Data points represent means of each group, and error bars represent standard errors of the mean (SEM, n=8). Group 1: [small circle] Vehicle control p.o, (BIWx2weeks) Group 2: [square] Compound A 50 mg/kg, p.o. (BIWx2weeks) Group 3: [triangle] rituximab 20 mg/kg, i.p. (BIWx2weeks) Group 4: [diamond] Compound A, 50 mg/kg, p.o.+ Rituximab, 20 mg/kg,i.p. (BIWx2weeks) Group 5: [large circle] Compound A, 50 mg/kg, p.o. (QDx2weeks). The y-axis measures tumor volume (mm^3) for each group of animals per length of the

experiment in days.

[006] FIG. 2 The Relative Change of Body Weights of the Mice in Different Groups (D1~D17). Data points represent mean body weights of each group. Error bars represent standard errors of the mean (SEM, n=8). Group 1: [small circle] Vehicle control p.o, (BIWx2weeks) Group 2: [square] Compound A 50 mg/kg, p.o. (BIWx2weeks) Group 3: [triangle] rituximab 20 mg/kg, i.p. (BIWx2weeks) Group 4: [diamond] Compound A, 50 mg/kg, p.o.+ rituximab, 20 mg/kg,i.p. (BIWx2weeks) Group 5: [large circle] Compound A, 50 mg/kg, p.o. (QDx2weeks). The y-axis reflects the RCBW for each group of animals in percent change versus vehicle control per length of experiment in days.

[007] FIG. 3 Effect upon combination treatment with Compound A and decitabine in AML cell lines. GDM-1 and MV4-11 cells were treated with indicated doses of Compound A and decitabine for 72-hrs, and cell viability was measured to generate dose response curves. IC_{50} values were calculated from treatment with Compound A alone, and in combination with decitabine, and these values were used to measure ZIP scores, see Table 4. Dose response graphs and IC_{50} calculations were generated using GraphPad Prism 9 (ver. 9.4.0). ZIP scores were calculated using SynergyFinder 3.0 (https://synergyfinder.fim m.fi/synergy/2022 0701215205193938/).

[008] FIG.4 Combination of Compound A with anti-PD-1 therapy Inhibits TumorGrowth in a CT26 model of syngeneic colon cancer in BALB/c mice. Data points represent tumor volume curves for four treatment groups. Group 1: [small circle] Vehicle control. Group 2: [triangle] Compound A 50 mg/kg, Group 3: [square] antiPD-1 2.5 mg/kg, Group 4: [triangle] Compound A, 50 mg/kg, + antiPD-1 2.5 mg/kg The y-axis reflects the tumor volumes in mm^2 for each group of animals per length of experiment - 15 days [x-axis].

[009] FIG 5 Combination of Compound A with anti-PD-1 therapy Improves Survival in a CT26 model of syngeneic colon cancer in BALB/c mice. Data points represent survival for four treatment groups. Group 1: [small circle] Vehicle control. Group 2: [triangle] Compound A 50 mg/kg, Group 3: [square] antiPD-1 2.5 mg/kg, Group 4: [triangle] Compound A, 50 mg/kg, + antiPD-1 2.5 mg/kg The y-axis reflects the number of mice surviving as a percentage of the total in each group of animals per length of experiment - 80 days [x-axis].

[010] FIG 6. Compound A Induces $CD8^+$ T Cell Infiltration in a CT26 model of syngeneic colon cancer in BALB/c mice. The bar graph represents the percent of CD8+ as a percent of CD45/CD3 for the treatment groups - Column 1: Vehicle control. Column 2: Compound A at 50 mg/kg.

DETAILED DESCRIPTION

[011] The present disclosure provides compounds and methods for blocking SUMOylation. The combinations of the present disclosure include SUMO inhibitors and at least one other anti-cancer agent that functions through a pathway other than SUMOylation. The SUMO inhibitors of the present disclosure bind to Uba2. The SUMO inhibitors of the present disclosure have an inhibitory effect on activating enzymes (E1) of SUMO.

[012] Disclosed here in is a method comprising: a) administering a therapeutically-effective amount of a compound to a subject in need thereof, wherein the compound blocks SUMOylation in the subject;

and b) after the administering, observing that the administering increases an immune response in the subject against a cancer. In some embodiments, the method comprises after the administering, obtaining a population of an immune cell in a biological sample obtained from the subject. In some embodiments, the biological sample is obtained from a tumor. In some embodiments, the administering increases a population of tumor infiltrating lymphocytes. In some embodiments, the administering increases a population of CD8+ cells. In some embodiments, the population of the immune cell is determined using a multiplexed immunofluorescence. In some embodiments, the population of the immune cell is determined using flow cytometry. In some embodiments, the population of the immune cell is determined using fluorescence activated cell sorting [FACS]. In some embodiments, the population of the immune cell is determined using antibody staining.

[013] The disclosure further provides methods of treatment of a cancerous lesion or a tumor harboring a SUMOylation.

[014] Cancer is a collection of related diseases characterized by uncontrolled proliferation of cells with the potential to metastasize throughout the body. Cancer can be classified into five broad categories including, for example: carcinomas, which can arise from cells that cover internal and external parts of the body such as the lung, breast, and colon; sarcomas, which can arise from cells that are located in bone, cartilage, fat, connective tissue, muscle, and other supportive tissues; lymphomas, which can arise in the lymph nodes and immune system tissues; leukemia, which can arise in the bone marrow and accumulate in the bloodstream; and adenomas, which can arise in the thyroid, the pituitary gland, the adrenal gland, and other glandular tissues.

[015] Although different cancers can develop in virtually any of the body's tissues, and contain unique features, the basic processes that cause cancer can be similar in all forms of the disease. Cancer begins when a cell breaks free from the normal restraints on cell division and begins to grow and divide out of control.

MECHANISM.

[016] SUMOylation is a reversible post-translational modification by small ubiquitin-like modifier (SUMO). SUMOylation controls many cellular functions and plays a critical role in the regulation of genome integrity, cell cycle progression, and the immune response (1). Three different enzyme components are involved in the SUMOylation cascade including a SUMO-activating enzyme E1 (SUMO E1 or SAE1/UBA2), an E2 enzyme (ubiquitin-conjugating enzyme 9 (UBC9)), and a limited set of E3 ligases. The process of SUMOylation starts when SUMO E1 activates SUMO through ATP hydrolysis and forms a thioester conjugate with SUMO. Next, SUMO is transferred and forms a new thioester conjugate with E2. Finally, SUMO is attached to target proteins, a step catalyzed by an E3 ligase. Specific small molecule inhibitors of the SUMO E1 enzyme have recently been developed that allow for the exploration of pharmacological SUMOylation inhibitors as novel anticancer therapeutics. Inhibition of SUMOylation by small molecules impairs cancer cell proliferation and triggers antitumor immune responses by stimulating the interferon (IFN) response (2). An allosteric covalent mechanism to inhibit

SUMO E1 was recently characterized (3), lending rationale towards the development of other novel pharmacological agents to block SUMOylation.

[017] One embodiment of the disclosure includes compounds that block SUMOylation when used in combination with other treatments for cancer.

Mechanism of compounds disclosed herein.

[018] To determine the ability of a compound of the disclosure to blocks SUMOylation, assays can be employed to detect, for example, binding of a compound to Uba2, or an inhibitory effect on activating enzymes (E1) of SUMO. Such assays are described in PCT application PCT/US22/73985.

[019] A compound of the disclosure can increase the inhibit SUMOylation by at least or up to about 0.1%, at least or up to about 0.2%, at least or up to about 0.3%, at least or up to about 0.4%, at least or up to about 0.5%, at least or up to about 0.6%, at least or up to about 0.7%, at least or up to about 0.8%, at least or up to about 0.9%, at least or up to about 1%, at least or up to about 2%, at least or up to about 3%, at least or up to about 4%, at least or up to about 5%, at least or up to about 6%, at least or up to about 7%, at least or up to about 8%, at least or up to about 9%, at least or up to about 10%, at least or up to about 11%, at least or up to about 12%, at least or up to about 13%, at least or up to about 14%, at least or up to about 15%, at least or up to about 16%, at least or up to about 17%, at least or up to about 18%, at least or up to about 19%, at least or up to about 20%, at least or up to about 21%, at least or up to about 22%, at least or up to about 23%, at least or up to about 24%, at least or up to about 25%, at least or up to about 26%, at least or up to about 27%, at least or up to about 28%, at least or up to about 29%, at least or up to about 30%, at least or up to about 31%, at least or up to about 32%, at least or up to about 33%, at least or up to about 34%, at least or up to about 35%, at least or up to about 36%, at least or up to about 37%, at least or up to about 38%, at least or up to about 39%, at least or up to about 40%, at least or up to about 41%, at least or up to about 42%, at least or up to about 43%, at least or up to about 44%, at least or up to about 45%, at least or up to about 46%, at least or up to about 47%, at least or up to about 48%, at least or up to about 49%, at least or up to about 50%, at least or up to about 51%, at least or up to about 52%, at least or up to about 53%, at least or up to about 54%, at least or up to about 55%, at least or up to about 56%, at least or up to about 57%, at least or up to about 58%, at least or up to about 59%, at least or up to about 60%, at least or up to about 61%, at least or up to about 62%, at least or up to about 63%, at least or up to about 64%, at least or up to about 65%, at least or up to about 66%, at least or up to about 67%, at least or up to about 68%, at least or up to about 69%, at least or up to about 70%, at least or up to about 71%, at least or up to about 72%, at least or up to about 73%, at least or up to about 74%, at least or up to about 75%, at least or up to about 76%, at least or up to about 77%, at least or up to about 78%, at least or up to about 79%, at least or up to about 80%, at least or up to about 81%, at least or up to about 82%, at least or up to about 83%, at least or up to about 84%, at least or up to about 85%, at least or up to about 86%, at least or up to about 87%, at least or up to about 88%, at least or up to about 89%, at least or up to about 90%, at least or up to about 91%, at least or up to about 92%, at least or up to about 93%, at least or up to about 94%, at least or up to about 95%, at least or up to about 96%, at least or up to about 97%, at

least or up to about 98%, at least or up to about 99%, at least or up to about 100%, at least or up to about 125%, at least or up to about 150%, at least or up to about 175%, at least or up to about 200%, at least or up to about 225%, or at least or up to about 250% as compared to the amount of SUMOylation in the absence of a compound of the disclosure.

[020] A compound described herein can bind SUMO E1 enzyme that is, for example, by at least or up to about 0.1%, at least or up to about 0.2%, at least or up to about 0.3%, at least or up to about 0.4%, at least or up to about 0.5%, at least or up to about 0.6%, at least or up to about 0.7%, at least or up to about 0.8%, at least or up to about 0.9%, at least or up to about 1%, at least or up to about 2%, at least or up to about 3%, at least or up to about 4%, at least or up to about 5%, at least or up to about 6%, at least or up to about 7%, at least or up to about 8%, at least or up to about 9%, at least or up to about 10%, at least or up to about 11%, at least or up to about 12%, at least or up to about 13%, at least or up to about 14%, at least or up to about 15%, at least or up to about 16%, at least or up to about 17%, at least or up to about 18%, at least or up to about 19%, at least or up to about 20%, at least or up to about 21%, at least or up to about 22%, at least or up to about 23%, at least or up to about 24%, at least or up to about 25%, at least or up to about 26%, at least or up to about 27%, at least or up to about 28%, at least or up to about 29%, at least or up to about 30%, at least or up to about 31%, at least or up to about 32%, at least or up to about 33%, at least or up to about 34%, at least or up to about 35%, at least or up to about 36%, at least or up to about 37%, at least or up to about 38%, at least or up to about 39%, at least or up to about 40%, at least or up to about 41%, at least or up to about 42%, at least or up to about 43%, at least or up to about 44%, at least or up to about 45%, at least or up to about 46%, at least or up to about 47%, at least or up to about 48%, at least or up to about 49%, at least or up to about 50%, at least or up to about 51%, at least or up to about 52%, at least or up to about 53%, at least or up to about 54%, at least or up to about 55%, at least or up to about 56%, at least or up to about 57%, at least or up to about 58%, at least or up to about 59%, at least or up to about 60%, at least or up to about 61%, at least or up to about 62%, at least or up to about 63%, at least or up to about 64%, at least or up to about 65%, at least or up to about 66%, at least or up to about 67%, at least or up to about 68%, at least or up to about 69%, at least or up to about 70%, at least or up to about 71%, at least or up to about 72%, at least or up to about 73%, at least or up to about 74%, at least or up to about 75%, at least or up to about 76%, at least or up to about 77%, at least or up to about 78%, at least or up to about 79%, at least or up to about 80%, at least or up to about 81%, at least or up to about 82%, at least or up to about 83%, at least or up to about 84%, at least or up to about 85%, at least or up to about 86%, at least or up to about 87%, at least or up to about 88%, at least or up to about 89%, at least or up to about 90%, at least or up to about 91%, at least or up to about 92%, at least or up to about 93%, at least or up to about 94%, at least or up to about 95%, at least or up to about 96%, at least or up to about 97%, at least or up to about 98%, at least or up to about 99%, at least or up to about 100%.

[021] A compound of the disclosure can be used, for example, to reduce cell proliferation or trigger antitumor immune response in a subject.

Compounds of the disclosure.

[022] In some embodiments, a compound of the disclosure comprises a substituted 4,5,6,7-

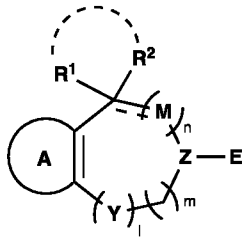
tetrahydrothieno[2,3-c]pyridine group, wherein the compound blocks SUMOylation. In some embodiments, the compound binds to Uba2. In some embodiments, the compound has an inhibitory effect on activating enzymes (E1) of SUMO.

[023] In some embodiments, the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group has a nitrile substituent at a 2-position of the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group. The nitrile substituent is alternatively described as a cyano group. In some embodiments, the compound has plasma protein binding of less than about 99.5% or less than that of an analogous compound that lacks the cyano substituent.

[024] In some embodiments, the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group has an electrophilic moiety at a 6-position of the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group. In some embodiments, the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group has an unsubstituted or substituted $C_{2\text{-}6}$ alkenylcarbonyl or an unsubstituted or substituted $C_{2\text{-}6}$ alkynylcarbonyl substituent at a 6-position of the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group. In some embodiments, the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group has an unsubstituted or substituted aminopropenylcarbonyl or an unsubstituted or substituted aminobutenylcarbonyl substituent at a 6-position of the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group.

[025] In some embodiments, the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group comprises a substituted phenyl substituent at a 4-position of the 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group. In some embodiments, a substituted pyrazole group is attached to the phenyl substituent.

[026] Non-limiting examples of compounds of the disclosure include compounds of the following formula:



(I)

wherein ==== is a single bond or double bond;

wherein l, m, n are each independently an integer from 0 to 2;

wherein M is selected from CR^3R^4, NR^5, C=O, O, S=O, O=S=O, and S;

wherein Y is selected from CR^6R^7, NR^8, C=O, O, S=O, O=S=O, and S;

wherein Z is CR^9, or N;

wherein ring A is selected from

a) 5- or 6-membered partially saturated heterocyclyl,

b) 5- or 6-membered aryl or heteroaryl,

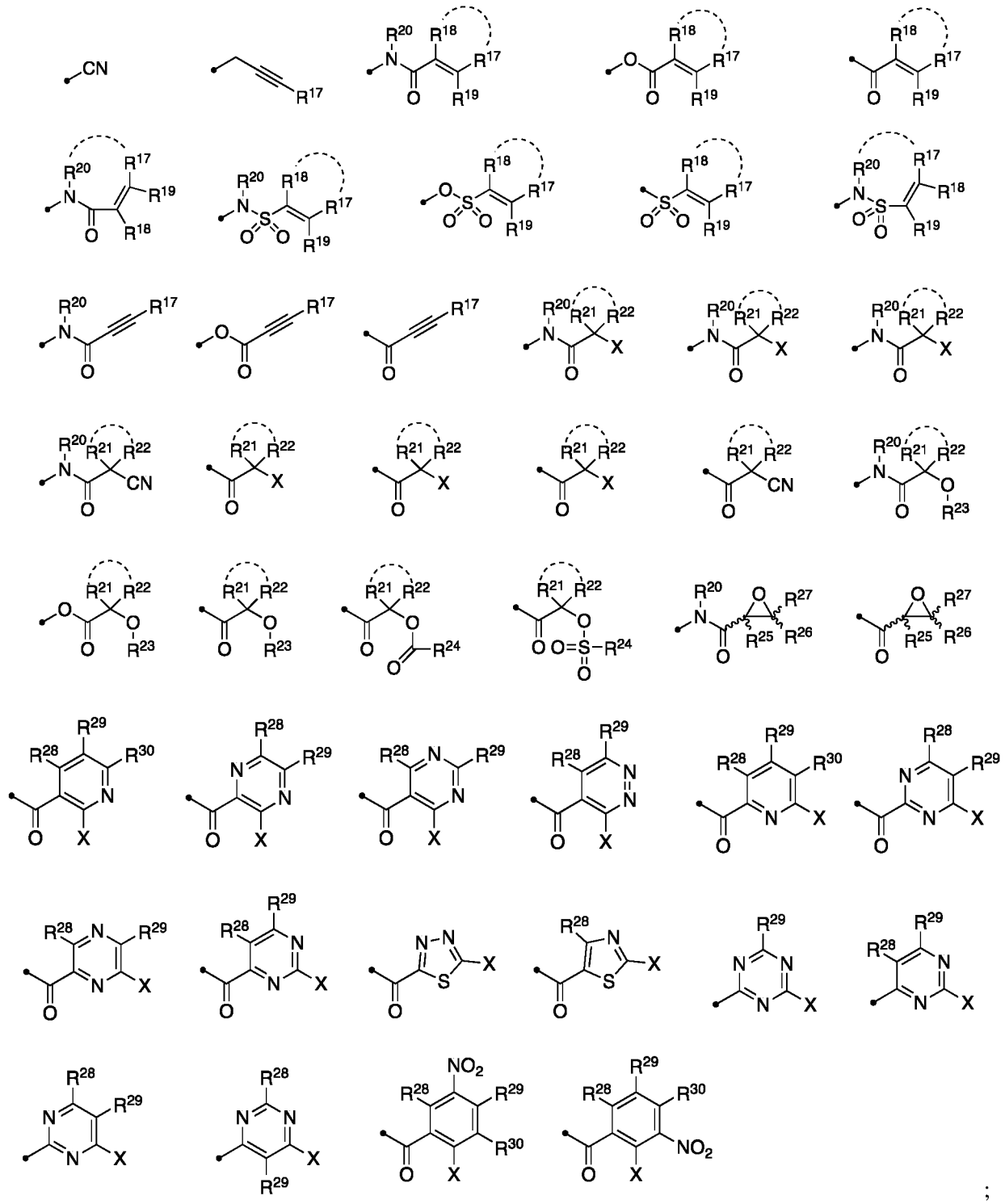
c) 9-, 10- or 11-membered fused partially saturated heterocyclyl,

d) 9- or 10-membered fused heteroaryl,

e) naphthyl, and

f) 4-, 5- or 6-membered cycloalkenyl;

wherein E is an electrophilic moiety, selected from:



;

Wherein R^1 is selected from hydrogen, halogen, $-C(X^1)_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-NHNR^{1A}R^{1B}$, $-C(O)R^{1A}$, $-C(O)-OR^{1A}$, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHNR^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$, $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, 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;

Wherein R^2 is selected from hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHNR^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHNR^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$, $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, 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; R^1 and R^2 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

Wherein R^3 is selected from hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHNR^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, 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;

Wherein R^4 is selected from hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHNR^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHNR^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, 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^3 and R^3 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

Wherein R^5 is selected from hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHNR^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHNR^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, 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;

Wherein R^6 is selected from hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-NHNR^{6A}R^{6B}$, $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHNR^{6A}R^{6B}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, 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;

Wherein R^7 is selected from hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$,

$-NR^{7A}R^{7B}$, $-NHNR^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHNR^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, 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;

Wherein R^8 is selected from hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, $-CN$, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}8^{7B}$, $-NHNR^{8A}R^{8B}$, $-C(O)R^{8A}$, $-C(O)-OR^{8A}$, $-C(O)NR^{8A}R^{8B}$, $-C(O)NHNR^{8A}R^{8B}$, $-OR^{8A}$, $-NR^{8A}SO_2R^{8B}$, $-NR^{8A}C(O)R^{8B}$, $-NR^{8A}C(O)OR^{8B}$, $-NR^{8A}OR^{8B}$, $-N_3$, 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;

Wherein R^9 is selected from hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, $-CN$, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHNR^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHNR^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, 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;

Wherein R^{10} is selected from hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, $-CN$, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNR^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNR^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, 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;

Wherein R^{11} is selected from hydrogen, halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, $-CN$, $-SO_{n11}R^{11A}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-NHNR^{11A}R^{11B}$, $-C(O)R^{11A}$, $-C(O)-OR^{11A}$, $-C(O)NR^{11A}R^{11B}$, $-C(O)NHNR^{11A}R^{11B}$, $-OR^{11A}$, $-NR^{11A}SO_2R^{11B}$, $-NR^{11A}C(O)R^{11B}$, $-NR^{11A}C(O)OR^{11B}$, $-NR^{11A}OR^{11B}$, $-N_3$, 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;

Wherein R^{12} is selected from hydrogen, halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, $-CN$, $-SO_{n12}R^{12A}$, $-SO_{v12}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m12}$, $-NR^{12A}R^{12B}$, $-NHNR^{12A}R^{12B}$, $-C(O)R^{12A}$, $-C(O)-OR^{12A}$, $-C(O)NR^{12A}R^{12B}$, $-C(O)NHNR^{12A}R^{12B}$, $-OR^{12A}$, $-NR^{12A}SO_2R^{12B}$, $-NR^{12A}C(O)R^{12B}$, $-NR^{12A}C(O)OR^{12B}$, $-NR^{12A}OR^{12B}$, $-N_3$, 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;

Wherein R^{13} is selected from hydrogen, halogen, $-CX^{13}_3$, $-CHX^{13}_2$, $-CH_2X^{13}$, $-OCX^{13}_3$, $-OCH_2X^{13}$, $-OCHX^{13}_2$, -CN, $-SO_{n13}R^{13A}$, $-SO_{v13}NR^{13A}R^{13B}$, $-NHC(O)NR^{13A}R^{13B}$, $-N(O)_{m13}$, $-NR^{13A}R^{13B}$, $-NHNR^{13A}R^{13B}$, $-C(O)R^{13A}$, $-C(O)-OR^{13A}$, $-C(O)NR^{13A}R^{13B}$, $-C(O)NHNR^{13A}R^{13B}$, $-OR^{13A}$, $-NR^{13A}SO_2R^{13B}$, $-NR^{13A}C(O)R^{13B}$, $-NR^{13A}C(O)OR^{13B}$, $-NR^{13A}OR^{13B}$, $-N_3$, 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;

Wherein R^{14} is selected from hydrogen, halogen, $-CX^{14}_3$, $-CHX^{14}_2$, $-CH_2X^{14}$, $-OCX^{14}_3$, $-OCH_2X^{14}$, $-OCHX^{14}_2$, -CN, $-SO_{n14}R^{14A}$, $-SO_{v14}NR^{14A}R^{14B}$, $-NHC(O)NR^{14A}R^{14B}$, $-N(O)_{m14}$, $-NR^{14A}R^{14B}$, $-NHNR^{14A}R^{14B}$, $-C(O)R^{14A}$, $-C(O)-OR^{14A}$, $-C(O)NR^{14A}R^{14B}$, $-C(O)NHNR^{14A}R^{14B}$, $-OR^{14A}$, $-NR^{14A}SO_2R^{14B}$, $-NR^{14A}C(O)R^{14B}$, $-NR^{14A}C(O)OR^{14B}$, $-NR^{14A}OR^{14B}$, $-N_3$, 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;

Wherein R^{15} is selected from hydrogen, halogen, $-CX^{15}_3$, $-CHX^{15}_2$, $-CH_2X^{15}$, $-OCX^{15}_3$, $-OCH_2X^{15}$, $-OCHX^{15}_2$, -CN, $-SO_{n15}R^{15A}$, $-SO_{v15}NR^{15A}R^{15B}$, $-NHC(O)NR^{15A}R^{15B}$, $-N(O)_{m15}$, $-NR^{15A}R^{15B}$, $-NHNR^{15A}R^{15B}$, $-C(O)R^{15A}$, $-C(O)-OR^{15A}$, $-C(O)NR^{15A}R^{15B}$, $-C(O)NHNR^{15A}R^{15B}$, $-OR^{15A}$, $-NR^{15A}SO_2R^{15B}$, $-NR^{15A}C(O)R^{15B}$, $-NR^{15A}C(O)OR^{15B}$, $-NR^{15A}OR^{15B}$, $-N_3$, 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;

R^{16} is selected from hydrogen, halogen, $-CX^{16}_3$, $-CHX^{16}_2$, $-CH_2X^{16}$, $-OCX^{16}_3$, $-OCH_2X^{16}$, $-OCHX^{16}_2$, -CN, $-SO_{n16}R^{16A}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-NHNR^{16A}R^{16B}$, $-C(O)R^{16A}$, $-C(O)-OR^{16A}$, $-C(O)NR^{16A}R^{16B}$, $-C(O)NHNR^{16A}R^{16B}$, $-OR^{16A}$, $-NR^{16A}SO_2R^{16B}$, $-NR^{16A}C(O)R^{16B}$, $-NR^{16A}C(O)OR^{16B}$, $-NR^{16A}OR^{16B}$, $-N_3$, 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;

R^{17} is selected from hydrogen, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-CH_2X^{17}$, $-OCX^{17}_3$, $-OCH_2X^{17}$, $-OCHX^{17}_2$, -CN, $-SO_{n17}R^{17A}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-C(O)R^{17A}$, $-C(O)-OR^{17A}$, $-C(O)NR^{17A}R^{17B}$, $-C(O)NHNR^{17A}R^{17B}$, $-OR^{17A}$, $-NR^{17A}SO_2R^{17B}$, $-NR^{17A}C(O)R^{17B}$, $-NR^{17A}C(O)OR^{17B}$, $-NR^{17A}OR^{17B}$, $-N_3$, 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;

R^{18} is selected from hydrogen, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-OCX^{18}_3$, $-OCH_2X^{18}$, $-OCHX^{18}_2$, -CN, $-SO_{n18}R^{18A}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-NHNR^{18A}R^{18B}$, $-C(O)R^{18A}$, $-C(O)-OR^{18A}$, $-C(O)NR^{18A}R^{18B}$, $-C(O)NHNR^{18A}R^{18B}$, $-OR^{18A}$, $-NR^{18A}SO_2R^{18B}$, $-NR^{18A}C(O)R^{18B}$, $-NR^{18A}C(O)OR^{18B}$, $-NR^{18A}OR^{18B}$, $-N_3$, 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; R^{17} and R^{18} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{19} is selected from hydrogen, halogen, $-CX^{19}_3$, $-CHX^{19}_2$, $-CH_2X^{19}$, $-OCX^{19}_3$, $-OCH_2X^{19}$, $-OCHX^{19}_2$, -CN, $-SO_{n19}R^{19A}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-NHNR^{19A}R^{19B}$, $-C(O)R^{19A}$, $-C(O)-OR^{19A}$, $-C(O)NR^{19A}R^{19B}$, $-C(O)NHNR^{19A}R^{19B}$, $-OR^{19A}$, $-NR^{19A}SO_2R^{19B}$, $-NR^{19A}C(O)R^{19B}$, $-NR^{19A}C(O)OR^{19B}$, $-NR^{19A}OR^{19B}$, $-N_3$, 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;

R^{20} is selected from hydrogen, halogen, $-CX^{20}_3$, $-CHX^{20}_2$, $-CH_2X^{20}$, $-OCX^{20}_3$, $-OCH_2X^{20}$, $-OCHX^{20}_2$, -CN, $-SO_{n20}R^{20A}$, $-SO_{v20}NR^{20A}R^{20B}$, $-NHC(O)NR^{20A}R^{20B}$, $-N(O)_{m20}$, $-NR^{20A}R^{20B}$, $-NHNR^{20A}R^{20B}$, $-C(O)R^{20A}$, $-C(O)-OR^{20A}$, $-C(O)NR^{20A}R^{20B}$, $-C(O)NHNR^{20A}R^{20B}$, $-OR^{20A}$, $-NR^{20A}SO_2R^{20B}$, $-NR^{20A}C(O)R^{20B}$, $-NR^{20A}C(O)OR^{20B}$, $-NR^{20A}OR^{20B}$, $-N_3$, 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; R^{17} and R^{20} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{21} is selected from hydrogen, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, -CN, $-SO_{n21}R^{21A}$, $-SO_{v21}NR^{21A}R^{21B}$, $-NHC(O)NR^{21A}R^{21B}$, $-N(O)_{m21}$, $-NR^{21A}R^{21B}$, $-NHNR^{21A}R^{21B}$, $-C(O)R^{21A}$, $-C(O)-OR^{21A}$, $-C(O)NR^{21A}R^{21B}$, $-C(O)NHNR^{21A}R^{21B}$, $-OR^{21A}$, $-NR^{21A}SO_2R^{21B}$, $-NR^{21A}C(O)R^{21B}$, $-NR^{21A}C(O)OR^{21B}$, $-NR^{21A}OR^{21B}$, $-N_3$, 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;

R^{22} is selected from hydrogen, halogen, $-CX^{22}_3$, $-CHX^{22}_2$, $-CH_2X^{22}$, $-OCX^{22}_3$, $-OCH_2X^{22}$, $-OCHX^{22}_2$, -CN, $-SO_{n22}R^{22A}$, $-SO_{v22}NR^{22A}R^{22B}$, $-NHC(O)NR^{22A}R^{22B}$, $-N(O)_{m22}$, $-NR^{22A}R^{22B}$, $-NHNR^{22A}R^{22B}$, $-C(O)R^{22A}$, $-C(O)-OR^{22A}$, $-C(O)NR^{22A}R^{22B}$, $-C(O)NHNR^{22A}R^{22B}$, $-OR^{22A}$, $-NR^{22A}SO_2R^{22B}$, $-NR^{22A}C(O)R^{22B}$, $-NR^{22A}C(O)OR^{22B}$, $-NR^{22A}OR^{22B}$, $-N_3$, 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; R^{21} and R^{22} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

wherein R^{23} is selected from hydrogen, halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-CH_2X^{23}$, $-OCX^{23}_3$, $-OCH_2X^{23}$, $-OCHX^{23}_2$, -CN, $-SO_{n23}R^{23A}$, $-SO_{v23}NR^{23A}R^{23B}$, $-NHC(O)NR^{23A}R^{23B}$, $-N(O)_{m23}$, $-NR^{23A}R^{23B}$, $-NHNR^{23A}R^{23B}$, $-C(O)R^{23A}$, $-C(O)-OR^{23A}$, $-C(O)NR^{23A}R^{23B}$, $-C(O)NHNR^{23A}R^{23B}$, $-OR^{23A}$, $-NR^{23A}SO_2R^{23B}$, $-NR^{23A}C(O)R^{23B}$, $-NR^{23A}C(O)OR^{23B}$, $-NR^{23A}OR^{23B}$, $-N_3$, 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;

wherein R^{24} is selected from hydrogen, halogen, $-CX^{24}_3$, $-CHX^{24}_2$, $-CH_2X^{24}$, $-OCX^{24}_3$, $-OCH_2X^{24}$, $-OCHX^{24}_2$, -CN, $-SO_{n24}R^{24A}$, $-SO_{v24}NR^{24A}R^{24B}$, $-NHC(O)NR^{24A}R^{24B}$, $-N(O)_{m24}$, $-NR^{24A}R^{24B}$, $-NHNR^{24A}R^{24B}$, $-C(O)R^{24A}$, $-C(O)-OR^{24A}$, $-C(O)NR^{24A}R^{24B}$, $-C(O)NHNR^{24A}R^{24B}$, $-OR^{24A}$, $-NR^{24A}SO_2R^{24B}$, $-NR^{24A}C(O)R^{24B}$, $-NR^{24A}C(O)OR^{24B}$, $-NR^{24A}OR^{24B}$, $-N_3$, 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;

wherein R^{25} is selected from hydrogen, halogen, $-CX^{25}_3$, $-CHX^{25}_2$, $-CH_2X^{25}$, $-OCX^{25}_3$, $-OCH_2X^{25}$, $-OCHX^{25}_2$, -CN, $-SO_{n25}R^{25A}$, $-SO_{v25}NR^{25A}R^{25B}$, $-NHC(O)NR^{25A}R^{25B}$, $-N(O)_{m25}$, $-NR^{25A}R^{25B}$, $-NHNR^{25A}R^{25B}$, $-C(O)R^{25A}$, $-C(O)-OR^{25A}$, $-C(O)NR^{25A}R^{25B}$, $-C(O)NHNR^{25A}R^{25B}$, $-OR^{25A}$, $-NR^{25A}SO_2R^{25B}$, $-NR^{25A}C(O)R^{25B}$, $-NR^{25A}C(O)OR^{25B}$, $-NR^{25A}OR^{25B}$, $-N_3$, 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;

wherein R^{26} is selected from hydrogen, halogen, $-CX^{26}_3$, $-CHX^{26}_2$, $-CH_2X^{26}$, $-OCX^{26}_3$, $-OCH_2X^{26}$, $-OCHX^{26}_2$, -CN, $-SO_{n26}R^{26A}$, $-SO_{v26}NR^{26A}R^{26B}$, $-NHC(O)NR^{26A}R^{26B}$, $-N(O)_{m26}$, $-NR^{26A}R^{26B}$, $-NHNR^{26A}R^{26B}$, $-C(O)R^{26A}$, $-C(O)-OR^{26A}$, $-C(O)NR^{26A}R^{26B}$, $-C(O)NHNR^{26A}R^{26B}$, $-OR^{26A}$, $-NR^{26A}SO_2R^{26B}$, $-NR^{26A}C(O)R^{26B}$, $-NR^{26A}C(O)OR^{26B}$, $-NR^{26A}OR^{26B}$, $-N_3$, 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;

wherein R^{27} is selected from hydrogen, halogen, $-CX^{27}_3$, $-CHX^{27}_2$, $-CH_2X^{27}$, $-OCX^{27}_3$, $-OCH_2X^{27}$, $-OCHX^{27}_2$, -CN, $-SO_{n27}R^{27A}$, $-SO_{v27}NR^{27A}R^{27B}$, $-NHC(O)NR^{27A}R^{27B}$, $-N(O)_{m27}$, $-NR^{27A}R^{27B}$, $-NHNR^{27A}R^{27B}$, $-C(O)R^{27A}$, $-C(O)-OR^{27A}$, $-C(O)NR^{27A}R^{27B}$, $-C(O)NHNR^{27A}R^{27B}$, $-OR^{27A}$, $-NR^{27A}SO_2R^{27B}$, $-NR^{27A}C(O)R^{27B}$, $-NR^{27A}C(O)OR^{27B}$, $-NR^{27A}OR^{27B}$, $-N_3$, 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;

Wherein R^{28} is selected from hydrogen, halogen, $-CX^{28}_3$, $-CHX^{28}_2$, $-CH_2X^{28}$, $-OCX^{28}_3$, $-OCH_2X^{28}$, $-OCHX^{28}_2$, -CN, $-SO_{n28}R^{28A}$, $-SO_{v28}NR^{28A}R^{28B}$, $-NHC(O)NR^{28A}R^{28B}$, $-N(O)_{m28}$, $-NR^{28A}R^{28B}$, $-NHNR^{28A}R^{28B}$, $-C(O)R^{28A}$, $-C(O)-OR^{28A}$, $-C(O)NR^{28A}R^{28B}$,

-C(O)NHNR^{28A}R^{28B}, -OR^{28A}, -NR^{28A}SO$_2$R^{28B}, -NR^{28A}C(O)R^{28B}, -NR^{28A}C(O)OR^{28B}, -NR^{28A}OR^{28B}, -N$_3$, 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;

Wherein R^{29} is selected from hydrogen, halogen, -CX$^{29}_3$, -CHX$^{29}_2$, -CH$_2$X^{29}, -OCX$^{29}_3$, -OCH$_2$X^{29}, -OCHX$^{29}_2$, -CN, -SO$_{n29}$R^{29A}, -SO$_{v29}$NR^{29A}R^{29B}, -NHC(O)NR^{29A}R^{29B}, -N(O)$_{m29}$, -NR^{29A}R^{29B}, -NHNR^{29A}R^{29B}, -C(O)R^{29A}, -C(O)-OR^{29A}, -C(O)NR^{29A}R^{29B}, -C(O)NHNR^{29A}R^{29B}, -OR^{29A}, -NR^{29A}SO$_2$R^{29B}, -NR^{29A}C(O)R^{29B}, -NR^{29A}C(O)OR^{29B}, -NR^{29A}OR^{29B}, -N$_3$, 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;

R^{30} is selected from hydrogen, halogen, -CX$^{30}_3$, -CHX$^{30}_2$, -CH$_2$X^{30}, -OCX$^{30}_3$, -OCH$_2$X^{30}, -OCHX$^{30}_2$, -CN, -SO$_{n30}$R^{30A}, -SO$_{v30}$NR^{30A}R^{30B}, -NHC(O)NR^{30A}R^{30B}, -N(O)$_{m30}$, -NR^{30A}R^{30B}, -NHNR^{30A}R^{30B}, -C(O)R^{30A}, -C(O)-OR^{30A}, -C(O)NR^{30A}R^{30B}, -C(O)NHNR^{30A}R^{30B}, -OR^{30A}, -NR^{30A}SO$_2$R^{30B}, -NR^{30A}C(O)R^{30B}, -NR^{30A}C(O)OR^{30B}, -NR^{30A}OR^{30B}, -N$_3$, 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;

Each R^{1A}, R^{1B}, R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{6A}, R^{6B}, R^{7A}, R^{7B}, R^{8A}, R^{8B}, R^{9A}, R^{9B}, R^{10A}, R^{10B}, R^{11A}, R^{11B}, R^{12A}, R^{12B}, R^{13A}, R^{13B}, R^{14A}, R^{14B}, R^{15A}, R^{15B}, R^{16A}, R^{16B}, R^{17A}, R^{17B}, R^{18A}, R^{18B}, R^{19A}, R^{19B}, R^{20A}, R^{20B}, R^{21A}, R^{21B}, R^{22A}, R^{22B}, R^{23A}, R^{23B}, R^{24A}, R^{24B}, R^{25A}, R^{25B}, R^{26A}, R^{26B}, R^{27A}, R^{27B}, R^{28A}, R^{28B}, R^{29A}, R^{29B}, R^{30A}, R^{30B} is independently selected from hydrogen, -CX$_3$, -CHX$_2$, -CH$_2$X, -C(O)OH, -C(O)NH$_2$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -NO$_2$, -SH, -SO$_3$H, -SO$_4$H, -SO$_2$NH$_2$, -NHNH$_2$, -ONH$_2$, -NHC=(O)NHNH$_2$, □NHC=(O)NH$_2$, -NHSO$_2$H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX$_3$, -OCHX$_2$, -OCH$_2$X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

wherein R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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^{5A} and R^{5B} 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^{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; 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; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{11A} and R^{11B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{12A} and R^{12B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{13A} and R^{13B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{14A} and R^{14B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{20A} and R^{20B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{21A} and R^{21B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{22A} and R^{22B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{23A} and R^{23B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{24A} and R^{24B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{25A} and R^{25B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{26A} and R^{26B} substituents bonded to

the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{27A} and R^{27B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{28A} and R^{28B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{29A} and R^{29B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{30A} and R^{30B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

Wherein each m1, m2, m3, m4, m5, m6, m7, m8, m9, m10, m11, m12, m13, m14, m15, m16, m17, m18, m19, m20, m21, m22, m23, m24, m25, m26, m27, m28, m29, and m30 are independently 1 or 2;

wherein each v1, v2, v3, v4, v5, v6, v7, v8, v9, v10, v11, v12, v13, v14, v15, v16, v17, v18, v19, v20, v21, v22, v23, v24, v25, v26, v27, v28, v29 and v30 are independently 1 or 2;

wherein each n1, n2, n3, n4, n5, n6, n7, n8, n9, n10, n11, n12, n13, n14, n15, n16, n17, n18, n19, n20, n21, n22, n23, n24, n25, n26, n27, n28, n29 and n30 are independently an integer from 0 to 2; and

wherein each X, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, X^{16}, X^{17}, X^{18}, X^{19}, X^{20}, X^{21}, X^{22}, X^{23}, X^{24}, X^{25}, X^{26}, X^{27}, X^{28}, X^{29} and X^{30} are independently -Cl, -Br, -I or –F.

[027] In some embodiments, l is 1; m is 0; and n is 1.

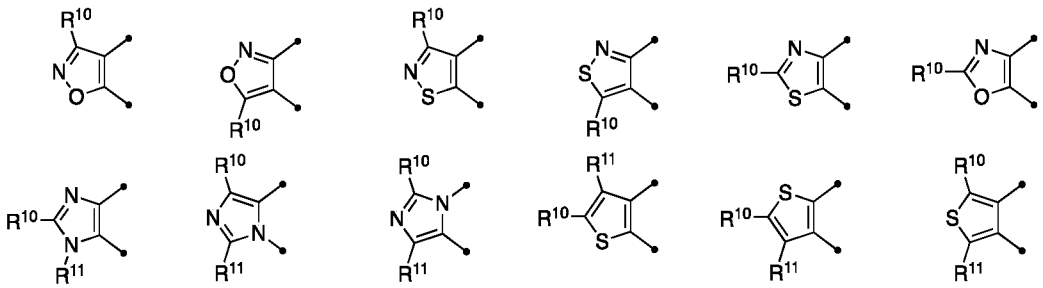
[028] In some embodiments, Z is N.

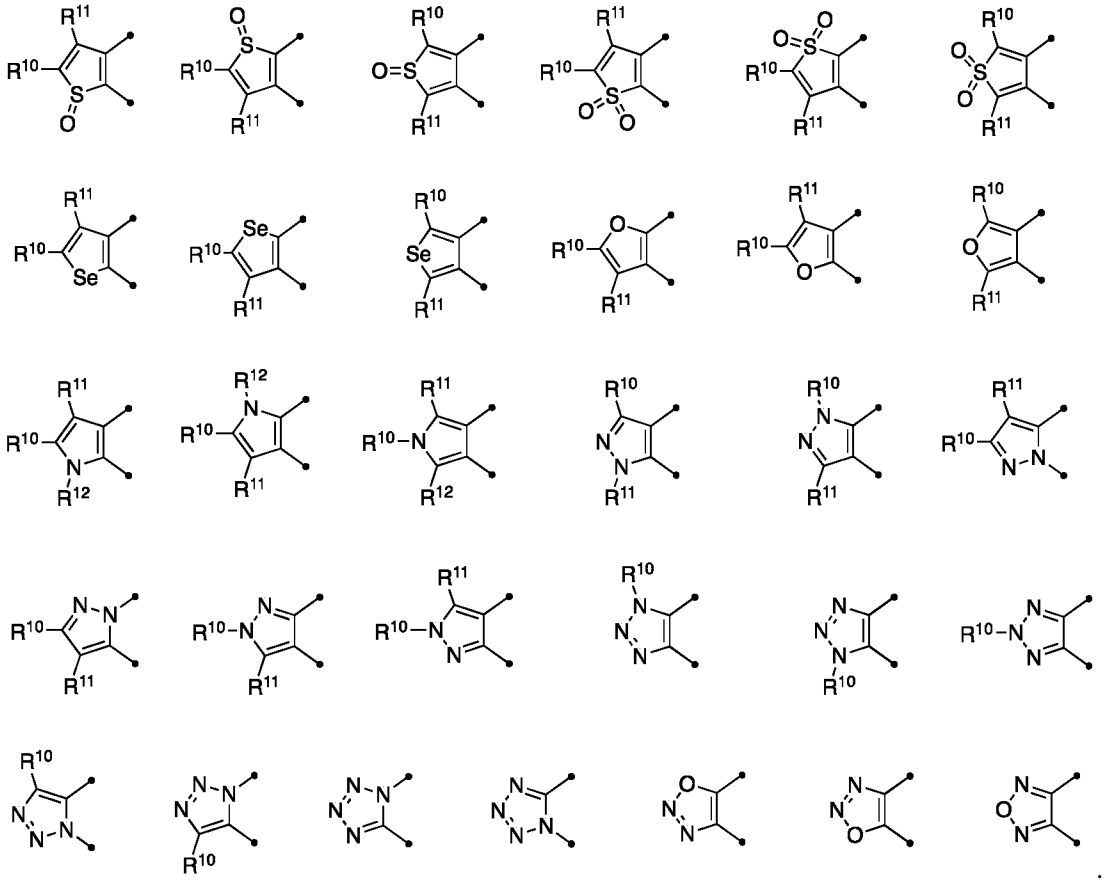
[029] In some embodiments, ring A is selected from 5-membered heteroaryl, wherein ring A is optionally substituted with one or more substituent groups.

[030] In some embodiments, R^2 is selected from substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[031] In some embodiments, ring A is selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl, wherein ring A is optionally substituted with one or more substituent groups.

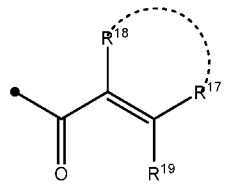
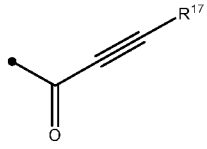
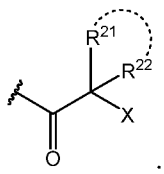
[032] In some embodiments, ring A is selected from





[033] In some embodiments, R^2 is selected from substituted or unsubstituted phenyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted 5- or 6-membered heteroaryl.

[034] In some embodiments, R^2 is selected from substituted or unsubstituted phenyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl and substituted or unsubstituted pyridyl.

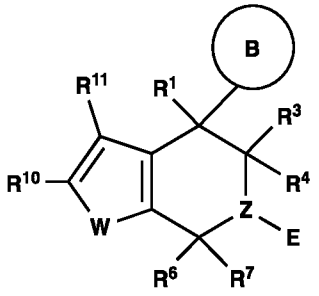
[035] In some embodiments, E is  ,  or  .

[036] In some embodiments, E is selected from -C(=O)CH=CH_2, -C(=O)-ethynyl, -C(=O)CH=$CHCF_3$, -C(=O)CH=$CHCHF_2$, -C(=O)CH=$CHCH_2F$, 4-(dimethylamino)but-2-en-1-one and -C(=O)CH_2Br.

[037] In some embodiments, M is CR^3R^4.

[038] In some embodiments, Y is CR^6R^7.

[039] Non-limiting examples of compounds of the disclosure include compounds of the following formula



(VIII)

wherein

Z is N, or CR^9;

W is selected from NR^{12}, O, S, S=O, O=S=O, and Se;

ring B is selected from

a) 5- or 6-membered cycloalkyl, saturated or partially saturated heterocyclyl,

b) 5- or 6-membered aryl or heteroaryl,

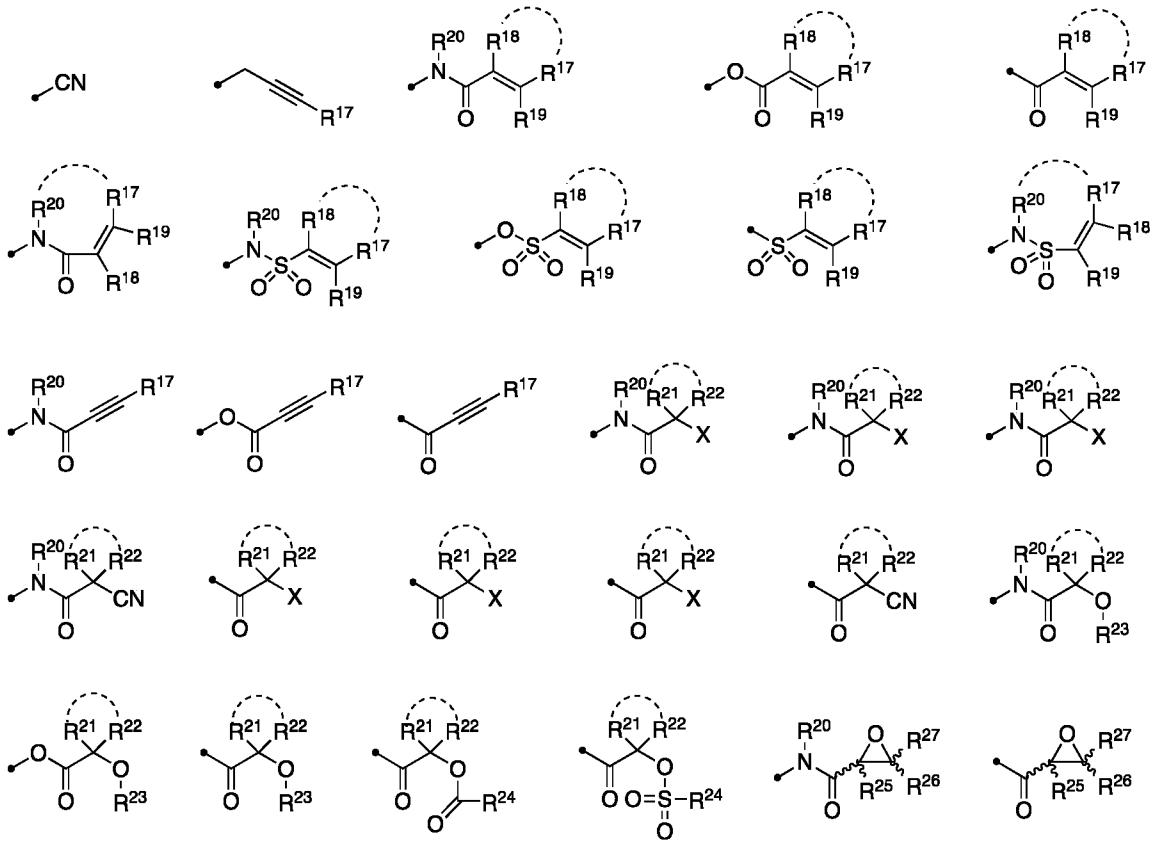
c) 9-, 10- or 11-membered fused partially saturated heterocyclyl,

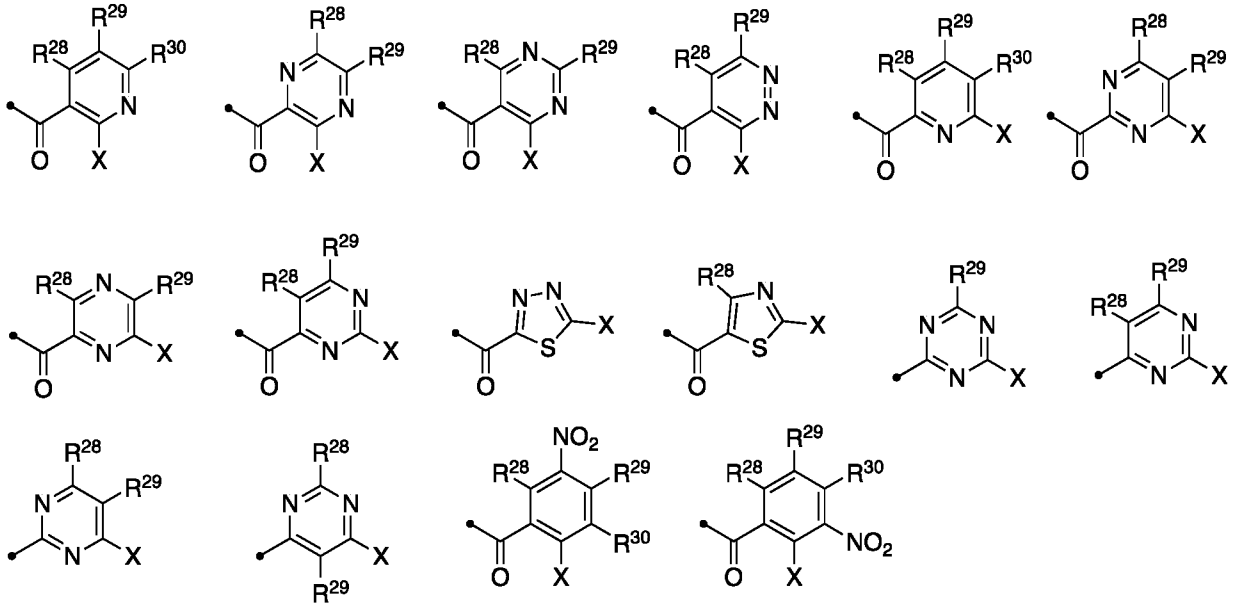
d) 9- or 10-membered fused heteroaryl,

e) naphthyl, and

f) 4-, 5- or 6-membered cycloalkenyl;

E is selected from an electrophilic moiety, selected from





;

R^1 is selected from hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-NHNR^{1A}R^{1B}$, $-C(O)R^{1A}$, $-C(O)$-OR^{1A}, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHNR^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$, $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, rand substituted or unsubstituted heteroaryl;

R^3 is selected from hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHNR^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)$-OR^{3A}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, 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;

R^4 is selected from hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHNR^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)$-OR^{4A}, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHNR^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, 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; R^3 and R^3 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^6 is selected from hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-NHNR^{6A}R^{6B}$, $-C(O)R^{6A}$, $-C(O)$-OR^{6A}, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHNR^{6A}R^{6B}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, 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;

R^7 is selected from hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHNR^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHNR^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, 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;

R^9 is selected from hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHNR^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHNR^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, 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;

R^{10} is selected from hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNR^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNR^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, 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;

R^{11} is selected from hydrogen, halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, -CN, $-SO_{n11}R^{11A}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-NHNR^{11A}R^{11B}$, $-C(O)R^{11A}$, $-C(O)-OR^{11A}$, $-C(O)NR^{11A}R^{11B}$, $-C(O)NHNR^{11A}R^{11B}$, $-OR^{11A}$, $-NR^{11A}SO_2R^{11B}$, $-NR^{11A}C(O)R^{11B}$, $-NR^{11A}C(O)OR^{11B}$, $-NR^{11A}OR^{11B}$, $-N_3$, 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;

R^{12} is selected from hydrogen, halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, -CN, $-SO_{n12}R^{12A}$, $-SO_{v12}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m12}$, $-NR^{12A}R^{12B}$, $-NHNR^{12A}R^{12B}$, $-C(O)R^{12A}$, $-C(O)-OR^{12A}$, $-C(O)NR^{12A}R^{12B}$, $-C(O)NHNR^{12A}R^{12B}$, $-OR^{12A}$, $-NR^{12A}SO_2R^{12B}$, $-NR^{12A}C(O)R^{12B}$, $-NR^{12A}C(O)OR^{12B}$, $-NR^{12A}OR^{12B}$, $-N_3$, 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;

R^{17} is selected from hydrogen, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-CH_2X^{17}$, $-OCX^{17}_3$, $-OCH_2X^{17}$, $-OCHX^{17}_2$, -CN, $-SO_{n17}R^{17A}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-C(O)R^{17A}$, $-C(O)$-OR^{17A}, $-C(O)NR^{17A}R^{17B}$, $-C(O)NHNR^{17A}R^{17B}$, $-OR^{17A}$, $-NR^{17A}SO_2R^{17B}$, $-NR^{17A}C(O)R^{17B}$, $-NR^{17A}C(O)OR^{17B}$, $-NR^{17A}OR^{17B}$, $-N_3$, 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;

R^{18} is selected from hydrogen, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-OCX^{18}_3$, $-OCH_2X^{18}$, $-OCHX^{18}_2$, -CN, $-SO_{n18}R^{18A}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-NHNR^{18A}R^{18B}$, $-C(O)R^{18A}$, $-C(O)$-OR^{18A}, $-C(O)NR^{18A}R^{18B}$, $-C(O)NHNR^{18A}R^{18B}$, $-OR^{18A}$, $-NR^{18A}SO_2R^{18B}$, $-NR^{18A}C(O)R^{18B}$, $-NR^{18A}C(O)OR^{18B}$, $-NR^{18A}OR^{18B}$, $-N_3$, 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; R^{16} and R^{18} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{19} is selected from hydrogen, halogen, $-CX^{19}_3$, $-CHX^{19}_2$, $-CH_2X^{19}$, $-OCX^{19}_3$, $-OCH_2X^{19}$, $-OCHX^{19}_2$, -CN, $-SO_{n19}R^{19A}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-NHNR^{19A}R^{19B}$, $-C(O)R^{19A}$, $-C(O)$-OR^{19A}, $-C(O)NR^{19A}R^{19B}$, $-C(O)NHNR^{19A}R^{19B}$, $-OR^{19A}$, $-NR^{19A}SO_2R^{19B}$, $-NR^{19A}C(O)R^{19B}$, $-NR^{19A}C(O)OR^{19B}$, $-NR^{19A}OR^{19B}$, $-N_3$, 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; R^{16} and R^{19} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{20} is selected from hydrogen, halogen, $-CX^{20}_3$, $-CHX^{20}_2$, $-CH_2X^{20}$, $-OCX^{20}_3$, $-OCH_2X^{20}$, $-OCHX^{20}_2$, -CN, $-SO_{n20}R^{20A}$, $-SO_{v20}NR^{20A}R^{20B}$, $-NHC(O)NR^{20A}R^{20B}$, $-N(O)_{m20}$, $-NR^{20A}R^{20B}$, $-NHNR^{20A}R^{20B}$, $-C(O)R^{20A}$, $-C(O)$-OR^{20A}, $-C(O)NR^{20A}R^{20B}$, $-C(O)NHNR^{20A}R^{20B}$, $-OR^{20A}$, $-NR^{20A}SO_2R^{20B}$, $-NR^{20A}C(O)R^{20B}$, $-NR^{20A}C(O)OR^{20B}$, $-NR^{20A}OR^{20B}$, $-N_3$, 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;

R^{21} is selected from hydrogen, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, -CN, $-SO_{n21}R^{21A}$, $-SO_{v21}NR^{21A}R^{21B}$, $-NHC(O)NR^{21A}R^{21B}$, $-N(O)_{m21}$, $-NR^{21A}R^{21B}$, $-NHNR^{21A}R^{21B}$, $-C(O)R^{21A}$, $-C(O)$-OR^{21A}, $-C(O)NR^{21A}R^{21B}$, $-C(O)NHNR^{21A}R^{21B}$, $-OR^{21A}$, $-NR^{21A}SO_2R^{21B}$, $-NR^{21A}C(O)R^{21B}$, $-NR^{21A}C(O)OR^{21B}$, $-NR^{21A}OR^{21B}$, $-N_3$, 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; R^{20} and R^{21} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{22} is selected from hydrogen, halogen, $-CX^{22}_3$, $-CHX^{22}_2$, $-CH_2X^{22}$, $-OCX^{22}_3$, $-OCH_2X^{22}$, $-OCHX^{22}_2$, -CN, $-SO_{n22}R^{22A}$, $-SO_{v22}NR^{22A}R^{22B}$, $-NHC(O)NR^{22A}R^{22B}$, $-N(O)_{m22}$, $-NR^{22A}R^{22B}$, $-NHNR^{22A}R^{22B}$, $-C(O)R^{22A}$, $-C(O)\text{-}OR^{22A}$, $-C(O)NR^{22A}R^{22B}$, $-C(O)NHNR^{22A}R^{22B}$, $-OR^{22A}$, $-NR^{22A}SO_2R^{22B}$, $-NR^{22A}C(O)R^{22B}$, $-NR^{22A}C(O)OR^{22B}$, $-NR^{22A}OR^{22B}$, $-N_3$, 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;

R^{23} is selected from hydrogen, halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-CH_2X^{23}$, $-OCX^{23}_3$, $-OCH_2X^{23}$, $-OCHX^{23}_2$, -CN, $-SO_{n23}R^{23A}$, $-SO_{v23}NR^{23A}R^{23B}$, $-NHC(O)NR^{23A}R^{23B}$, $-N(O)_{m23}$, $-NR^{23A}R^{23B}$, $-NHNR^{23A}R^{23B}$, $-C(O)R^{23A}$, $-C(O)\text{-}OR^{23A}$, $-C(O)NR^{23A}R^{23B}$, $-C(O)NHNR^{23A}R^{23B}$, $-OR^{23A}$, $-NR^{23A}SO_2R^{23B}$, $-NR^{23A}C(O)R^{23B}$, $-NR^{23A}C(O)OR^{23B}$, $-NR^{23A}OR^{23B}$, $-N_3$, 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;

R^{24} is selected from hydrogen, halogen, $-CX^{24}_3$, $-CHX^{24}_2$, $-CH_2X^{24}$, $-OCX^{24}_3$, $-OCH_2X^{24}$, $-OCHX^{24}_2$, -CN, $-SO_{n24}R^{24A}$, $-SO_{v24}NR^{24A}R^{24B}$, $-NHC(O)NR^{24A}R^{24B}$, $-N(O)_{m24}$, $-NR^{24A}R^{24B}$, $-NHNR^{24A}R^{24B}$, $-C(O)R^{24A}$, $-C(O)\text{-}OR^{24A}$, $-C(O)NR^{24A}R^{24B}$, $-C(O)NHNR^{24A}R^{24B}$, $-OR^{24A}$, $-NR^{24A}SO_2R^{24B}$, $-NR^{24A}C(O)R^{24B}$, $-NR^{24A}C(O)OR^{24B}$, $-NR^{24A}OR^{24B}$, $-N_3$, 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;

R^{25} is selected from hydrogen, halogen, $-CX^{25}_3$, $-CHX^{25}_2$, $-CH_2X^{25}$, $-OCX^{25}_3$, $-OCH_2X^{25}$, $-OCHX^{25}_2$, -CN, $-SO_{n25}R^{25A}$, $-SO_{v25}NR^{25A}R^{25B}$, $-NHC(O)NR^{25A}R^{25B}$, $-N(O)_{m25}$, $-NR^{25A}R^{25B}$, $-NHNR^{25A}R^{25B}$, $-C(O)R^{25A}$, $-C(O)\text{-}OR^{25A}$, $-C(O)NR^{25A}R^{25B}$, $-C(O)NHNR^{25A}R^{25B}$, $-OR^{25A}$, $-NR^{25A}SO_2R^{25B}$, $-NR^{25A}C(O)R^{25B}$, $-NR^{25A}C(O)OR^{25B}$, $-NR^{25A}OR^{25B}$, $-N_3$, 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;

R^{26} is selected from hydrogen, halogen, $-CX^{26}_3$, $-CHX^{26}_2$, $-CH_2X^{26}$, $-OCX^{26}_3$, $-OCH_2X^{26}$, $-OCHX^{26}_2$, -CN, $-SO_{n26}R^{26A}$, $-SO_{v26}NR^{26A}R^{26B}$, $-NHC(O)NR^{26A}R^{26B}$, $-N(O)_{m26}$, $-NR^{26A}R^{26B}$, $-NHNR^{26A}R^{26B}$, $-C(O)R^{26A}$, $-C(O)\text{-}OR^{26A}$, $-C(O)NR^{26A}R^{26B}$, $-C(O)NHNR^{26A}R^{26B}$, $-OR^{26A}$, $-NR^{26A}SO_2R^{26B}$, $-NR^{26A}C(O)R^{26B}$, $-NR^{26A}C(O)OR^{26B}$, $-NR^{26A}OR^{26B}$, $-N_3$, 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;

R^{27} is selected from hydrogen, halogen, $-CX^{27}_3$, $-CHX^{27}_2$, $-CH_2X^{27}$, $-OCX^{27}_3$, $-OCH_2X^{27}$, $-OCHX^{27}_2$, -CN, $-SO_{n27}R^{27A}$, $-SO_{v27}NR^{27A}R^{27B}$, $-NHC(O)NR^{27A}R^{27B}$, $-N(O)_{m27}$, $-NR^{27A}R^{27B}$, $-NHNR^{27A}R^{27B}$, $-C(O)R^{27A}$, $-C(O)\text{-}OR^{27A}$, $-C(O)NR^{27A}R^{27B}$,

$-C(O)NHNR^{27A}R^{27B}$, $-OR^{27A}$, $-NR^{27A}SO_2R^{27B}$, $-NR^{27A}C(O)R^{27B}$, $-NR^{27A}C(O)OR^{27B}$, $-NR^{27A}OR^{27B}$, $-N_3$, 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;

R^{28} is selected from hydrogen, halogen, $-CX^{28}_3$, $-CHX^{28}_2$, $-CH_2X^{28}$, $-OCX^{28}_3$, $-OCH_2X^{28}$, $-OCHX^{28}_2$, -CN, $-SO_{n28}R^{28A}$, $-SO_{v28}NR^{28A}R^{28B}$, $-NHC(O)NR^{28A}R^{28B}$, $-N(O)_{m28}$, $-NR^{28A}R^{28B}$, $-NHNR^{28A}R^{28B}$, $-C(O)R^{28A}$, $-C(O)-OR^{28A}$, $-C(O)NR^{28A}R^{28B}$, $-C(O)NHNR^{28A}R^{28B}$, $-OR^{28A}$, $-NR^{28A}SO_2R^{28B}$, $-NR^{28A}C(O)R^{28B}$, $-NR^{28A}C(O)OR^{28B}$, $-NR^{28A}OR^{28B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted and unsubstituted heteroaryl;

R^{29} is selected from hydrogen, halogen, $-CX^{29}_3$, $-CHX^{29}_2$, $-CH_2X^{29}$, $-OCX^{29}_3$, $-OCH_2X^{29}$, $-OCHX^{29}_2$, -CN, $-SO_{n29}R^{29A}$, $-SO_{v29}NR^{29A}R^{29B}$, $-NHC(O)NR^{29A}R^{29B}$, $-N(O)_{m29}$, $-NR^{29A}R^{29B}$, $-NHNR^{29A}R^{29B}$, $-C(O)R^{29A}$, $-C(O)-OR^{29A}$, $-C(O)NR^{29A}R^{29B}$, $-C(O)NHNR^{29A}R^{29B}$, $-OR^{29A}$, $-NR^{29A}SO_2R^{29B}$, $-NR^{29A}C(O)R^{29B}$, $-NR^{29A}C(O)OR^{29B}$, $-NR^{29A}OR^{29B}$, $-N_3$, 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;

R^{30} is selected from hydrogen, halogen, $-CX^{30}_3$, $-CHX^{30}_2$, $-CH_2X^{30}$, $-OCX^{30}_3$, $-OCH_2X^{30}$, $-OCHX^{30}_2$, -CN, $-SO_{n30}R^{30A}$, $-SO_{v30}NR^{30A}R^{30B}$, $-NHC(O)NR^{30A}R^{30B}$, $-N(O)_{m30}$, $-NR^{30A}R^{30B}$, $-NHNR^{30A}R^{30B}$, $-C(O)R^{30A}$, $-C(O)-OR^{30A}$, $-C(O)NR^{30A}R^{30B}$, $-C(O)NHNR^{30A}R^{30B}$, $-OR^{30A}$, $-NR^{30A}SO_2R^{30B}$, $-NR^{30A}C(O)R^{30B}$, $-NR^{30A}C(O)OR^{30B}$, $-NR^{30A}OR^{30B}$, $-N_3$, 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;

R^{31} is selected from hydrogen, halogen, $-CX^{31}_3$, $-CHX^{31}_2$, $-CH_2X^{31}$, $-OCX^{31}_3$, $-OCH_2X^{31}$, $-OCHX^{31}_2$, -CN, $-SO_{n31}R^{31A}$, $-SO_{v31}NR^{31A}R^{31B}$, $-NHC(O)NR^{31A}R^{31B}$, $-N(O)_{m31}$, $-NR^{31A}R^{31B}$, $-NHNR^{31A}R^{31B}$, $-C(O)R^{31A}$, $-C(O)-OR^{31A}$, $-C(O)NR^{31A}R^{31B}$, $-C(O)NHNR^{31A}R^{31B}$, $-OR^{31A}$, $-NR^{31A}SO_2R^{31B}$, $-NR^{31A}C(O)R^{31B}$, $-NR^{31A}C(O)OR^{31B}$, $-NR^{31A}OR^{31B}$, $-N_3$, 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;

R^{32} is selected from hydrogen, halogen, $-CX^{32}_3$, $-CHX^{32}_2$, $-CH_2X^{32}$, $-OCX^{32}_3$, $-OCH_2X^{32}$, $-OCHX^{32}_2$, -CN, $-SO_{n32}R^{32A}$, $-SO_{v32}NR^{32A}R^{32B}$, $-NHC(O)NR^{32A}R^{32B}$, $-N(O)_{m32}$, $-NR^{32A}R^{32B}$, $-NHNR^{32A}R^{32B}$, $-C(O)R^{32A}$, $-C(O)-OR^{32A}$, $-C(O)NR^{32A}R^{32B}$, $-C(O)NHNR^{32A}R^{32B}$, $-OR^{32A}$, $-NR^{32A}SO_2R^{32B}$, $-NR^{32A}C(O)R^{32B}$, $-NR^{32A}C(O)OR^{32B}$, $-NR^{32A}OR^{32B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted

or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted and unsubstituted heteroaryl;

R^{33} is selected from hydrogen, halogen, $-CX^{33}_3$, $-CHX^{33}_2$, $-CH_2X^{33}$, $-OCX^{33}_3$, $-OCH_2X^{33}$, $-OCHX^{33}_2$, -CN, $-SO_{n33}R^{33A}$, $-SO_{v33}NR^{33A}R^{33B}$, $-NHC(O)NR^{33A}R^{33B}$, $-N(O)_{m33}$, $-NR^{33A}R^{33B}$, $-NHNR^{33A}R^{33B}$, $-C(O)R^{33A}$, $-C(O)-OR^{33A}$, $-C(O)NR^{33A}R^{33B}$, $-C(O)NHNR^{33A}R^{33B}$, $-OR^{33A}$, $-NR^{33A}SO_2R^{33B}$, $-NR^{33A}C(O)R^{33B}$, $-NR^{33A}C(O)OR^{33B}$, $-NR^{33A}OR^{33B}$, $-N_3$, 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;

R^{34} is selected from hydrogen, halogen, $-CX^{34}_3$, $-CHX^{34}_2$, $-CH_2X^{34}$, $-OCX^{34}_3$, $-OCH_2X^{34}$, $-OCHX^{34}_2$, -CN, $-SO_{n34}R^{34A}$, $-SO_{v34}NR^{34A}R^{34B}$, $-NHC(O)NR^{34A}R^{34B}$, $-N(O)_{m34}$, $-NR^{34A}R^{34B}$, $-NHNR^{34A}R^{34B}$, $-C(O)R^{34A}$, $-C(O)-OR^{34A}$, $-C(O)NR^{34A}R^{34B}$, $-C(O)NHNR^{34A}R^{34B}$, $-OR^{34A}$, $-NR^{34A}SO_2R^{34B}$, $-NR^{34A}C(O)R^{34B}$, $-NR^{34A}C(O)OR^{34B}$, $-NR^{34A}OR^{34B}$, $-N_3$, 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;

R^{35} is selected from hydrogen, halogen, $-CX^{35}_3$, $-CHX^{35}_2$, $-CH_2X^{35}$, $-OCX^{35}_3$, $-OCH_2X^{35}$, $-OCHX^{35}_2$, -CN, $-SO_{n35}R^{35A}$, $-SO_{v35}NR^{35A}R^{35B}$, $-NHC(O)NR^{35A}R^{35B}$, $-N(O)_{m35}$, $-NR^{35A}R^{35B}$, $-NHNR^{35A}R^{35B}$, $-C(O)R^{35A}$, $-C(O)-OR^{35A}$, $-C(O)NR^{35A}R^{35B}$, $-C(O)NHNR^{35A}R^{35B}$, $-OR^{35A}$, $-NR^{35A}SO_2R^{35B}$, $-NR^{35A}C(O)R^{35B}$, $-NR^{35A}C(O)OR^{35B}$, $-NR^{35A}OR^{35B}$, $-N_3$, 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;

Each R^{1A}, R^{1B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{6A}, R^{6B}, R^{7A}, R^{7B}, R^{9A}, R^{9B}, R^{10A}, R^{10B}, R^{11A}, R^{11B}, R^{17A}, R^{17B}, R^{18A}, R^{18B}, R^{19A}, R^{19B}, R^{20A}, R^{20B}, R^{21A}, R^{21B}, R^{22A}, R^{22B}, R^{23A}, R^{23B}, R^{24A}, R^{24B}, R^{25A}, R^{25B}, R^{26A}, R^{26B}, R^{27A}, R^{27B}, R^{28A}, R^{28B}, R^{29A}, R^{29B}, R^{30A}, R^{30B}, R^{31A}, R^{31B}, R^{32A}, R^{32B}, R^{33A}, R^{33B}, R^{34A}, R^{34B}, R^{35A}, R^{35B}, is independently selected from hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, -C(O)OH, $-C(O)NH_2$, -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, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, 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^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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^{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; R^{13A} and R^{13B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{14A} and R^{14B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{20A} and R^{20B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{21A} and R^{21B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{22A} and R^{22B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{23A} and R^{23B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{24A} and R^{24B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{25A} and R^{25B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{26A} and R^{26B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{27A} and R^{27B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{28A} and R^{28B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{29A} and R^{29B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{30A} and R^{30B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

Each m1, m3, m4, m6, m7, m9, m10, m11, m17, m18, m19, m20, m21, m22, m23, m24, m25, m26, m27, m28, m29, m30, m31, m32, m33, m34 and m35 is independently 1 or 2;

Each v1, v3, v4, v6, v7, v9, v10, v11, v17, v18, v19, v20, v21, v22, v23, v24, v25, v26, v27, v28, v29, v30, v31, v32, v33, v34 and v35 is independently 1 or 2;

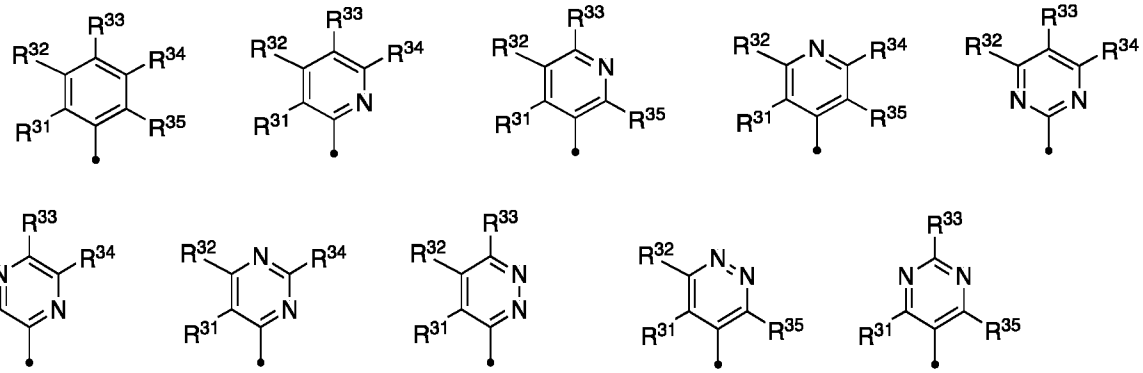
Each n1, n3, n4, n6, n7, n9, n10, n11, n17, n18, n19, n20, n21, n22, n23, n24, n25, n26, n27, n28, n29, n30, n31, n32, n33, n34 and n35 is independently an integer from 0 to 2; and

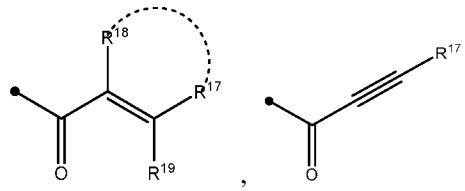
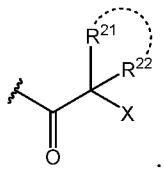
Each X^1, X^3, X^4, X^6, X^7, X^9, X^{10}, X^{11}, X^{17}, X^{18}, X^{19}, X^{20}, X^{21}, X^{22}, X^{23}, X^{24}, X^{25}, X^{26}, X^{27}, X^{28}, X^{29}, X^{30}, X^{31}, X^{32}, X^{33}, X^{34}, and X^{35} is independently -Cl, -Br, -I or –F.

[040] In some embodiments, ring B is selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl, wherein Ring B is optionally substituted with one or more substituents.

[041] In some embodiments, ring B is selected from phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl, wherein ring B is optionally substituted with one or more substituent groups.

[042] In some embodiments, ring B is selected from



[043] In some embodiments, E is  , , or  .

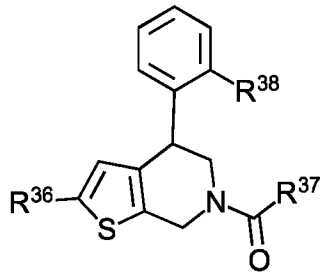
[044] In some embodiments, E is selected from -C(=O)CH=CH_2, -C(=O)-ethynyl, -C(=O)CH=$CHCF_3$, -C(=O)CH=$CHCHF_2$, -C(=O)CH=$CHCH_2F$, 4-(dimethylamino)but-2-en-1-one and -C(=O)CH_2Br.

[045] In some embodiments, W is S.

[046] In some embodiments, R^{10} is selected from hydrogen, fluoro, chloro, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, substituted or unsubstituted 6-10 membered aryl, and substituted or unsubstituted 5-10 membered heteroaryl; and R^{11} is selected from hydrogen, fluoro, chloro, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, substituted or unsubstituted 6-10 membered aryl, and substituted or unsubstituted 5-10 membered heteroaryl.

[047] Non-limiting examples of compounds of the disclosure include compounds of the following

formula



[XIA]

wherein R^{36} is H, halo, C_1-C_4 alkyl, C_2-C_4 alkenyl or C_3-C_6 cycloalkyl;

R^{37} is substituted or unsubstituted C_2-C_4 alkenyl or C_2-C_4 alkynyl; and

R^{38} is selected from substituted or unsubstituted nitrogen containing 5-membered heteroaryl, substituted or unsubstituted nitrogen containing 5- or 6- membered partially unsaturated heterocyclyl and substituted or unsubstituted nitrogen containing 6-10 membered heteroaryl; provided R^{38} is not 4-pyridyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof.

[048] In some embodiments, R^{38} is selected from substituted or unsubstituted nitrogen containing 5-membered heteroaryl selected from pyrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, thiazolyl, triazolyl and imidazolyl; substituted or unsubstituted nitrogen containing 6- membered heteroaryl selected from pyridinyl, pyrimidinyl and pyrazinyl; substituted or unsubstituted nitrogen containing 5-membered partially unsaturated heterocyclyl selected from pyrrolinyl, and imidazolidinyl; and substituted or unsubstituted dihydropyridinyl.

[049] In some embodiments, R^{36} is selected from chloro, methyl, ethyl, isopropyl, allylyl, and cyclopropyl;.

[050] In some embodiments, R^{38} is selected from substituted 5-pyrazolyl, substituted 4-pyrazolyl, substituted 1-pyrazolyl, substituted or unsubstituted 4-isoxazolyl, substituted or unsubstituted 4-isothiazolyl, substituted or unsubstituted 3-pyrrolyl, substituted or unsubstituted 5-thiazolyl, substituted or unsubstituted 5-imidazolyl, substituted or unsubstituted 1-imidazolyl, substituted or unsubstituted [1,2,4]triazol-5-yl, substituted or unsubstituted 3-pyridyl, and substituted or unsubstituted 5-pyrimidinyl.

[051] In some embodiments, R^{38} is selected from 3-trifluoromethyl-pyrazol-4-yl, 1-isopropyl-3-trifluoromethyl-pyrazol-4-yl, 1-ethyl-3-trifluoromethyl-pyrazol-4-yl, 1-methyl-3-difluoromethyl-pyrazol-4-yl, 1-butyl-3-trifluoromethyl-pyrazol-4-yl, 1-methoxymethyl-3-trifluoromethyl-pyrazol-4-yl, 1-propyl-3-trifluoromethyl-pyrazol-4-yl, 1,3-dimethyl-pyrazol-4-yl, 1,3,5-trimethyl-pyrazol-4-yl, 1-methyl-3-cyclopropyl-pyrazol-4-yl, 1-methyl-3-trifluoromethyl-pyrazol-4-yl, 1-ethyl-3-amino-pyrazol-4-yl, 1-ethyl-3-methoxy-pyrazol-4-yl, 1-hydroxyethyl-3-trifluoromethyl-pyrazol-4-yl, 1-[2-hydroxypropyl]-3-trifluoromethyl-pyrazol-4-yl, 1-[2-hydroxyisobutyl]-3-trifluoromethyl-pyrazol-4-yl, 1-methoxyethyl-3-trifluoromethyl-pyrazol-4-yl, 1-[N,N-dimethylaminoethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-[N-methylaminocarbonylmethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-[N-methylaminocarbonylethyl]-3-

trifluoromethyl-pyrazol-4-yl, 1-[N,N-dimethylaminocarbonylmethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-aminocarbonylmethyl-3-trifluoromethyl-pyrazol-4-yl, 1-methylcarbonylaminoethyl-3-trifluoromethyl-pyrazol-4-yl, 1-methylcarbonylaminobutyl-3-trifluoromethyl-pyrazol-4-yl, 1-aminocarbonylethyl-3-trifluoromethyl-pyrazol-4-yl, 1-aminocarbonylpropyl-3-trifluoromethyl-pyrazol-4-yl, 1-aminocarbonylisopropyl-3-trifluoromethyl-pyrazol-4-yl, 1-cyanopropyl-3-trifluoromethyl-pyrazol-4-yl, 1-[N,N-dimethylaminocarbonylethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-carboxyethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-carboxymethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-methoxycarbonylmethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-ethyl-3-carboxy-pyrazol-4-yl, 1-ethyl-5-carboxy-pyrazol-4-yl, 1-ethyl-3-methylaminocarbonyl-pyrazol-4-yl, 1-ethyl-3-[N,N-dimethylaminocarbonyl]-pyrazol-4-yl, 1-ethyl-5-methylaminocarbonyl-pyrazol-4-yl, 1-ethyl-5-[N,N-dimethylaminocarbonyl]-pyrazol-4-yl, 1-benzyl-3-methyl-pyrazol-4-yl, 1-(cyclopropylmethyl)-3-trifluoromethyl-pyrazol-4-yl, 1-cyclopropyl-3-trifluoromethyl-pyrazol-4-yl, 1-[1-methylazetidin-3-yl]-3-trifluoromethyl-pyrazol-4-yl, 1-[1-methylpyrrolidin-3-yl]-3-trifluoromethyl-pyrazol-4-yl, 1-[1-methylpiperidin-3-yl]-3-trifluoromethyl-pyrazol-4-yl, 1-[1-methylpiperidin-4-yl]-3-trifluoromethyl-pyrazol-4-yl, 1-(3-pyridinylmethyl)-3-methyl-pyrazol-4-yl, 1-(2-pyridinylmethyl)-3-methyl-pyrazol-4-yl, 1-[2-pyridyl]-3-methyl-pyrazol-4-yl, 1-methyl-5-pyrazolyl, 1-ethyl-5-trifluoromethylpyrazol-4-yl, 1,3-dimethyl-5-pyrazolyl, 1-methyl-3-cyclopropyl-pyrazol-5-yl, 1-methyl-4-pyrazolyl, 1-ethyl-3-methylpyrazol-4-yl, 1,5-dimethyl-4-pyrazolyl, 1,3,5-trimethyl-4-pyrazolyl, 1-methyl-3-pyrazolyl, 4-methyl-3-pyrazolyl, 1-methyl-[1,2,4]triazol-3-yl, 4-bromo-2-methyl-[1,2,4]triazol-5-yl, 4-bromo-2-ethyl-[1,2,4]triazol-5-yl, 1-methyl-[1,2,4]triazol-5-yl, 4-isothiazolyl, 4-methyl-2-oxazolyl, isoxazol-4-yl, 2,4-dimethylthiazol-5-yl, 3,5-dimethylisoxazol-4-yl, 2-methyl-5-thiazolyl and 4-methyl-5-thiazolyl.

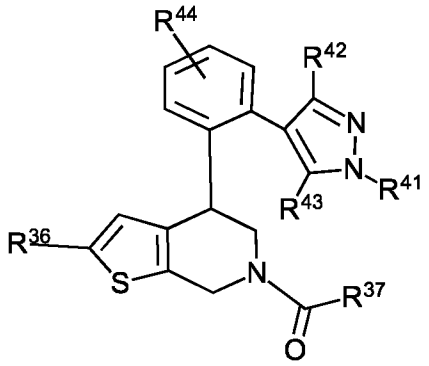
[052] In some embodiments, R^{38} is selected from 5-pyrimidinyl, 2-methyl-5-pyrimidinyl, 4-methyl-5-pyrimidinyl, 4,6-dimethoxy-5-pyrimidinyl, 4,6-dimethyl-5-pyrimidinyl, 4-triflouromethyl-5-pyrimidinyl, 4-pyrimidinyl, 2-methyl-4-pyrimidinyl, 4-methyl-6-pyrimidinyl, 2,4-dimethyl-6-pyrimidinyl, 3-pyridinyl, 2-pyridinyl, 4-methyl-2-pyridinyl, 2-triflouromethyl-3-pyridinyl, 4-triflouromethyl-3-pyridinyl, 2-methyl-3-pyridinyl, 2,5-dimethyl-3-pyridinyl, 2,6-dimethyl-3-pyridinyl, 2,4-dimethyl-3-pyridinyl, 2-ethyl-3-pyridinyl, 5-methyl-3-pyridinyl, 2-ethoxy-3-pyridinyl, 2-ethoxy-5-methyl-3-pyridinyl, 2-methoxy-3-pyridinyl, 2-methoxy-6-methyl-3-pyridinyl, 2-ethoxy-6-methyl-3-pyridinyl, 2-isopropoxy-3-pyridinyl, 2-(3-pentoxy)-3-pyridinyl, 2-methoxyethoxy-3-pyridinyl, 2-cyclopropoxy-3-pyridinyl, 2-cyclopentyloxy-3-pyridinyl, 2-cyclohexloxy-3-pyridinyl, 2-fluoro-3-pyridinyl, 2-chloro-3-pyridinyl, 2-phenyl-3-pyridinyl, 2-flouro-3-methyl-5-pyridinyl, 2-flouro-3-chloro-5-pyridinyl, 3-fluoro-5-pyridinyl, 3-chloro-5-pyridinyl, 2-chloro-4-methyl-5-pyridinyl, 2-methoxy-5-pyridinyl, 3-methoxy-5-pyridinyl, 2-ethoxy-5-pyridinyl, 3-ethoxy-5-pyridinyl, 3-triflouromethyl-5-pyridinyl, 3-ethyl-5-pyridinyl, 2,3-dimethyl-5-pyridinyl, 2-(2-hydroxymethylpyrrolidin-1-yl)-5-pyridinyl, 2-(morpholin-1-yl)-3-chloro-5-pyridinyl, 2-(dimethylaminoethoxy)-5-pyridinyl, 2-(2-dimethylaminomethylpyrrolidin-1-yl)-5-pyridinyl, 2-phenyl-5-pyridinyl, 2-methyl-6-pyridinyl, 2,4-dimethyl-6-pyridinyl and 2-ethyl-6-pyridinyl.

[053] In some embodiments, R^{38} is selected from substituted or unsubstituted tetrahydroquinolinyl, substituted or unsubstituted 1-pyrrolin-3-yl, substituted or unsubstituted 1-imidazolidinyl, and substituted or unsubstituted dihydropyridin-3-yl.

[054] In some embodiments, R^{38} is selected from 4-isoquinolinyl, 1-methoxy-4-isoquinolinyl, 1-chloro-4-isoquinolinyl, 6-methyl-4-isoquinolinyl, 1-oxo-2-methyl-4-isoquinolinyl, 3-quinolinyl, 4-quinolinyl, 5-pyrrolopyridinyl, [1,3,3a]-triazainden-5-yl, 1-ethyl-3-pyrrolopyridinyl, and 1-methyl-5-pyrrolopyridinyl.

[055] In some embodiments, R^{37} is selected from ethenyl, fluoroethenyl, propynyl, dialkylaminopropenyl, alkylaminopropenyl, aminopropenyl and nitrogen-containing heterocyclyl-propenyl.

[056] Non-limiting examples of compounds of the disclosure include compounds of the following formula



XIV

wherein R^{36} is selected from H, halo, C_1-C_4 alkyl, C_2-C_4 alkenyl and C_3-C_6 cycloalkyl;

R^{37} is substituted or unsubstituted C_2-C_4 alkenyl, or C_2-C_4 alkynyl; and

R^{41} is selected from H, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylamino-C_{1-6} alkyl, C_{1-6} alkylaminocarbonyl-C_{1-6} alkyl, aminocarbonyl-C_{1-6} alkyl, C_{1-6} alkoxycarbonyl-C_{1-6} alkyl, carboxy-C_{1-6} alkyl, C_{1-6} alkylcarbonylamino-C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, aryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heteroaryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heterocyclyl and substituted or unsubstituted 5 or 6 membered heteroaryl;

R^{42} is selected from H, carboxy, amino, C_{1-6} alkyl, C_{1-3} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylaminocarbonyl, and C_{3-6} cycloalkyl;

R^{43} is selected from H, carboxy, C_{1-4} alkyl, C_{1-3} haloalkyl, and C_{1-6} alkylaminocarbonyl; or an isomer or stereoisomer of any of the foregoing, and

R^{44} is one or more substituents selected from H, halo, alkoxy and hydroxy; or a mixture thereof or a pharmaceutically acceptable salt thereof.

[057] In one embodiment, R^{41} is selected from H, ethyl, isopropyl, butyl, propyl, methyl, D_3-methyl, 1-hydroxyethyl, 2-hydroxymethylethyl, 1-hydroxy-2,2-dimethylethyl, 2-hydroxypropyl, 2-hydroxy-2-

methylpropyl, methoxymethyl, methoxyethyl, dimethylaminoethyl, carboxymethyl, carboxyethyl, methoxycarbonylmethyl, dimethylaminocarbonylmethyl, dimethylaminocarbonylethyl, methylaminocarbonylethyl, methylaminocarbonylmethyl, aminocarbonylmethyl, aminocarbonylethyl, aminocarbonyl-1,1-dimethylmethyl, methylcarbonylaminoethyl, 1-methylcarbonylamino-2.2-dimethylethyl, 2-cyano-2-methylethyl, cyanomethyl, cyanoethyl, cyclopropyl, cyclopropylmethyl, benzyl, 3-pyridinylmethyl, 2-pyridinylmethyl, 4-oxazolylmethyl, oxadiazol-5-ylmethyl, 1-methylazetidin-3-yl, 1-methylpyrrolidin-3-yl, 1-methylpiperidin-4-yl, 1-methylpiperidin-3-yl, 3,5-difluoro-4-pyridyl, 3-chloro-4-pyridyl, 4-pyridyl and 2-pyridyl.

[058] In one embodiment, R^{36} is H, chloro, methyl, ethyl, isopropyl, propenyl, trifluoromethyl, 2-furyl, 2-pyridinyl, or cyclopropyl.

[059] In one embodiment, R^{37} is selected from ethenyl, fluoroethenyl, fluoropropenyl, propynyl, dialkylaminopropenyl, alkylaminopropenyl, aminopropenyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-ethenyl and substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-propenyl.

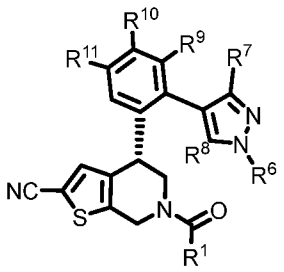
[060] In one embodiment, R^{37} is azetidin-1-ylpropenyl, 1-methylpyrrolidin-2-ylethenyl, dimethylaminopropenyl, methylaminopropenyl, piperidin-1-ylpropenyl, 4-hydroxy-piperidin-1-ylpropenyl, pyrrolidin-1-ylpropenyl, 3-hydroxypyrrolidin-1-ylpropenyl, morpholin-1-ylpropenyl, or aminopropenyl.

[061] In one embodiment, R^{42} is selected from H, trifluoromethyl, difluoromethyl, methyl, ethyl, methoxy, amino, dimethylamino, carboxy. methylaminocarbonyl, dimethylaminocarbonyl, and cyclopropyl.

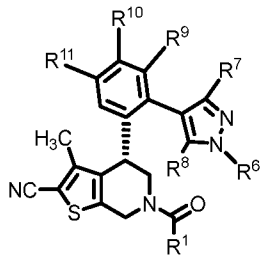
[062] In one embodiment, R^{43} is selected from H, trifluoromethyl, methyl, ethyl, carboxy, cyano and methylaminocarbonyl.

[063] In one embodiment, R^{44} is one or more substituents selected from H, hydroxy, fluoro and methoxyl.

[064] Non-limiting examples of compounds of the disclosure include compounds of any one of the following formulae



IV or



V

wherein

R^1 is substituted or unsubstituted C_2-C_6 alkenyl, or substituted or unsubstituted C_2-C_6 alkynyl;

R^6 is selected from H, C_{1-6} alkyl, C_{2-4} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylamino-C_{1-6} alkyl, C_{1-6} alkylaminocarbonyl-C_{1-6} alkyl, aminocarbonyl-C_{1-6} alkyl, C_{1-6} alkoxycarbonyl-C_{1-6} alkyl, carboxy-C_{1-6} alkyl, C_{1-6} alkylcarbonylamino-C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{1-6} alkylsulfonyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, aryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heteroaryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heterocyclyl and substituted or unsubstituted 5 or 6 membered heteroaryl;

R^7 is selected from H, carboxy, amino, C_{1-6} alkyl, C_{1-3} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylaminocarbonyl, and C_{3-6} cycloalkyl;

R^8 is selected from H, carboxy, cyano, C_{1-4} alkyl, C_{1-3} haloalkyl, and C_{1-6} alkylaminocarbonyl;

R^9 is selected from H, halo, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, amino, C_{1-3} alkylcarbonylamino, C_{1-3} alkylsulfonylamino, and C_{1-3} alkylaminocarbonylamino;

R^{10} is selected from H, halo, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, amino, C_{1-3} alkylcarbonylamino, C_{1-3} alkylsulfonylamino, and C_{1-3} alkylaminocarbonylamino; and

R^{11} is selected from H, halo, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, amino, C_{1-3} alkylcarbonylamino, C_{1-3} alkylsulfonylamino, and C_{1-3} alkylaminocarbonylamino;

or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[065] In some embodiments, R^1 is selected from C_2-C_6 alkenyl, halo-substituted C_2-C_6 alkenyl; alkoxy substituted C_2-C_6 alkenyl; dialkylamino substituted C_2-C_6 alkenyl, alkylamino substituted C_2-C_6 alkenyl, amino substituted C_2-C_6 alkenyl, hydroxy substituted amino-C_2-C_6 alkenyl, phenyl substituted amino-C_2-C_6 alkenyl, amino substituted C_2-C_6 alkynyl, dialkylamino substituted C_2-C_6 alkynyl, alkylamino substituted C_2-C_6 alkynyl, alkoxy substituted C_2-C_6 alkynyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl- substituted C_2-C_6 alkynyl, substituted or unsubstituted 3-7 membered cycloalkyl- substituted C_2-C_6 alkenyl, substituted or unsubstituted 3-7 membered oxygen-containing heterocyclyl- substituted C_2-C_6 alkenyl, substituted or unsubstituted 3-7 membered oxygen-containing heterocyclyl- substituted C_2-C_6 alkynyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl- substituted C_2-C_6 alkenyl, and substituted or unsubstituted 3-7 membered cycloalkyl-substituted C_2-C_6 alkynyl .

[066] In some embodiments, R^1 is selected from ethenyl, fluoropropenyl, 3,3-difluoropropenyl, 3,3,3-trifluoropropenyl, 3,3,3-trifluoroprop-1-enyl, alkoxypropenyl, dialkylaminopropenyl, alkylaminopropenyl, aminopropenyl, 3-amino-4-hydroxy-butenyl, 3-amino-4-phenyl-butenyl, dialkylaminobutenyl, alkylaminobutenyl, aminobutenyl, dialkylaminopentenyl, alkylaminopentenyl, aminopentenyl, aminopropynyl, dialkylaminopropynyl, alkylaminopropynyl, methoxypropynyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-propynyl, substituted or unsubstituted 3-7 membered cycloalkyl-ethenyl, substituted or unsubstituted 3-7 membered cycloalkyl-propenyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-ethynyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-propynyl, substituted or unsubstituted 3-7 membered oxygen-

containing heterocyclyl-ethenyl, substituted or unsubstituted 3-7 membered oxygen-containing heterocyclyl-propenyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-ethenyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-propenyl, substituted or unsubstituted 3-7 membered cycloalkyl-ethynyl, substituted or unsubstituted 3-7 membered cycloalkyl-propynyl, substituted or unsubstituted 3-7 membered cycloalkyl-ethynyl, and substituted or unsubstituted 3-7 membered cycloalkyl-propynyl.

[067] In some embodiments, R^1 is selected from ethenyl, fluoropropenyl, 3,3-difluoropropenyl, 3,3,3-trifluoropropenyl, 3,3,3-trifluoroprop-1-enyl, methoxypropenyl, ethoxypropenyl, aminopropenyl, 3-amino-butenyl, 3-methylamino-butenyl, 3-amino-4-hydroxy-butenyl, 3-methylamino-4-methoxy-butenyl, 3-amino-4-phenyl-butenyl, 3-amino-pentenyl, aminopropynyl, methoxypropynyl, dimethylaminopropenyl, di(d1,d2,d3-methyl)aminopropenyl, diethylaminopropenyl, 3-(N,N-dimethylamino)-3-phenyl-propenyl, 3-(N,N-dimethylamino)-3-cyclopropyl-propenyl, (cyclopropylamino)propenyl, bicyclo[1.1.1]pent-1-ylamino, (1-methylcyclopropylamino)propenyl, (3-methyloxetan-3-yl)aminopropenyl, (3-methyltetrahydrofur-3-yl)aminopropenyl, (4-methyl-tetrahydropyran-4-yl)aminopropenyl, methylaminopropenyl, N-benzyl-N-methylaminopropenyl, N-(tert-butyl)aminopropenyl, N-sec-butylaminopropenyl, N-butylaminopropenyl, N-(isopropyl)aminopropenyl, N-(d2-isopropyl)aminopropenyl, ethylaminopropenyl, N-[3,3-difluorocyclobutyl]aminopropenyl, 1-hydroxymethyl-1-methyl-ethylaminopropenyl, 3-dimethylamino-butenyl, 3-(N-methylamino)-butenyl, methylaminobutenyl, N,N-dimethylaminobutenyl, piperidin-2-ylpropenyl, pyrrolidin-1-ylpropenyl, 3-methyl-oxetan-3-ylpropenyl, 4-methyl-tetrahydropyran-4-ylpropenyl, piperidin-2-ylethenyl, pyrrolidin-2-ylethenyl, azetidin-2-ylethenyl, morpholin-3-ylethenyl, 1-methylpyrrolidin-2-ylethenyl, 3-methylpyrrolidin-5-ylethenyl, 3-ethylpyrrolidin-5-ylethenyl, 2-methylpyrrolidin-5-ylethenyl, 2,2-dimethylpyrrolidin-5-ylethenyl, 3-methoxypyrrolidin-5-ylethenyl, 3-fluoropyrrolidin-5-ylethenyl, 3,3-difluoropyrrolidin-5-ylethenyl, 5-azaspiro[2.4]heptan-6-ylethenyl, 2-azabicyclo[3.1.0]hexan-3-ylethenyl, 3,3-dimethylpyrrolidin-5-ylethenyl, 3-methylpyrrolidin-1-ylpropenyl, 2-methylpyrrolidin-1-ylpropenyl, 1-methylcarbonylpyrrolidin-3-ylethenyl, 2-carboxypyrrolidin-1-ylpropenyl, 3-carboxypyrrolidin-1-ylpropenyl, tetrahydrofur-3-ylpropenyl, dimethylaminopropynyl, methylaminopropynyl, 2-amino-2-methylbutynyl, 2-(1-amino-cyclopropyl)-ethynyl, 2-(1-amino-cyclobutyl)-ethynyl, 2-(1-amino-cyclopentyl)-ethynyl, azetidin-2-ylethynyl, pyrrolidin-2-ylethynyl, pyrrolidin-3-ylethynyl, 2-methyl-pyrrolidin-2-ylethynyl, 4-methyl-piperazin-1-ylpropynyl, and piperidin-3-ylethynyl.

[068] In some embodiments, R^6 is selected from H, ethyl, isopropyl, butyl, propyl, methyl, propynyl, 1-hydroxyethyl, 2-hydroxymethylethyl, 1-hydroxy-2,2-dimethylethyl, 2-hydroxypropyl, 2-hydroxy-2-methylpropyl, methoxymethyl, methoxyethyl, dimethylaminoethyl, carboxymethyl, carboxyethyl, carboxypropyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, ethoxycarbonylpropyl, dimethylaminocarbonylmethyl, dimethylaminocarbonyl-1-ethyl, methylaminocarbonyl-1-ethyl, methylaminocarbonylethyl, methylaminocarbonylmethyl, aminocarbonylmethyl, aminocarbonylethyl, 1-aminocarbonylethyl, aminocarbonyl-1,1-dimethylmethyl,

methylcarbonylaminoethyl, 1-methylcarbonylamino-2,2-dimethylethyl, 2-cyano-2-methylethyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methylsulfonyl, cyclopropyl, cyclopropylmethyl, benzyl, 4-pyridinylethyl, 2-pyridinylethyl, 3-pyridinylmethyl, 2-pyridinylmethyl, 4-oxazolylmethyl, 1,3,4-oxadiazol-2-yl]methyl, 1,2,4-oxadiazol-2-yl]methyl 1-methylazetidin-3-yl, 1-methylpyrrolidin-3-yl, 1-methylpiperidin-4-yl, 1-methylpiperidin-3-yl, 5-methoxypyrimidin-4-yl, 2-amino-4-pyridyl, 3-chloro-5-fluoro-4-pyridyl, 3,5-difluoro-4-pyridyl, 3-fluoro-2-pyridyl, 3-methoxy-2-pyridyl, 3-fluoro-4-pyridyl, 3-chloro-4-pyridyl, 4-pyridyl and 2-pyridyl.

[069] In some embodiments, R^7 is selected from H, trifluoromethyl, difluoromethyl, 1,1-difluoroethyl, methyl, ethyl, methoxy, amino, dimethylamino, carboxy. methylaminocarbonyl, dimethylaminocarbonyl, and cyclopropyl.

[070] In some embodiments, R^8 is selected from H, trifluoromethyl, methyl, ethyl, carboxy, cyano and methylaminocarbonyl.

[071] In some embodiments, R^9 is selected from H, fluoro, chloro, methyl, and cyano.

[072] In some embodiments, R^{10} is selected from H, fluoro, methylcarbonylamino, chloro, amino, hydroxy, methyl, difluoromethyl, methylsulfonylamino, and methylaminocarbonylamino.

[073] In some embodiments, R^{11} is H or fluoro.

[074] In some embodiments, R^6 is ethyl; R^7 is trifluoromethyl; and R^8 is H.

[075] In some embodiments, R^6 is methyl; R^7 is trifluoromethyl; and R^8 is H.

[076] In some embodiments, R^6 is H; R^7 is trifluoromethyl; and R^8 is H.

[077] In some embodiments, R^6 is 3,5-difluoropyridin-4-yl; R^7 is trifluoromethyl; and R^8 is H.

[078] In some embodiments, R^1 is substituted ethenyl.

[079] In some embodiments, R^1 is dimethylaminopropenyl.

[080] In some embodiments, R^1 is methylaminopropenyl.

[081] In some embodiments, R^1 is 3,3-difluoropropenyl.

[082] In some embodiments, R^1 is 2-(azetin-2-yl)ethenyl.

[083] In some embodiments, R^1 is 2-(2-methyl-pyrrolidiny-5-yl)ethenyl.

[084] In some embodiments, R^1 is 3-(methylamino)butenyl.

[085] In some embodiments, R^1 is ethylaminopropenyl.

[086] In some embodiments, R^1 is 2-(3-methoxypyrrolidiny-5-yl)ethenyl.

[087] In some embodiments, R^1 is 2-(3-fluoropyrrolidiny-5-yl)ethenyl.

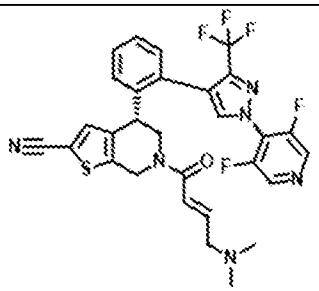
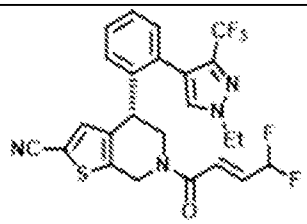
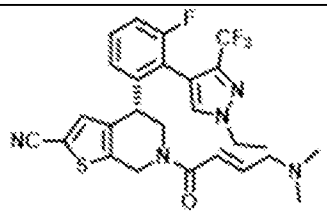
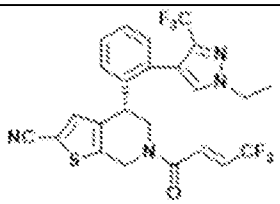
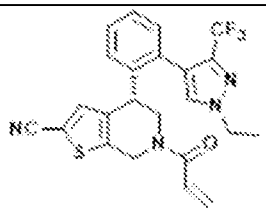
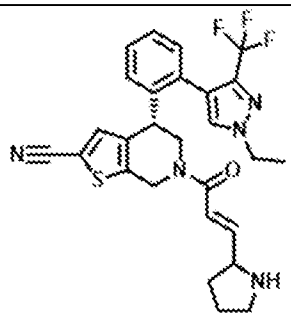
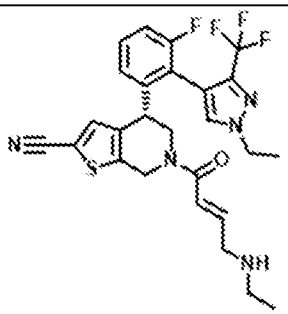
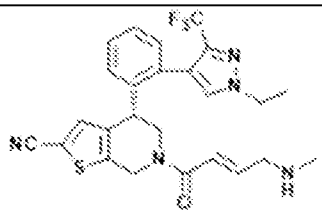
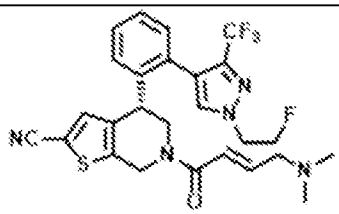
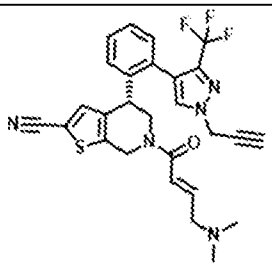
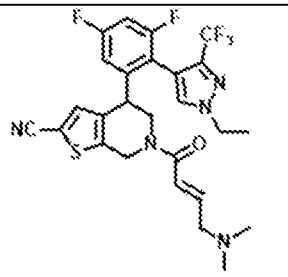
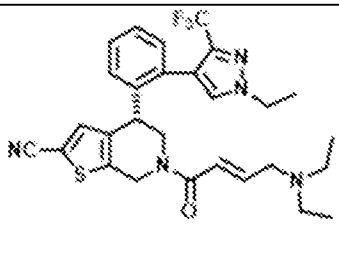
[088] In some embodiments, R^1 is 2-(pyrrolidiny-2-yl)ethenyl.

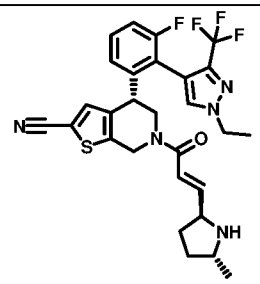
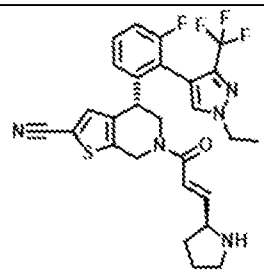
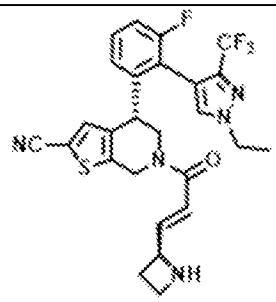
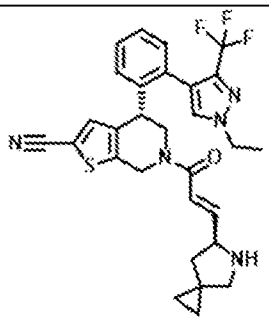
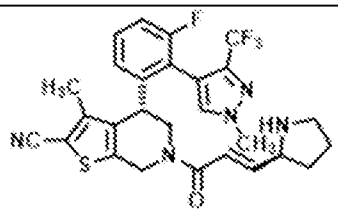
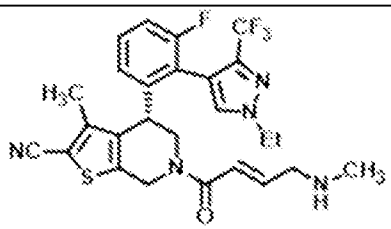
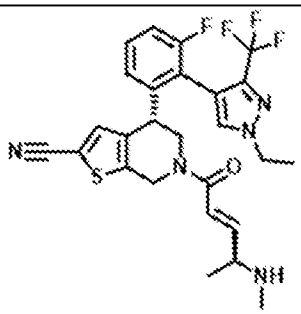
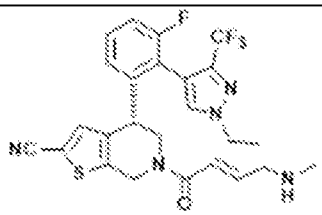
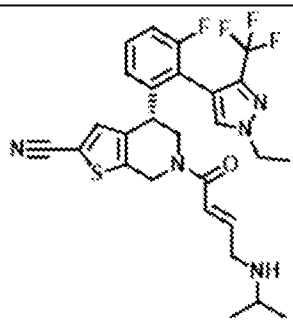
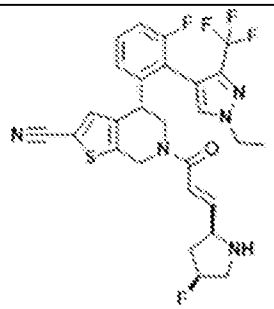
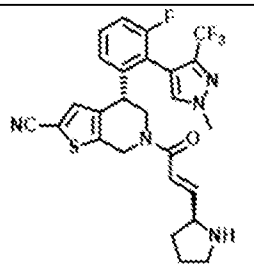
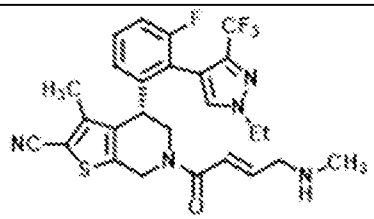
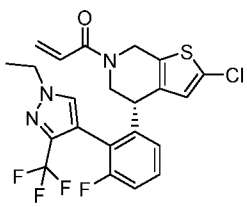
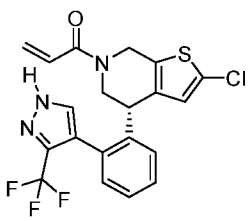
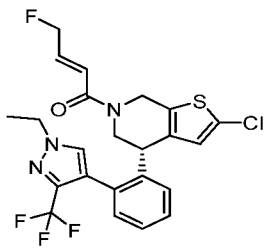
[089] In some embodiments, R^1 is aminopropenyl.

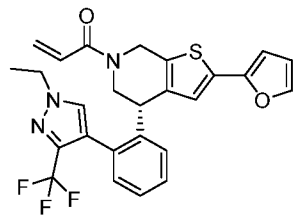
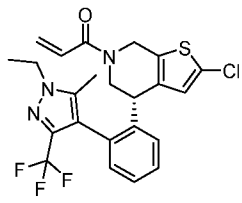
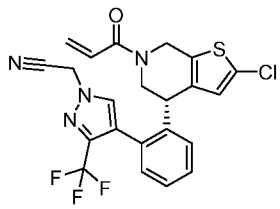
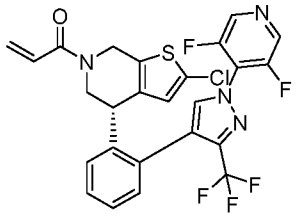
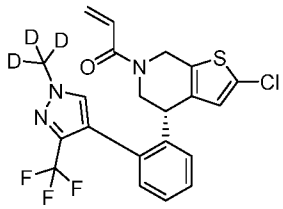
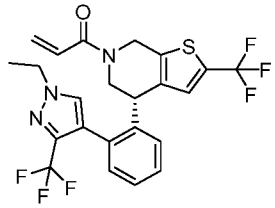
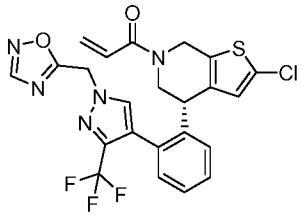
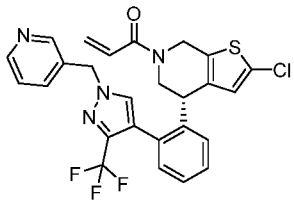
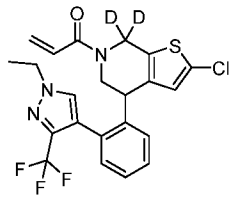
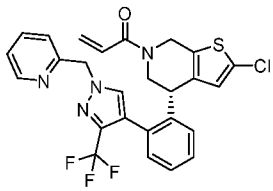
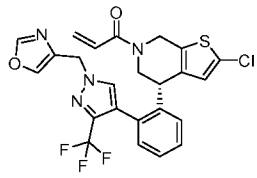
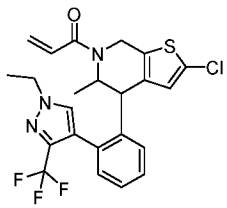
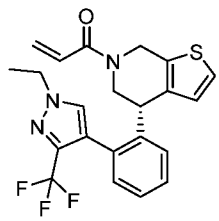
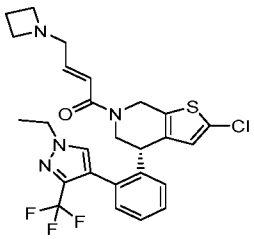
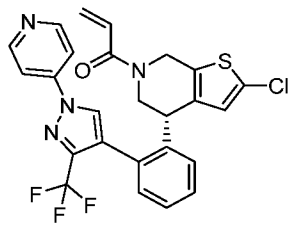
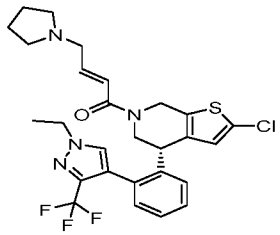
[090] In some embodiments, R^9 is fluoro; R^{10} is H; and R^{11} is H.

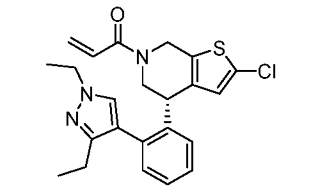
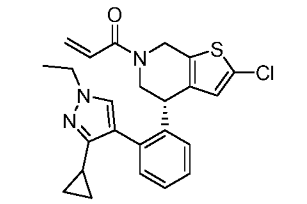
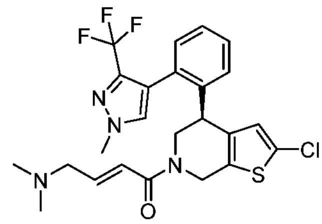
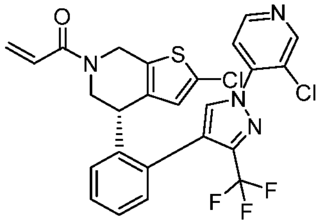
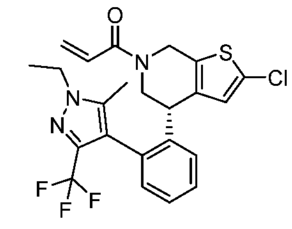
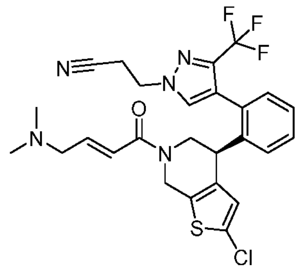
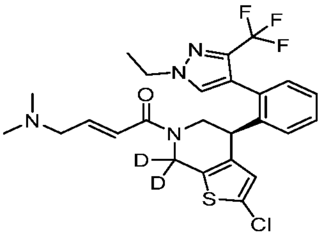
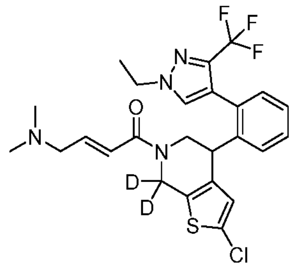
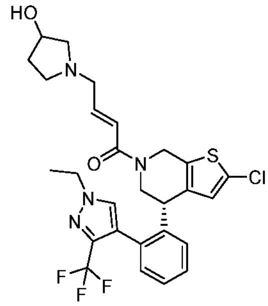
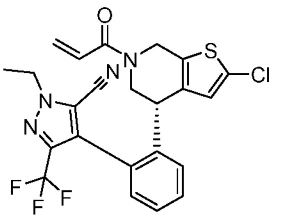
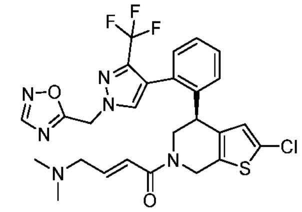
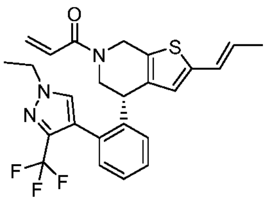
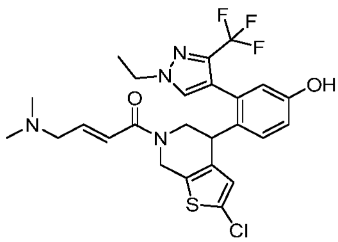
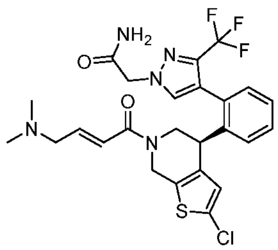
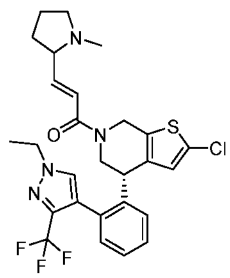
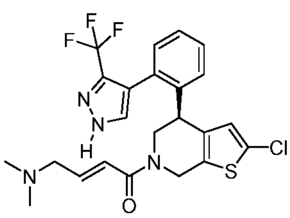
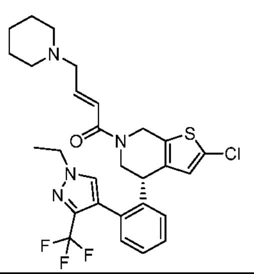
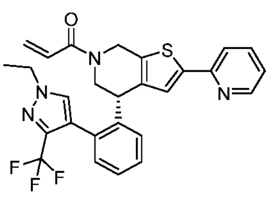
[091] Non-limiting examples of compounds of the current disclosure include the following compounds identified in Table A:

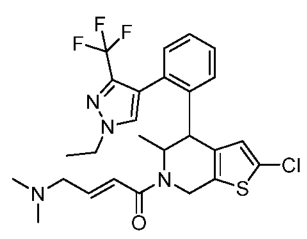
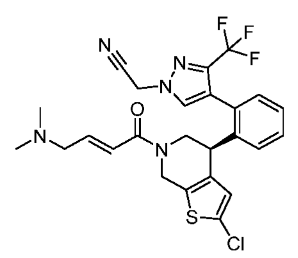
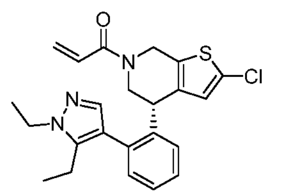
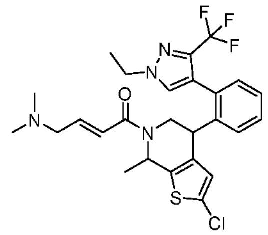
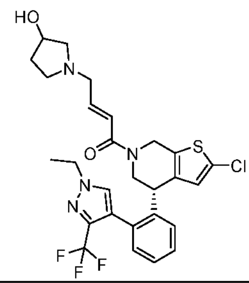
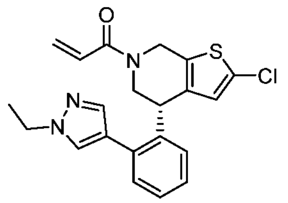
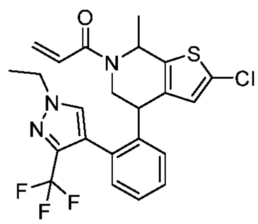
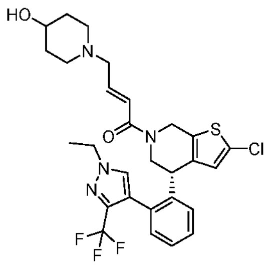
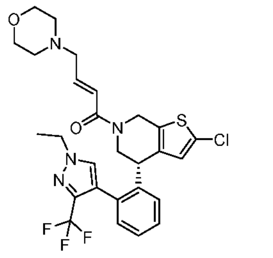
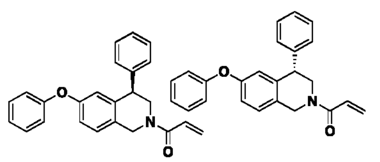
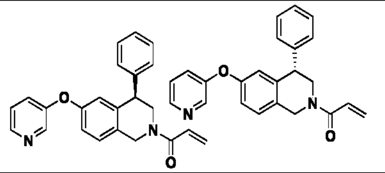
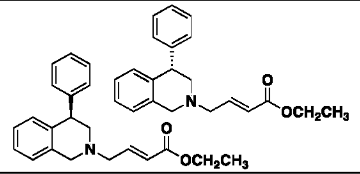
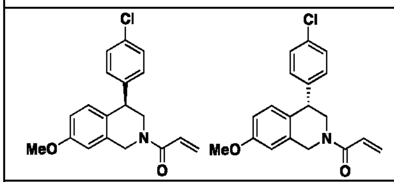
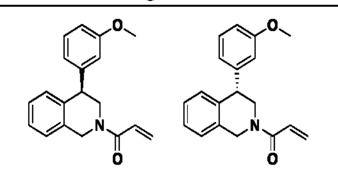
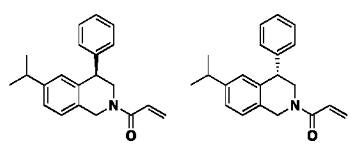
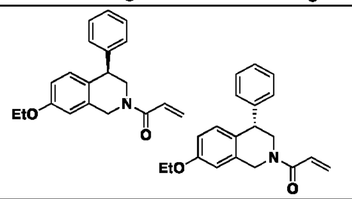
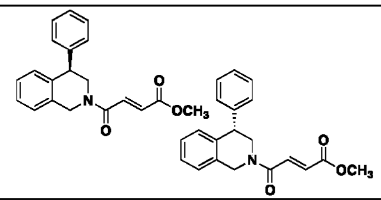
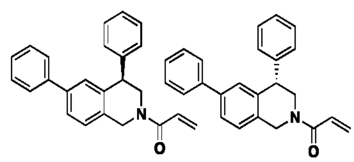
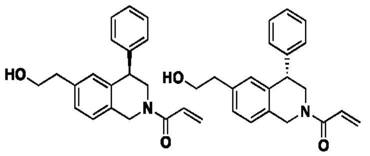
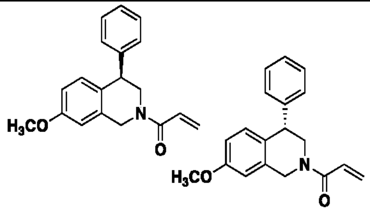
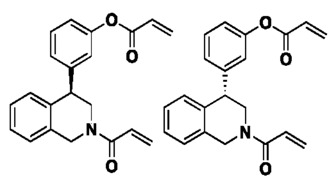
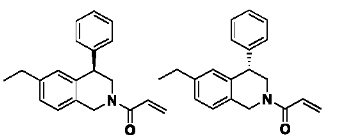
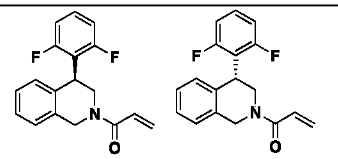
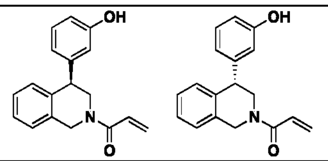
TABLE A

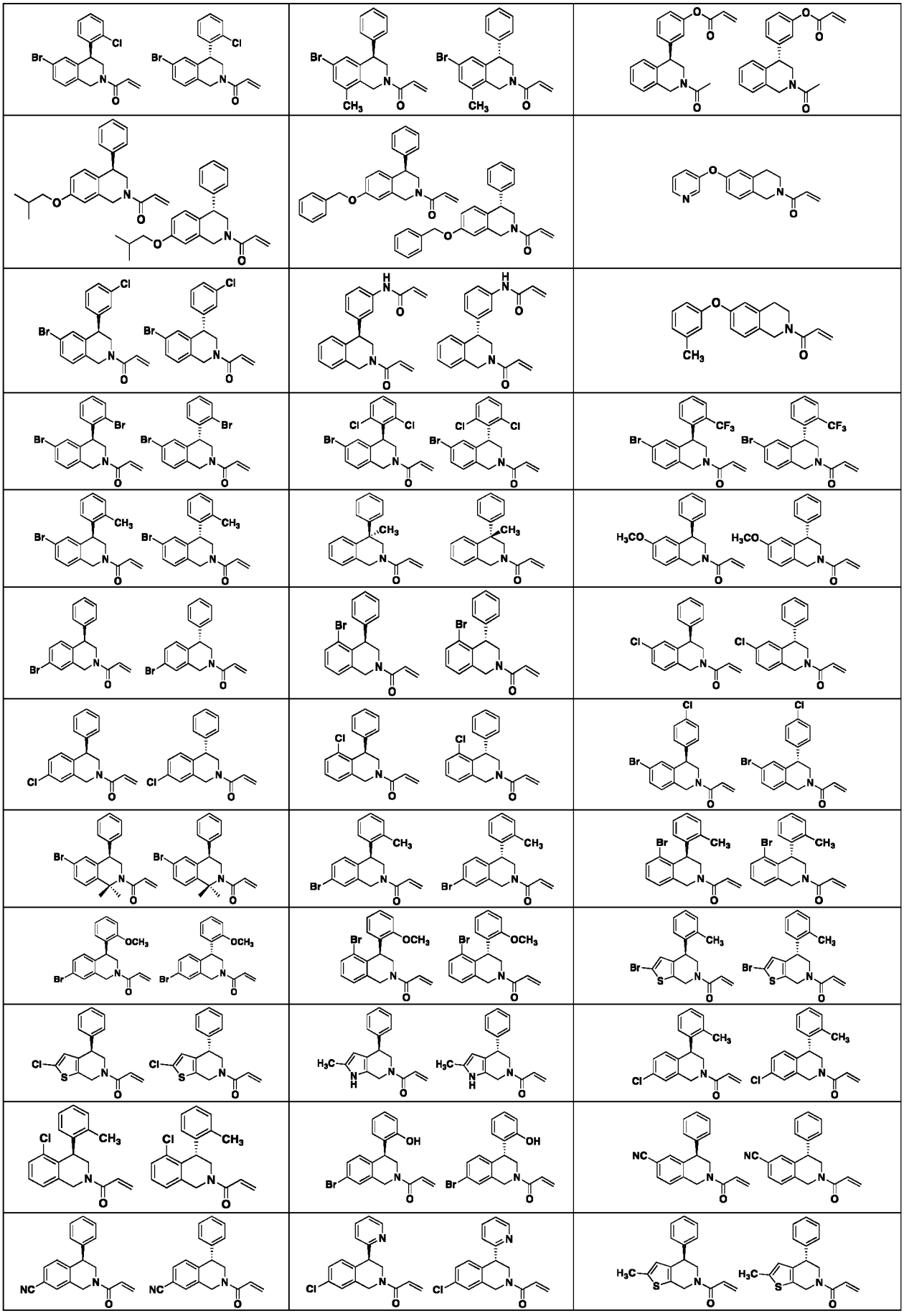
		
		
		
		

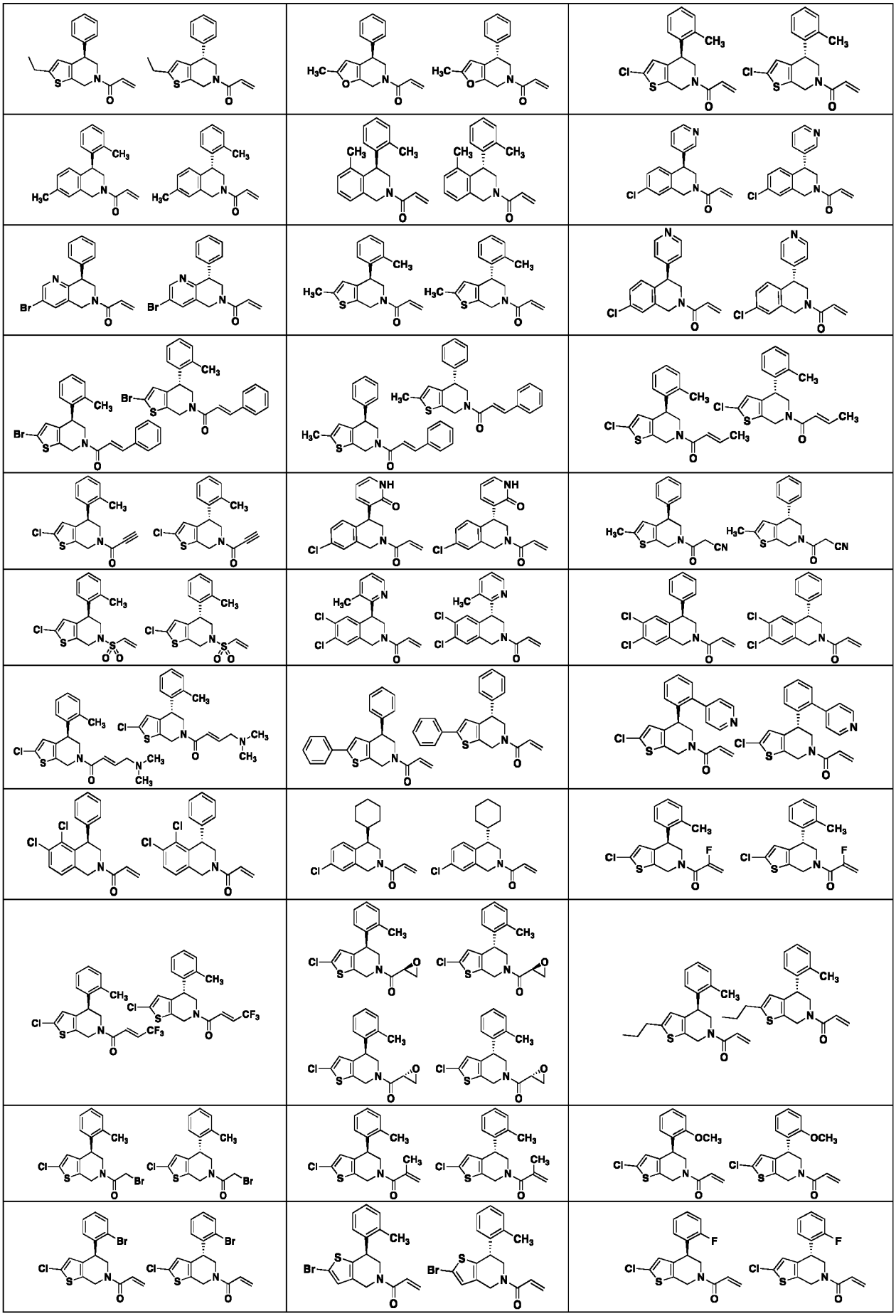
		
		
		
		
		

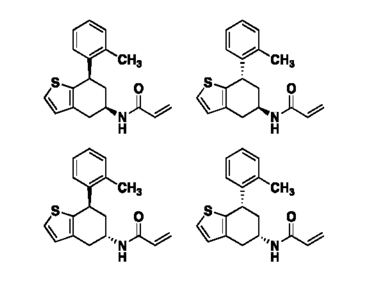
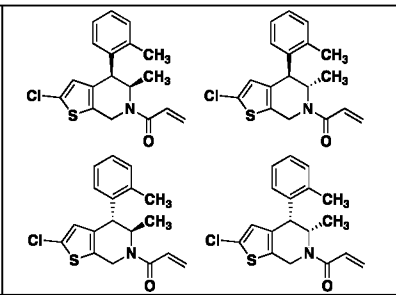
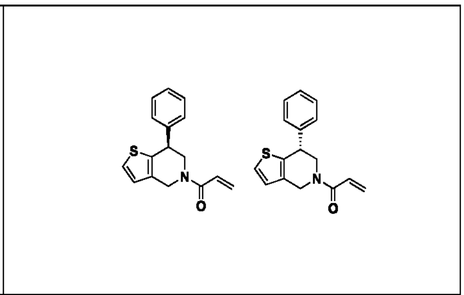
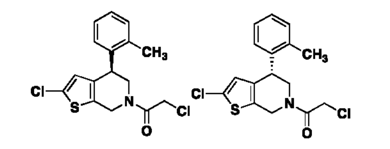
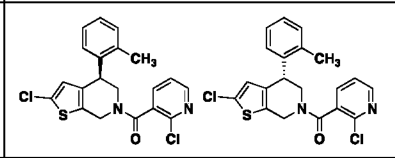
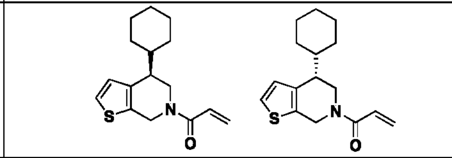
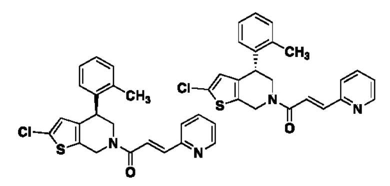
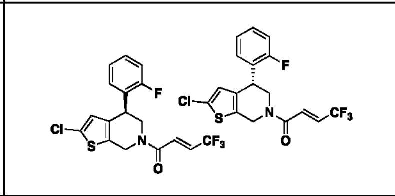
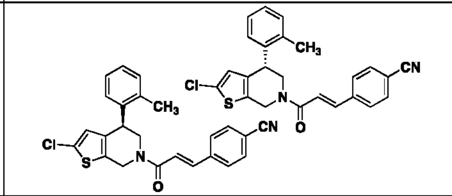
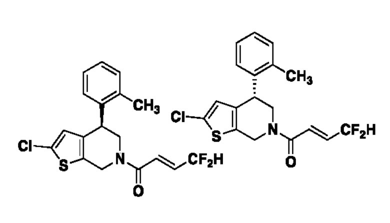
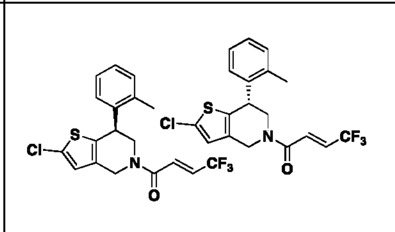
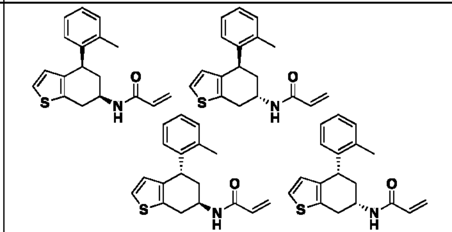
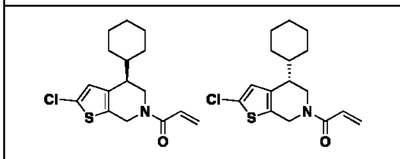
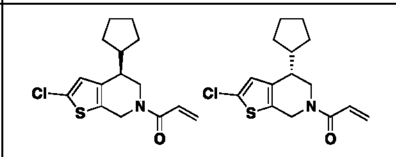
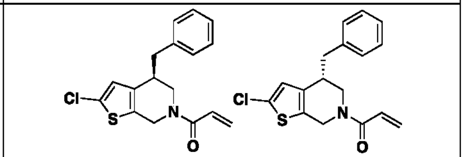
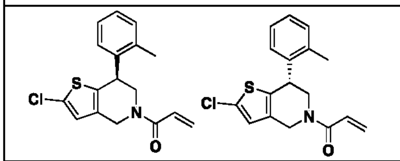
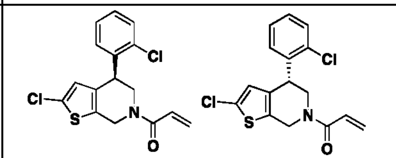
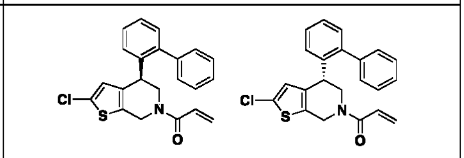
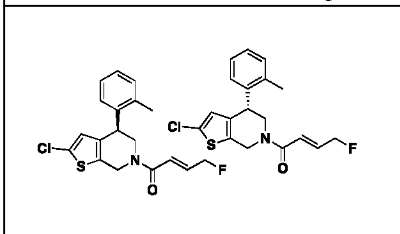
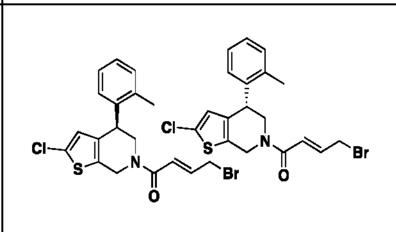
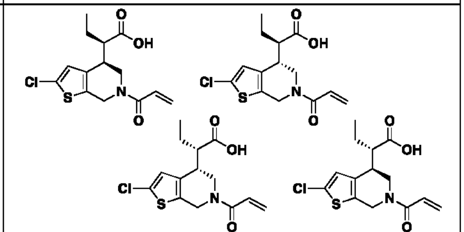
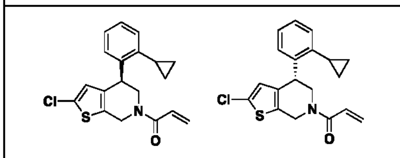
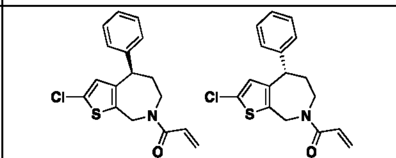
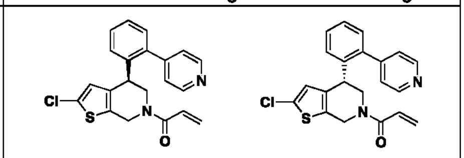
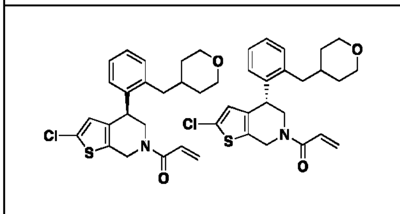
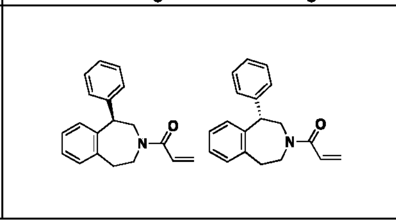
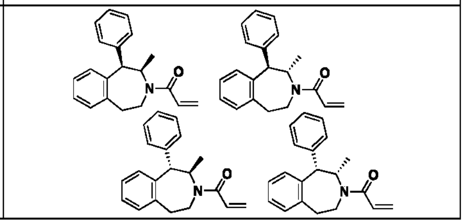
		
		
		
Blank		
Blank		
		

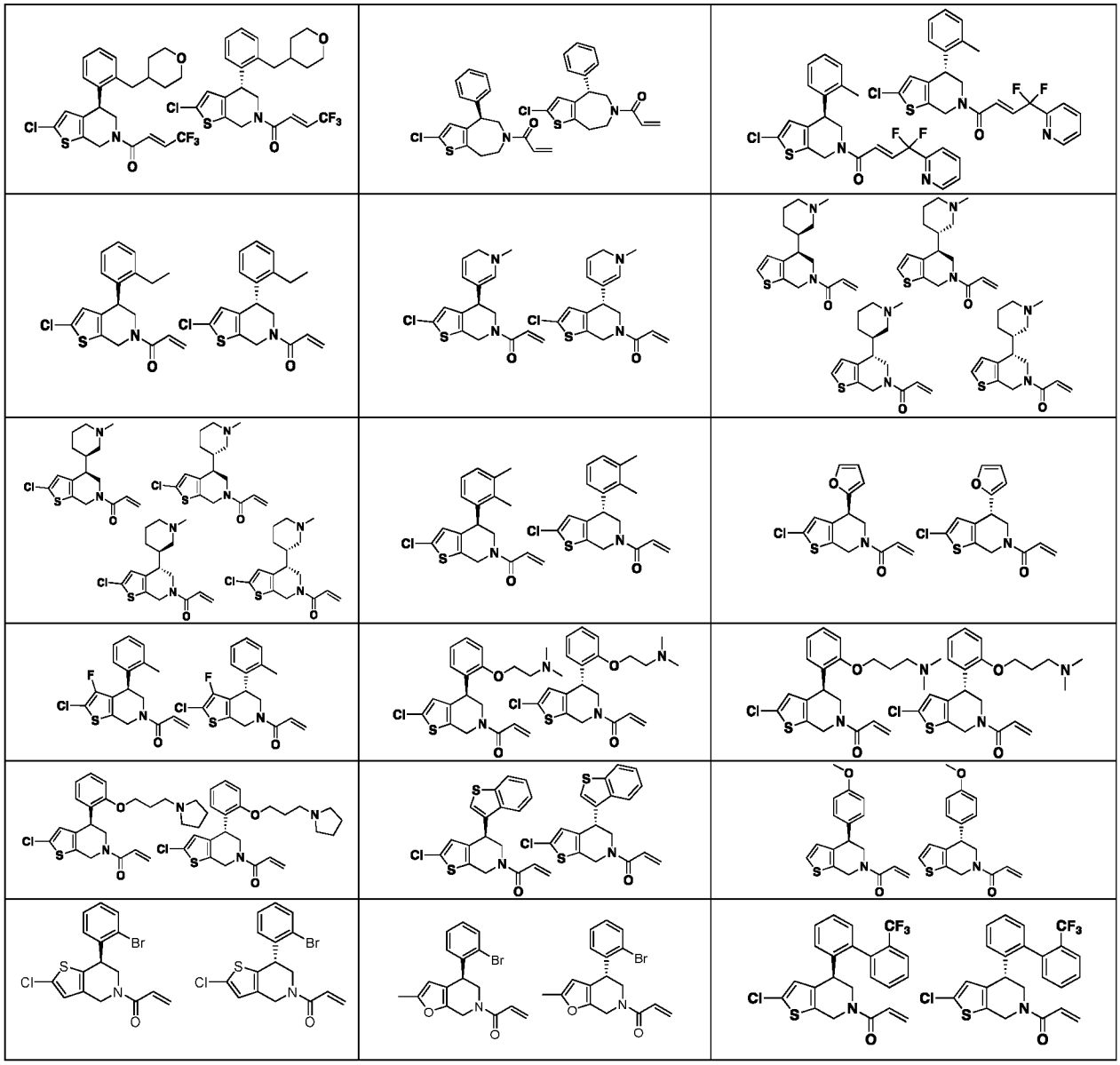
		
		
		
		
		
		







Definitions

[092] 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.

[093] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Preferred alkyl substituents are C_1-C_6 alkyl. 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. 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, -$CH_2CH_2CH_2CH_2$-.

[094] An unsaturated alkyl group is one having one or more double bonds or triple bonds referred to as "alkenyl" or "alkynyl" groups, respectively. Preferred alkenyl substituents are C_2-C_6 alkenyl and preferred alkynyl substituents are C_2-C_6 alkynyl. Examples of alkenyl or alkynyl groups include, but are not limited to, ethenyl, vinyl, 2-propenyl, butenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1-propynyl, 3-propynyl, and 3-butynyl.

[095] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, S, B, As, or Si), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., O, N, P, S, B, As, or Si) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Heteroalkyl also includes terms such as alkoxy, and alkylamino.

[096] An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). Preferred alkoxy substituents include C_{1-4} alkoxy. Examples of alkoxy groups include, but are not limited to methoxy, ethoxy and propoxy. Preferred alkylamino substituents include mono substituted C_{1-4} alkylamino and disubstituted alkylamino. Examples of alkylamino groups include, but are not limited to methylamino, dimethylamino and diethylamino.

[097] Another subgroup of heteroalkyl includes "alkoxyalkyl" where an alkyl group is substituted with an alkoxy group, as defined above. Preferred alkoxyalkyl substituents include C_{1-4} alkoxy- C_{1-4} alkyl. Examples of alkoxyalkyl groups include, but are not limited to methoxymethyl, ethoxymethyl and methoxyethyl.

[098] 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 $-SO_2R'$.

[099] The term "cycloalkyl" by itself or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl". Cycloalkyl are not fully aromatic rings. Preferred cycloalkyl substituents include C_3-C_6 cycloalkyl. A "cycloalkylene" alone or as part of another substituent, means a divalent radical derived from a cycloalkyl. For example, a cycloalkyl group having 3 to 8 ring members may be referred to as a (C_3-C_8)cycloalkyl, a cycloalkyl group having 3 to 7 ring members may be referred to as a (C_3-C_7)cycloalkyl and a cycloalkyl group having 4 to 7 ring members may be referred to as a (C_4-C_7)cycloalkyl. In certain embodiments, the cycloalkyl group can be a (C_3-C_{10})cycloalkyl, a (C_3-C_8)cycloalkyl, a (C_3-C_7)cycloalkyl, a (C_3-C_6)cycloalkyl, or a (C_4-C_7)cycloalkyl group and these may be referred to as C_3-C_{10} cycloalkyl, C_3-C_8 cycloalkyl, C_3-C_7 cycloalkyl, C_3-C_6 cycloalkyl, or C_4-C_7 cycloalkyl groups.

[0100] The term "cycloalkenyl" by itself or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkenyl". Cycloalkenyl are not fully aromatic rings. Preferred cycloalkenyl substituents include C_4-C_6 cycloalkenyl. For example, a cycloalkenyl group having 4 to 8 ring members may be referred to as a (C_4-C_8)cycloalkenyl, a cycloalkenyl group having 3 to 7 ring members may be referred to as a (C_3-C_7)cycloalkenyl and a cycloalkenyl group having 4 to 6 ring members may be referred to as a (C_4-C_6)cycloalkenyl.

[0101] The term "heterocycloalkyl" by itself or in combination with other terms, mean, unless otherwise stated, cyclic versions of "heteroalkyl". Heterocycloalkyl rings are not fully aromatic. Heterocycloalkyl is also referred by the term heterocyclyl. Preferred heterocyclyl substituents include C_3-C_7 oxygen or nitrogen containing rings, or both nitrogen and oxygen atms. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. A "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from heterocycloalkyl. "Heterocyclyl" refers to a cyclic group that includes at least one saturated, partially unsaturated, but non-aromatic, cyclic ring. Heterocyclyl groups include at least one heteroatom as a ring member. Typical heteroatoms include, O, S and N and are independently chosen. Heterocyclyl groups include monocyclic ring systems and bicyclic ring systems. Bicyclic heterocyclyl groups include at least one non-aromatic ring with at least one heteroatom ring member that may be fused to a cycloalkyl ring or may be fused to an aromatic ring where the aromatic ring may be carbocyclic or may include one or more heteroatoms. The point of attachment of a bicyclic heterocyclyl group may be at the non-aromatic cyclic ring that includes at least one heteroatom or at another ring of the heterocyclyl group. For example, a heterocyclyl group derived by removal of a hydrogen atom from one of the 9 membered heterocyclic compounds shown below may be attached to the rest of the molecule at the 5-membered ring or at the 6-membered ring. In some embodiments, a heterocyclyl group includes 5 to 10 ring members of which 1, 2, 3 or 4 or 1, 2, or 3 are heteroatoms independently selected from O, S, or N. In other embodiments, a heterocyclyl group includes 3 to 7 ring members of which 1, 2, or 3 heteroatom are independently selected from O, S, or N. In such 3-7 membered heterocyclyl groups, only 1 of the ring atoms is a heteroatom when the ring includes only 3 members and includes 1 or 2 heteroatoms when the ring includes 4 members. In some embodiments, a heterocyclyl group includes 3 or 4 ring members of which 1 is a heteroatom selected from O, S, or N. In other embodiments, a heterocyclyl group includes 5 to 7 ring members of which 1, 2, or 3 are heteroatoms independently selected from O, S, or N. Typical heterocyclyl groups include, but are not limited to, groups derived from epoxides, aziridine, azetidine, imidazolidine, morpholine, piperazine, piperidine, hexahydropyrimidine, 1,4,5,6-tetrahydropyrimidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran, benzimidazolone, pyridinone, and the like. Heterocyclyl groups may be fully saturated, but may also include one or more double bonds. Examples of such heterocyclyl groups include, but are not limited to, 1,2,3,6-tetrahydropyridinyl, 3,6-dihydro-2H-pyranyl, 3,4-dihydro-2H-pyranyl, 2,5-dihydro-1H-pyrolyl, 2,3-dihydro-1H-pyrolyl, 1H-azirinyl, 1,2-dihydroazetenyl, and the like. Substituted heterocyclyl also includes ring systems substituted with one or more oxo (=O) or oxide (-O-) substituents, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-

thiomorpholinyl, pyridinonyl, benzimidazolonyl, benzo[d]oxazol-2(3H)-only, 3,4-dihydroisoquinolin-1(2H)-only, indolin-only, 1H-imidazo[4,5-c]pyridin-2(3H)-only, 7H-purin-8(9H)-only, imidazolidin-2-only, 1H-imidazol-2(3H)-only, 1,1-dioxo-1-thiomorpholinyl, and the like.

[0102] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

[0103] The term "haloalkyl" is meant to include monohaloalkyl and polyhaloalkyl. For example, the term "C_1-C_3-haloalkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 3-bromopropyl, and the like.

[0104] 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.

[0105] 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.

[0106] 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 heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. "Heteroaryl" refers to a monovalent heteroaromatic group derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Heteroaryl groups typically include 5- to 14-membered, but more typically include 5- to 10-membered aromatic, monocyclic, bicyclic, and tricyclic rings containing one or more, for example, 1, 2, 3, or 4, or in certain embodiments, 1, 2, or 3, heteroatoms chosen from O, S, or N, with the remaining ring atoms being carbon. In monocyclic heteroaryl groups, the single ring is aromatic and includes at least one heteroatom. In some embodiments, a monocyclic heteroaryl group may include 5 or 6 ring members and may include 1, 2, 3, or 4 heteroatoms, 1, 2, or 3 heteroatoms, 1 or 2 heteroatoms, or 1 heteroatom where the heteroatom(s) are independently selected from O, S, or N. In bicyclic aromatic rings, both rings are aromatic. In bicyclic heteroaryl groups, at least one of the rings must include a heteroatom, but it is not necessary that both rings include a heteroatom although it is permitted for them to do so. For example, the term "heteroaryl" includes a 5- to 7-membered heteroaromatic ring fused to a carbocyclic aromatic ring or fused to another heteroaromatic ring. In tricyclic aromatic rings, all three of the rings are aromatic and at least one of the rings includes at least one heteroatom. For fused, bicyclic and tricyclic heteroaryl ring systems where only one of the rings contains one or more heteroatoms, the point of attachment may be at the ring including at least one heteroatom or at a carbocyclic ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In certain embodiments, the total number of S and O atoms in

the heteroaryl group is not more than 2. In certain embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Heteroaryl does not encompass or overlap with aryl as defined above. Examples of heteroaryl groups include, but are not limited to, groups derived from acridine, carbazole, cinnoline, furan, imidazole, indazole, indole, indolizine, isobenzofuran, isochromene, isoindole, isoquinoline, isothiazole, 2H-benzo[d][1,2,3]triazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, and the like. In certain embodiments, the heteroaryl group can be between 5 to 20 membered heteroaryl, such as, for example, a 5 to 14 membered or 5 to 10 membered heteroaryl. In certain embodiments, heteroaryl groups can be those derived from thiophene, pyrrole, benzothiophene, 2H-benzo[d][1,2,3]triazole benzofuran, indole, pyridine, quinoline, imidazole, benzimidazole, oxazole, tetrazole, and pyrazine.

[0107] An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively.

[0108] The term "carbonyl" refers to the radical–C(O) which may also be referred to as –C(=O) group.

[0109] The term "carboxy" refers to the radical–C(O)OH which may also be referred to as–C(=O)OH.

[0110] The term "cyano" refers to the radical -CN.

[0111] The term "amino" referes to the radical $-NH_2$.

[0112] The term "aminocarbonyl" refers to the radical $-CO-NH_2$. Aminocarbonyl radicals may be substituted with one or two alkyl groups to form "alkylaminocarbonyl" groups.

[0113] The term "alkylcarbonyl" refers to the radical alkyl-CO-.

[0114] The terms "hydroxyl" and "hydroxy" refers to the radical -OH.

[0115] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0116] Each of the above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl," "heterocycloalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical.

[0117] 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"', $-NR"C(O)_2R'$, -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -NR'NR"R"', -ONR'R", -NR'C(O)NR"NR"'R"", -CN, $-NO_2$, $-NR'SO_2R"$, -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R"', and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently

selected as are each R', R", R'", and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0118] Such substituted alkyl groups include hydroxyalkyl; carboxyalkyl, alkoxycarbonylalkyl, cyanoalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, alkylaminoalkyl, alkylcarbonylaminoalkyl, cycloalkylalkyl, aralkyl, heteroarylalkyl and heterocyclylalkyl; wherein the heterocyclyl, heteroaryl, aryl, cycloalkyl, hydroxyl; carboxyl, alkoxy, cyano, aminocarbonyl, alkylaminocarbonyl, alkylamino, and alkylcarbonylamino groups are defined above.

[0119] Similarly, alkenyl and alkynyl groups can be specifically substituted to form halo-substituted C_2-C_6 alkenyl; alkoxy substituted C_2-C_6 alkenyl; dialkylamino substituted C_2-C_6 alkenyl, alkylamino substituted C_2-C_6 alkenyl, amino substituted C_2-C_6 alkenyl, hydroxy substituted amino-C_2-C_6 alkenyl, phenyl substituted amino-C_2-C_6 alkenyl, amino substituted C_2-C_6 alkynyl, dialkylamino substituted C_2-C_6 alkynyl, alkylamino substituted C_2-C_6 alkynyl, alkoxy substituted C_2-C_6 alkynyl, heterocyclyl- substituted C_2-C_6 alkynyl, cycloalkyl- substituted C_2-C_6 alkenyl, oxygen-containing heterocyclyl- substituted C_2-C_6 alkenyl, oxygen-containing heterocyclyl- substituted C_2-C_6 alkynyl, nitrogen-containing heterocyclyl-substituted C_2-C_6 alkenyl, and cycloalkyl- substituted C_2-C_6 alkynyl groups; where the amino, halo, dialkylamino, alkylamino, alkoxy, cycloalkyl, oxygen-containing heterocyclyl, and nitrogen-containing heterocyclyl radicals are defined elswhere.

[0120] The term "alkylsufonyl" refers to the radical alkyl-SO_2-; where alkyl is defined elseqhere.

[0121] Substituted amino groups include "alkylcarbonylamino," "alkylsulfonylamino," "alkylaminocarbonylamino" and "alkylsulfonylamino"; wherein the amino radical is substituted, preferably with one substituent selected from alkylcarbonyl, alkylsulfonyl, alkylaminocarbonyl, defined elsewhere.

[0122] 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', $-CO_2$R', -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, fluoro(C_1-C_4)alkyl, $-NR'SO_2$R", -NR'C(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is

independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

[0123] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0124] 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.

[0125] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), Boron (B), and silicon (Si).

[0126] A “substituent group,” as used herein, means a group selected from the following moieties: (A) halogen, oxo, cyano, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHOH, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCI_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-N_3$, unsubstituted alkyl

(e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered), and (B) alkyl (e.g., C_1-C_{20}, C_1-C_{12}, C_1-C_8, C_1-C_6, C_1-C_4, or C_1-C_2), heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), cycloalkyl (e.g., C_3-C_{10}, C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6), heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), aryl (e.g., C_6-C_{12}, C_6-C_{10}, or phenyl), or heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered), substituted with at least one substituent selected from: oxo, halo, haloalkyl cyano, hydroxyl, amino, carboxyl, amnocarbonyl, nitro, aminosulfonyl, haloalkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] In embodiments, a substituted or unsubstituted moiety (e.g., substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, and/or substituted or unsubstituted heteroarylene) is unsubstituted (e.g., is an unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted alkylene, unsubstituted heteroalkylene, unsubstituted cycloalkylene, unsubstituted heterocycloalkylene, unsubstituted arylene, and/or unsubstituted heteroarylene, respectively). In embodiments, a substituted or unsubstituted moiety (e.g., substituted or

unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, and/or substituted or unsubstituted heteroarylene) is substituted (e.g., is a 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, respectively).

[0133] In embodiments, a substituted moiety (e.g., 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) is substituted with at least one substituent group, wherein if the substituted moiety is substituted with a plurality of substituent groups, each substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of substituent groups, each substituent group is different.

[0134] In embodiments, a substituted moiety (e.g., 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) is substituted with at least one size-limited substituent group, wherein if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group is different.

[0135] In embodiments, a substituted moiety (e.g., 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) is substituted with at least one lower substituent group, wherein if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group is different.

[0136] In embodiments, a substituted moiety (e.g., 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) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted moiety is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of groups selected from

substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group is different.

[0137] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (*R*)-or (*S*)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (*R*)- and (*S*)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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. As used herein and unless otherwise indicated, the term "stereoisomer" or "stereomerically pure" means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the mirror image enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. A bond drawn with a wavy line indicates that both stereoisomers are encompassed. This is not to be confused with a wavy line drawn perpendicular to a bond which indicates the point of

attachment of a group to the rest of the molecule. As described above, this invention encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular compound of the invention may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., et al., Enantiomers, Racemates and Resolutions (Wiley-Interscience, New York, 1981); Wilen, S. H., et al. (1997) Tetrahedron 33:2725; Eliel, E. L., Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S. H., Tables of Resolving Agents and Optical Resolutions p.268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[0142] 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 [D] or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this is selected from invention.

[0143] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0144] 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.

[0145] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (XV)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group.

[0146] Any compound herein can be purified. A compound herein can be least 1% pure, at least 2% pure, at least 3% pure, at least 4% pure, at least 5% pure, at least 6% pure, at least 7% pure, at least 8% pure, at least 9% pure, at least 10% pure, at least 11% pure, at least 12% pure, at least 13% pure, at least 14% pure, at least 15% pure, at least 16% pure, at least 17% pure, at least 18% pure, at least 19% pure, at least 20% pure, at least 21% pure, at least 22% pure, at least 23% pure, at least 24% pure, at least 25% pure, at least 26% pure, at least 27% pure, at least 28% pure, at least 29% pure, at least 30% pure, at least 31% pure, at least 32% pure, at least 33% pure, at least 34% pure, at least 35% pure, at least 36% pure, at least 37% pure, at least 38% pure, at least 39% pure, at least 40% pure, at least 41% pure, at least 42% pure, at least

43% pure, at least 44% pure, at least 45% pure, at least 46% pure, at least 47% pure, at least 48% pure, at least 49% pure, at least 50% pure, at least 51% pure, at least 52% pure, at least 53% pure, at least 54% pure, at least 55% pure, at least 56% pure, at least 57% pure, at least 58% pure, at least 59% pure, at least 60% pure, at least 61% pure, at least 62% pure, at least 63% pure, at least 64% pure, at least 65% pure, at least 66% pure, at least 67% pure, at least 68% pure, at least 69% pure, at least 70% pure, at least 71% pure, at least 72% pure, at least 73% pure, at least 74% pure, at least 75% pure, at least 76% pure, at least 77% pure, at least 78% pure, at least 79% pure, at least 80% pure, at least 81% pure, at least 82% pure, at least 83% pure, at least 84% pure, at least 85% pure, at least 86% pure, at least 87% pure, at least 88% pure, at least 89% pure, at least 90% pure, at least 91% pure, at least 92% pure, at least 93% pure, at least 94% pure, at least 95% pure, at least 96% pure, at least 97% pure, at least 98% pure, at least 99% pure, at least 99.1% pure, at least 99.2% pure, at least 99.3% pure, at least 99.4% pure, at least 99.5% pure, at least 99.6% pure, at least 99.7% pure, at least 99.8% pure, or at least 99.9% pure.

[0147] In some embodiments, compounds as disclosed herein can be used to treat cancer in a subject. A compound as disclosed herein can, for example, slow the proliferation of cancer cell lines, or kill cancer cells. Non-limiting examples of cancer that can be treated by a compound as disclosed herein include: acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, AIDS-related cancers, AIDS-related lymphoma, anal cancer, appendix cancer, astrocytomas, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancers, brain tumors, such as cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, visual pathway and hypothalamic glioma, breast cancer, bronchial adenomas, Burkitt lymphoma, carcinoma of unknown primary origin, central nervous system lymphoma, cerebellar astrocytoma, cervical cancer, childhood cancers, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, cutaneous T-cell lymphoma, desmoplastic small round cell tumor, endometrial cancer, ependymoma, esophageal cancer, Ewing's sarcoma, germ cell tumors, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gliomas, hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, Hypopharyngeal cancer, intraocular melanoma, islet cell carcinoma, Kaposi sarcoma, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liposarcoma, liver cancer, lung cancers, such as non-small cell and small cell lung cancer, lymphomas, leukemias, macroglobulinemia, malignant fibrous histiocytoma of bone/osteosarcoma, medulloblastoma, melanomas, mesothelioma, metastatic squamous neck cancer with occult primary, mouth cancer, multiple endocrine neoplasia syndrome, myelodysplastic syndromes, myeloid leukemia, nasal cavity and paranasal sinus cancer, nasopharyngeal carcinoma, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma/malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, pancreatic cancer, pancreatic cancer islet cell, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineal astrocytoma, pineal germinoma, pituitary adenoma, pleuropulmonary blastoma, plasma cell neoplasia, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis and ureter transitional

cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcomas, skin cancers, skin carcinoma merkel cell, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach cancer, T-cell lymphoma, throat cancer, thymoma, thymic carcinoma, thyroid cancer, trophoblastic tumor (gestational), cancers of unknown primary site, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, and Wilms tumor.

[0148] In some embodiments, the compounds of the disclosure show non-lethal toxicity.

Pharmaceutically-acceptable salts.

[0149] The disclosure provides the use of pharmaceutically-acceptable salts of any therapeutic compound described herein. Pharmaceutically-acceptable salts include, for example, acid-addition salts and base-addition salts. The acid that is added to the compound to form an acid-addition salt can be an organic acid or an inorganic acid. A base that is added to the compound to form a base-addition salt can be an organic base or an inorganic base. In some embodiments, a pharmaceutically-acceptable salt is a metal salt. In some embodiments, a pharmaceutically-acceptable salt is an ammonium salt.

[0150] Metal salts can arise from the addition of an inorganic base to a compound of the invention. The inorganic base consists of a metal cation paired with a basic counterion, such as, for example, hydroxide, carbonate, bicarbonate, or phosphate. The metal can be an alkali metal, alkaline earth metal, transition metal, or main group metal. In some embodiments, the metal is lithium, sodium, potassium, cesium, cerium, magnesium, manganese, iron, calcium, strontium, cobalt, titanium, aluminum, copper, cadmium, or zinc.

[0151] In some embodiments, a metal salt is a lithium salt, a sodium salt, a potassium salt, a cesium salt, a cerium salt, a magnesium salt, a manganese salt, an iron salt, a calcium salt, a strontium salt, a cobalt salt, a titanium salt, an aluminum salt, a copper salt, a cadmium salt, or a zinc salt.

[0152] Ammonium salts can arise from the addition of ammonia or an organic amine to a compound of the invention. In some embodiments, the organic amine is triethyl amine, diisopropyl amine, ethanol amine, diethanol amine, triethanol amine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, N-ethylpiperidine, dibenzylamine, piperazine, pyridine, pyrrazole, pipyrrazole, imidazole, pyrazine, or pipyrazine.

[0153] In some embodiments, an ammonium salt is a triethyl amine salt, a diisopropyl amine salt, an ethanol amine salt, a diethanol amine salt, a triethanol amine salt, a morpholine salt, an N-methylmorpholine salt, a piperidine salt, an N-methylpiperidine salt, an N-ethylpiperidine salt, a dibenzylamine salt, a piperazine salt, a pyridine salt, a pyrrazole salt, a pipyrrazole salt, an imidazole salt, a pyrazine salt, or a pipyrazine salt.

[0154] Acid addition salts can arise from the addition of an acid to a compound of the invention. In some embodiments, the acid is organic. In some embodiments, the acid is inorganic. In some embodiments, the acid is hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, nitrous acid, sulfuric acid, sulfurous acid, a phosphoric acid, isonicotinic acid, lactic acid, salicylic acid, tartaric acid, ascorbic acid, gentisinic acid, gluconic acid, glucaronic acid, saccaric acid, formic acid, benzoic acid, glutamic acid, pantothenic acid, acetic acid, propionic acid, butyric acid, fumaric acid, succinic acid, methanesulfonic

acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, citric acid, oxalic acid, or maleic acid.

[0155] In some embodiments, the salt is a hydrochloride salt, a hydrobromide salt, a hydroiodide salt, a nitrate salt, a nitrite salt, a sulfate salt, a sulfite salt, a phosphate salt, isonicotinate salt, a lactate salt, a salicylate salt, a tartrate salt, an ascorbate salt, a gentisinate salt, a gluconate salt, a glucaronate salt, a saccarate salt, a formate salt, a benzoate salt, a glutamate salt, a pantothenate salt, an acetate salt, a propionate salt, a butyrate salt, a fumarate salt, a succinate salt, a methanesulfonate (mesylate) salt, an ethanesulfonate salt, a benzenesulfonate salt, a p-toluenesulfonate salt, a citrate salt, an oxalate salt , or a maleate salt.

Pharmaceutical Compositions of the disclosure.

[0156] A pharmaceutical composition of the disclosure can be used, for example, before, during, or after treatment of a subject with, for example, another pharmaceutical agent.

[0157] Subjects can be, for example, elderly adults, adults, adolescents, pre-adolescents, children, toddlers, infants, neonates, and non-human animals. In some embodiments, a subject is a patient.

[0158] A pharmaceutical composition of the disclosure can be a combination of any pharmaceutical compounds described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can be administered in therapeutically-effective amounts as pharmaceutical compositions by various forms and routes including, for example, intravenous, subcutaneous, intramuscular, oral, parenteral, ophthalmic, subcutaneous, transdermal, nasal, vaginal, and topical administration.

[0159] A pharmaceutical composition can be administered in a local manner, for example, via injection of the compound directly into an organ, optionally in a depot or sustained release formulation or implant. Pharmaceutical compositions can be provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. A rapid release form can provide an immediate release. An extended release formulation can provide a controlled release or a sustained delayed release.

[0160] For oral administration, pharmaceutical compositions can be formulated by combining the active compounds with pharmaceutically-acceptable carriers or excipients. Such carriers can be used to formulate liquids, gels, syrups, elixirs, slurries, or suspensions, for oral ingestion by a subject. Non-limiting examples of solvents used in an oral dissolvable formulation can include water, ethanol, isopropanol, saline, physiological saline, DMSO, dimethylformamide, potassium phosphate buffer, phosphate buffer saline (PBS), sodium phosphate buffer, 4-2-hydroxyethyl-1-piperazineethanesulfonic acid buffer (HEPES), 3-(N-morpholino)propanesulfonic acid buffer (MOPS), piperazine-N,N′-bis(2-ethanesulfonic acid) buffer (PIPES), and saline sodium citrate buffer (SSC). Non-limiting examples of co-solvents used in an oral dissolvable formulation can include sucrose, urea, cremaphor, DMSO, and potassium phosphate buffer.

[0161] Pharmaceutical compositions can be formulated for intravenous administration. The pharmaceutical compositions can be in a form suitable for parenteral injection as a sterile suspension, solution or emulsion in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Suspensions of the active compounds can be prepared as oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. The suspension can also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0162] The active compounds can be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams, and ointments. Such pharmaceutical compositions can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0163] The compounds of the disclosure can be applied topically to the skin, or a body cavity, for example, oral, vaginal, bladder, cranial, spinal, thoracic, or pelvic cavity of a subject. The compounds of the disclosure can be applied to an accessible body cavity.

[0164] The compounds can also be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, and PEG. In suppository forms of the compositions, a low-melting wax such as a mixture of fatty acid glycerides, optionally in combination with cocoa butter, can be melted.

[0165] In practicing the methods of treatment or use provided herein, therapeutically-effective amounts of the compounds described herein are administered in pharmaceutical compositions to a subject having a disease or condition to be treated. In some embodiments, the subject is a mammal such as a human. A therapeutically-effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compounds used, and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[0166] Pharmaceutical compositions can be formulated using one or more physiologically-acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations that can be used pharmaceutically. Compositions can be modified depending upon the route of administration chosen. Pharmaceutical compositions comprising a compound described herein can be manufactured, for example, by mixing, dissolving, emulsifying, encapsulating, entrapping, or compression processes.

[0167] The pharmaceutical compositions can include at least one pharmaceutically-acceptable carrier, diluent, or excipient and compounds described herein as free-base or pharmaceutically-acceptable salt form. Pharmaceutical compositions can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0168] Methods for the preparation of compositions comprising the compounds described herein include formulating the compounds with one or more inert, pharmaceutically-acceptable excipients or carriers to form a solid, semi-solid, or liquid composition. Solid compositions include, for example, powders, tablets, dispersible granules, capsules, and cachets. Liquid compositions include, for example, solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, for example, gels, suspensions and creams. The compositions can be in liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions can also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and other pharmaceutically-acceptable additives.

[0169] Non-limiting examples of dosage forms suitable for use in the disclosure include liquid, powder, gel, nanosuspension, nanoparticle, microgel, aqueous or oily suspensions, emulsion, and any combination thereof.

[0170] Non-limiting examples of pharmaceutically-acceptable excipients suitable for use in the disclosure include binding agents, disintegrating agents, anti-adherents, anti-static agents, surfactants, anti-oxidants, coating agents, coloring agents, plasticizers, preservatives, suspending agents, emulsifying agents, anti-microbial agents, spheronization agents, and any combination thereof.

[0171] A composition of the disclosure can be, for example, an immediate release form or a controlled release composition. An immediate release composition can be formulated to allow the compounds to act rapidly. Non-limiting examples of immediate release compositions include readily dissolvable formulations. A controlled release compositions can be a pharmaceutical composition that has been adapted such that release rates and release profiles of the active agent can be matched to physiological and chronotherapeutic requirements or, alternatively, has been formulated to effect release of an active agent at a programmed rate. Non-limiting examples of controlled release compositions include granules, delayed release granules, hydrogels (e.g., of synthetic or natural origin), other gelling agents (*e.g.*, gel-forming dietary fibers), matrix-based compositions (*e.g.,* compositions comprising a polymeric material having at least one active ingredient dispersed through), granules within a matrix, polymeric mixtures, and granular masses.

[0172] In some, a controlled release composition is a delayed release form. A delayed release form can be formulated to delay a compound's action for an extended period of time. A delayed release form can be formulated to delay the release of an effective dose of one or more compounds, for example, for about 4, about 8, about 12, about 16, or about 24 hours.

[0173] A controlled release composition can be a sustained release form. A sustained release form can be formulated to sustain, for example, the compound's action over an extended period of time. A sustained release form can be formulated to provide an effective dose of any compound described herein (e.g., provide a physiologically-effective blood profile) over about 4, about 8, about 12, about 16 or about 24 hours.

[0174] Non-limiting examples of pharmaceutically-acceptable excipients can be found, for example, in

Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), each of which is incorporated by reference in its entirety.

[0175] Multiple therapeutic agents can be administered in any order or simultaneously. In some embodiments, a compound of the disclosure is administered in combination with, before, or after treatment with another therapeutic agent. If simultaneously, the multiple therapeutic agents can be provided in a single, unified form, or in multiple forms, for example, as multiple separate pills. The agents can be packed together or separately, in a single package or in a plurality of packages. One or all of the therapeutic agents can be given in multiple doses. If not simultaneous, the timing between the multiple doses can vary to as much as about a month.

[0176] Therapeutic agents described herein can be administered before, during, or after the occurrence of a disease or condition, and the timing of administering the composition containing a therapeutic agent can vary. For example, the compositions can be used as a prophylactic and can be administered continuously to subjects with a propensity to conditions or diseases in order to lessen a likelihood of the occurrence of the disease or condition. The compositions can be administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the therapeutic agents can be initiated within the first 48 hours of the onset of the symptoms, within the first 24 hours of the onset of the symptoms, within the first 6 hours of the onset of the symptoms, or within 3 hours of the onset of the symptoms. The initial administration can be via any route practical, such as by any route described herein using any formulation described herein.

[0177] A compound can be administered as soon as is practical after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months. In some embodiments, the length of time a compound can be administered can be about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 1 month, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 2 months, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 3 months, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 4 months, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 5 months, about 21 weeks, about 22 weeks, about 23 weeks, about 24 weeks, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 1 year, about 13 months, about 14 months, about 15 months, about 16 months, about 17 months, about 18 months, about 19 months, about 20 months, about 21 months, about 22 months about 23 months, about 2 years, about 2.5 years, about 3 years, about 3.5 years, about 4 years, about 4.5 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years. The length of treatment can vary for each subject.

[0178] Pharmaceutical compositions described herein can be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses

containing appropriate quantities of one or more compounds. The unit dosage can be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged injectables, vials, or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Multiple-dose reclosable containers can be used, for example, in combination with or without a preservative. Formulations for injection can be presented in unit dosage form, for example, in ampoules, or in multi-dose containers with a preservative.

[0179] Pharmaceutical compositions provided herein, can be administered in conjunction with other therapies, for example, chemotherapy, radiation, surgery, anti-inflammatory agents, and selected vitamins. The other agents can be administered prior to, after, or concomitantly with the pharmaceutical compositions.

[0180] Depending on the intended mode of administration, the pharmaceutical compositions can be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, or gels, for example, in unit dosage form suitable for single administration of a precise dosage.

[0181] For solid compositions, nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, and magnesium carbonate.

[0182] Non-limiting examples of pharmaceutically active agents suitable for combination with compositions of the disclosure include anti-infectives, i.e., aminoglycosides, antiviral agents, antimicrobials, anticholinergics/antispasmotics, antidiabetic agents, antihypertensive agents, antineoplastics, cardiovascular agents, central nervous system agents, coagulation modifiers, hormones, immunologic agents, immunosuppressive agents, and ophthalmic preparations.

[0183] Compounds can be delivered via liposomal technology. The use of liposomes as drug carriers can increase the therapeutic index of the compounds. Liposomes are composed of natural phospholipids, and can contain mixed lipid chains with surfactant properties (e.g., egg phosphatidylethanolamine). A liposome design can employ surface ligands for attaching to unhealthy tissue. Non-limiting examples of liposomes include the multilamellar vesicle (MLV), the small unilamellar vesicle (SUV), and the large unilamellar vesicle (LUV). Liposomal physicochemical properties can be modulated to optimize penetration through biological barriers and retention at the site of administration, and to reduce a likelihood of developing premature degradation and toxicity to non-target tissues. Optimal liposomal properties depend on the administration route: large-sized liposomes show good retention upon local injection, small-sized liposomes are better suited to achieve passive targeting. PEGylation reduces the uptake of the liposomes by the liver and spleen, and increases the circulation time, resulting in increased localization at the inflamed site due to the enhanced permeability and retention (EPR) effect. Additionally, liposomal surfaces can be modified to achieve selective delivery of the encapsulated drug to specific target cells. Non-limiting examples of targeting ligands include monoclonal antibodies, vitamins, peptides, and polysaccharides specific for receptors concentrated on the surface of cells associated with the disease.

[0184] Non-limiting examples of dosage forms suitable for use in the disclosure include liquid, elixir,

nanosuspension, aqueous or oily suspensions, drops, syrups, and any combination thereof. Non-limiting examples of pharmaceutically-acceptable excipients suitable for use in the disclosure include granulating agents, binding agents, lubricating agents, disintegrating agents, sweetening agents, glidants, anti-adherents, anti-static agents, surfactants, anti-oxidants, gums, coating agents, coloring agents, flavoring agents, coating agents, plasticizers, preservatives, suspending agents, emulsifying agents, plant cellulosic material and spheronization agents, and any combination thereof.

[0185] Compositions of the disclosure can be packaged as a kit. In some embodiments, a kit includes written instructions on the administration/use of the composition. The written material can be, for example, a label. The written material can suggest conditions methods of administration. The instructions provide the subject and the supervising physician with the best guidance for achieving the optimal clinical outcome from the administration of the therapy. The written material can be a label. In some embodiments, the label can be approved by a regulatory agency, for example the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), or other regulatory agencies.

Dosing.

[0186] Pharmaceutical compositions described herein can be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the composition is divided into unit doses containing appropriate quantities of one or more compounds. The unit dosage can be in the form of a package containing discrete quantities of the composition. Non-limiting examples are liquids in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Multiple-dose reclosable containers can be used, for example, in combination with a preservative. Compositions for parenteral injection can be presented in unit dosage form, for example, in ampoules, or in multi-dose containers with a preservative.

[0187] A compound described herein can be present in a composition in a range of from about 1 mg to about 2000 mg; from about 10 mg to about 1000 mg; from about 100 mg to about 750 mg; from about 250 mg to about 500 mg, from about 100 mg to about 500 mg, from about 200 mg to about 500 mg, from about 250 mg to about450 mg, from about 100 mg to about 200 mg, from about 1 mg to about 50 mg, from about 50 mg to about 100 mg, from about 100 mg to about 150 mg, from about 150 mg to about 200 mg, from about 200 mg to about 250 mg, from about 250 mg to about 300 mg, from about 300 mg to about 350 mg, from about 350 mg to about 400 mg, from about 400 mg to about 450 mg, from about 450 mg to about 500 mg, from about 500 mg to about 550 mg, from about 550 mg to about 600 mg, from about 600 mg to about 650 mg, from about 650 mg to about 700 mg, from about 700 mg to about 750 mg, from about 750 mg to about 800 mg, from about 800 mg to about 850 mg, from about 850 mg to about 900 mg, from about 900 mg to about 950 mg, or from about 950 mg to about 1000 mg.

[0188] A compound described herein can be present in a composition in an amount of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about

125 mg, about 150 mg, about 175 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg.

[0189] In some embodiments, a dose can be expressed in terms of an amount of the drug divided by the mass of the subject, for example, milligrams of drug per kilograms of subject body mass. In some embodiments, a compound is administered in an amount ranging from about 1 mg/kg to about 20 mg/kg, or about 5 mg/kg to about 10 mg/kg. In some embodiments, a compound is administered in an amount of about 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, about 7 mg/kg, 8 mg/kg, about 9 mg/kg, or about 10 mg/kg.

Combination Treatment with an anti-cancer agent

[0190] Combination therapy with a compound of the disclosure and an anti-cancer agent described herein can be used to treat a condition. In some embodiments, the combination therapy can produce a significantly better therapeutic result than the additive effects achieved by each individual constituent when administered alone at a therapeutic dose. In some embodiments, the dosage of the compound or anti-cancer agent described herein, in combination therapy can be reduced as compared to monotherapy with each agent, while still achieving an overall therapeutic effect. In some embodiments, a compound and an anti-cancer agent described herein, can exhibit a synergistic effect. In some embodiments, the synergistic effect of a compound and anti-cancer agent described herein, can be used to reduce the total amount drugs administered to a subject, which decrease side effects experienced by the subject.

[0191] The compounds of the disclosure can be used in combination with at least one anti-cancer agent described herein. In some embodiments, the at least one anti-cancer agent described herein, can modulate the same or a different target as the compounds of the disclosure. In some embodiments, the at least one anti-cancer agent described herein, can modulate the same target as the compounds of the disclosure, or other components of the same pathway, or overlapping sets of target enzymes. In some embodiments, the at least one anti-cancer agent described herein, can modulate a different target from the compounds of the disclosure.

[0192] Accordingly, in one aspect, the present disclosure provides a method for treating cancer, the method comprising administering to a subject in need thereof (a) an effective amount of a compound of the disclosure and (b) an effective amount of at least one anti-cancer agent described herein, to provide a combination therapy. In some embodiments, the combination therapy may have an enhanced therapeutic effect compared to the effect of the compound and the at least one anti-cancer agent each administered alone. According to certain exemplary embodiments, the combination therapy has a synergistic therapeutic effect. According to this embodiment, the combination therapy produces a significantly better therapeutic result (*e.g.*, anti-cancer, cell growth arrest, apoptosis, induction of differentiation, cell death, etc.) than the additive effects achieved by each individual constituent when administered alone at a therapeutic dose.

[0193] Combination therapy includes but is not limited to the combination of compounds of the disclosure with anti-cancer agents such as chemotherapeutic agents, therapeutic antibodies, or radiation

treatment, to provide a synergistic therapeutic effect. In some embodiments, the compounds of the disclosure are used in combination with one or more anti-cancer (antineoplastic or cytotoxic) chemotherapy drug. Suitable chemotherapeutic agents for use in the combinations of the present disclosure include, but are not limited to, alkylating agents, antibiotic agents, antimetabolic agents, hormonal agents, plant-derived agents, anti-angiogenic agents, differentiation inducing agents, cell growth arrest inducing agents, apoptosis inducing agents, cytotoxic agents, agents affecting cell bioenergetics, biologic agents, *e.g.*, monoclonal antibodies, kinase inhibitors and inhibitors of growth factors and their receptors, gene therapy agents, cell therapy, or any combination thereof.

a. Combination treatment with estrogen receptor antagonists

[0194] In some embodiments, a compound of the disclosure is used in combination with an estrogen receptor antagonist. In some embodiments, a compound of the disclosure is used in combination with toremifene (Fareston®), fulvestrant (Faslodex®), or tamoxifen citrate (Soltamox®).

[0195] Fulvestrant is a selective estrogen receptor degrader (SERD) and is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. Fulvestrant is a complete estrogen receptor antagonist with little to no agonist effects and accelerates the proteasomal degradation of the estrogen receptor. Fulvestrant has poor oral bioavailability and is administered via intramuscular injection. Fulvestrant-induced expression of ErbB3 and ErbB4 receptors sensitizes estrogen receptor-positive breast cancer cells to heregulin beta1. In some embodiments, a compound of the disclosure is used in combination with fulvestrant.

b. Combination treatment with aromatase inhibitors

[0196] In some embodiments, a compound of the disclosure is used in combination with an aromatase inhibitor. Aromatase inhibitors are used in the treatment of breast cancer in post-menopausal women and gynecomastia in men. Aromatase inhibitors can be used off-label to reduce estrogen conversion when using external testosterone. Aromatase inhibitors can also be used for chemoprevention in high-risk women.

[0197] In some embodiments, a compound of the disclosure is used in combination with a non-selective aromatase inhibitor. In some embodiments, a compound of the disclosure is used in combination with a non-selective aromatase inhibitor, such as aminoglutethimide or testolactone (Teslac®). In some embodiments, a compound of the disclosure is used in combination with a selective aromatase inhibitor. In some embodiments, a compound of the disclosure is used in combination with a selective aromatase inhibitor, such as anastrozole (Arimidex®), letrozole (Femara®), exemestane (Aromasin®), vorozole (Rivizor®), formestane (Lentaron®), or fadrozole (Afema®). In some embodiments, a compound of the disclosure is used in combination with exemestane. In some embodiments, a compound of the disclosure is used in combination with an aromatase inhibitor such as 1,4,6-androstatrien-3,17-dione (ATD) or 4-androstene-3,6,17-trione.

c. Combination treatment with mTOR inhibitors

[0198] In some embodiments, a compound of the disclosure is used in combination with an mTOR inhibitor. mTOR inhibitors are drugs that inhibit the mechanistic target of rapamycin (mTOR), which is a

serine/threonine-specific protein kinase that belongs to the family of phosphatidylinositol-3 kinase (PI3K)-related kinases (PIKKs). mTOR regulates cellular metabolism, growth, and proliferation by forming and signaling through the protein complexes mTORC1 and mTORC2.

[0199] In some embodiments, a compound of the disclosure is used in combination with an mTOR inhibitor, such as rapamycin, temsirolimus (CCI-779), everolimus (RAD001), ridaforolimus (AP-23573). In some embodiments, a compound of the disclosure is used in combination with everolimus (Afinitor®). Everolimus affects the mTORC1 protein complex and can lead to hyper-activation of the kinase AKT, which can lead to longer survival in some cell types. Everolimus binds to FKBP12, a protein receptor which directly interacts with mTORC1 and inhibits downstream signaling. mRNAs that codify proteins implicated in the cell cycle and in the glycolysis process are impaired or altered as a result, inhibiting tumor growth and proliferation.

[0200] In some embodiments, a compound of the disclosure is used in combination with a mTOR inhibitor and an aromatase inhibitor. For example, a compound of the disclosure is used in combination with everolimus and exemestane.

d. Combination treatment with antimetabolites

[0201] Antimetabolites are chemotherapy treatments that are similar to normal substances within the cell. When cells incorporate the antimetabolites into the cellular metabolism, the cells are unable to divide. Antimetabolites are cell-cycle specific and attack cells at specific phases in the cell cycle.

[0202] In some examples, a compound of the disclosure is used in combination with one or more antimetabolites, such as a folic acid antagonist, pyrimidine antagonist, purine antagonist, or an adenosine deaminase inhibitor. In some embodiments, a compound of the disclosure is used in combination with an antimetabolite, such as methotrexate, 5-fluorouracil, foxuridine, cytarabine, capecitabine, gemcitabine, 6-mercaptopurine, 6-thioguanine, cladribine, fludarabine, nelarabine, or pentostatin. In some embodiments, a compound of the disclosure is used in combination with capecitabine (Xeloda®), gemcitabine (Gemzar®), or cytarabine (Cytosar-U®).

e. Combination treatment with plant alkaloids

[0203] In some embodiments, a compound of the disclosure is used in combination with a plant alkaloid. In some embodiments, a compound of the disclosure is used in combination with a plant alkaloid, such as vinca alkaloids, taxanes, podophyllotoxins, or camptothecan analogues. In some embodiments, a compound of the disclosure is used in combination with plant alkaloids, such as vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, etoposide, tenisopide, irinotecan, or topotecan.

[0204] In some embodiments, a compound of the disclosure is used in combination with a taxane, such as paclitaxel (Abraxane® or Taxol®) and docetaxel (Taxotere®). In some embodiments, a compound of the disclosure is used in combination with paclitaxel. In some embodiments, a compound of the disclosure is used in combination with docetaxel.

f. Combination treatment with therapeutic antibodies

[0205] In some embodiments, a compound of the disclosure is used in combination with therapeutic antibodies. In some embodiments, a compound of the disclosure is used in combination with monoclonal

antibodies, such as alemtuzumab (Campath®) or trastuzumab (Herceptin®). In some embodiments, a compound of the disclosure is used in combination with conjugated monoclonal antibodies, such as radiolabeled antibodies or chemolabeled antibodies. In some embodiments, a compound of the disclosure is used in combination with conjugated monoclonal antibodies, such as ibritumomab tiuxetan (Zevalin®), brentuximab vedotin (Adcetris®), ado-trastuzumab emtansine (Kadcyla®), or denileukin diftitox (Ontak®). In some embodiments, a compound of the disclosure is used in combination with bispecific monoclonal antibodies, such as blinatumomab (Blincyto®).

[0206] In some embodiments, a compound of the disclosure is used in combination with an anti-CD20 antibody, such as rituximab (Mabthera®/ Rituxan®), obinutuzumab (Gazyva®), ibritumomab tiuxetan, tositumomab, ofatumumab (Genmab®), ocaratuzumab, ocrelizumab, TRU-015, or veltuzumab.

g. Combination treatment with PD-L1 and/or PD-1 antagonists

[0207] The PD-1 pathway comprises the immune cell co-receptor Programmed Death-1 (PD-1) and the PD-1 ligands PD-L1 and PD-L2. The PD-1 pathway mediates local immunosuppression in the tumor microenvironment. PD-1 and PD-L1 antagonists suppress the immune system. In some embodiments, a PD-1 or PD-L1 antagonist is a monoclonal antibody or antigen binding fragment thereof that specifically binds to, blocks, or downregulates PD-1 or PD-L1, respectively. In some embodiments, a PD-1 or PD-L1 antagonist is a compound or biological molecule that specifically binds to, blocks, or downregulates PD-1 or PD-L1, respectively.

[0208] In some embodiments, the compounds of the disclosure are used in combination with a PD-1 or PD-L1 antagonist. In some embodiments, the compounds of the disclosure are used in combination with a PD-1/PD-L1 antagonist, for example, MK-3475, nivolumab (Opdivo®), pembrolizumab (Keytruda®), humanized antibodies (i.e., h409Al l, h409A16 and h409A17), AMP-514, BMS-936559, MEDI0680, MEDI4736, MPDL3280A, MSB0010718C, MDX-1105, MDX-1106, or pidilzumab. In some embodiments, the compounds of the disclosure are used in combination with a PD-1/PD-L1 antagonist that is an immunoadhesion molecule, such as AMP-224. In some embodiments, the compounds of the disclosure are used in combination with a PD-1/PD-L1 antagonist to treat cancer cells or a tumor that overexpresses PD-1 or PD-L1. In some embodiments, the compounds of the disclosure are used in combination with a PD-1/PD-L1 antagonist to treat cancer cells or a tumor that overexpresses miR-34.

h. Combination treatment with anti-hormone therapy

[0209] Anti-hormone therapy uses an agent to suppress selected hormones or the effects. Anti-hormone therapy is achieved by antagonizing the function of hormones with a hormone antagonist and/or by preventing the production of hormones. In some embodiments, the suppression of hormones can be beneficial to subjects with certain cancers that grow in response to the presence of specific hormones. In some embodiments, a compound of the disclosure is used in combination with a hormone antagonist.

[0210] In some embodiments, a compound of the disclosure is used in combination with anti-androgens, anti-estrogens, aromatase inhibitors, or luteinizing hormone-releasing hormone (LHRH) agonists. In some embodiments, a compound of the disclosure is used in combination with anti-androgens, such as bicalutamide (Casodex®), cyproterone (Androcur®), flutamide (Euflex®), or nilutamide (Anandron®). In

some embodiments, a compound of the disclosure is used in combination with anti-estrogens, such as fulvestrant (Faslodex®), raloxifene (Evista®), or tamoxifen (Novaladex®, Tamofen®). In some embodiments, a compound of the disclosure is used in combination with LHRH agonists, such as buserelin (Suprefact®), goserelin (Zoladex®), or leuprolide (Lupron®, Lupron Depot®, Eligard®).

i. Combination treatment with hypomethylating (demethylating) agents (HMAs)

[0211] Treatment of these and other types of cancer may be improved by examining combinations that increase anti-tumor activities and may allow for similar activity at reduced doses compared to single agent treatment, leading to improved patient outcomes, and limiting adverse events. Hypomethylating (demethylating) agents inhibit DNA methylation, which affects cellular function through successive generations of cells without changing the underlying DNA sequence. Hypomethylating agents can block the activity of DNA methyltransferase. Two examples of HMAs for treatment of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients are decitabine and azacitidine. In some embodiments, a compound of the disclosure is used in combination with hypomethylating agents, such as azacitidine (Vidaza®, Azadine®) or decitabine (Dacogen®).

j. Combination treatment with anti-inflammatory agents

[0212] In some embodiments, a compound of the disclosure is used in combination with nonsteroidal anti-inflammatory drugs (NSAIDs), specific COX-2 inhibitors, or corticosteroids. In some embodiments, a compound of the disclosure is used in combination with NSAIDs, such as aspirin, ibuprofen, naproxen, celecoxib, ketorolac, or diclofenac. In some embodiments, a compound of the disclosure is used in combination with specific COX-2 inhibitors, such as celecoxib (Celebrex®), rofecoxib, or etoricoxib. In some embodiments, a compound of the disclosure is used in combination with corticosteroids, such as dexamethasone or glucosteroids (e.g., hydrocortisone and prednisone).

k. Combination treatment with HDAC inhibitors

[0213] Histone deacetylase (HDAC) inhibitors are chemical compounds that inhibit histone deacetylase. HDAC inhibitors can induce p21 expression, a regulator of p53 activity. In some embodiments, a compound of the disclosure is used in combination with an HDAC inhibitor. In some embodiments, a compound of the disclosure is used in combination with an HDAC inhibitor, such as vorinostat, romidepsin (Istodax®), chidamide, panobinostat (Farydak®), belinostat (PDX101), panobinostat (LBH589), valproic acid, mocetinostat (MGCD0103), abexinostat (PCI-24781), entinostat (MS-275), SB939, resminostat (4SC-201), givinostat (ITF2357), quisinostat (JNJ-26481585), HBI-8000, kevetrin, CUDC-101, AR-42, CHR-2845, CHR-3996, 4SC-202, CG200745, ACY-1215, ME-344, sulforaphane, or trichostatin A.

l. Combination treatment with platinum-based antineoplastic drugs

[0214] Platinum-based antineoplastic drugs are coordinated complex of platinum. In some embodiments, a compound of the disclosure is used in combination with a platinum-based antineoplastic drug, such as cisplatin, oxaliplatin, carboplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin. In some embodiments, a compound of the disclosure is used in combination with cisplatin or carboplatin. In some embodiments, a compound of the disclosure is used in combination with cisplatinum,

platamin, neoplatin, cismaplat, cis-diamminedichloroplatinum(II), or CDDP; Platinol®) and carboplatin (also known as cis-diammine(1,1-cyclobutanedicarboxylato)platinum(II); tradenames Paraplatin® and Paraplatin-AQ®).

m. Combination treatment with kinase inhibitors

[0215] Abnormal activation of protein phosphorylation is frequently either a driver of direct consequence of cancer. Kinase signaling pathways are involved in the phenotypes of tumor biology, including proliferation, survival, motility, metabolism, angiogenesis, and evasion of antitumor immune responses.

[0216] **MEK inhibitors**: MEK inhibitors are drugs that inhibit the mitogen-activated protein kinase enzymes MEK1 and/or MEK2. In some embodiments, a compound of the disclosure is used in combination with a MEK1 inhibitor. In some embodiments, a compound of the disclosure is used in combination with a MEK2 inhibitor. In some embodiments, a compound of the disclosure is used in combination with an agent that can inhibit MEK1 and MEK2. In some embodiments, a compound of the disclosure is used in combination with a MEK1/MEK2 inhibitor, such as trametinib (Mekinist®), cobimetinib, binimetinib, selumetinib (AZD6244), pimasertibe (AS-703026), PD-325901, CI-1040, PD035901, or TAK-733. In some embodiments, a compound of the disclosure is used in combination with trametinib. In some embodiments, a compound of the disclosure is used in combination with cobimetinib.

[0217] **BRAF inhibitors**: BRAF inhibitors are drugs that inhibit the serine/threonine-protein kinase B-raf (BRAF) protein. In some embodiments, a compound of the disclosure is used in combination with a BRAF inhibitor. In some embodiments, a compound of the disclosure is used in combination with a BRAF inhibitor that can inhibit wild type BRAF. In some embodiments, a compound of the disclosure is used in combination with a BRAF inhibitor that can inhibit mutated BRAF. In some embodiments, a compound of the disclosure is used in combination with a BRAF inhibitor that can inhibit V600E mutated BRAF. In some embodiments, a compound of the disclosure is used in combination with a BRAF inhibitor, such as vemurafenib (Zelboraf®), dabrafenib (Tafinlar®), C-1, NVP-LGX818, or sorafenib (Nexavar®).

[0218] **KRAS inhibitors**: KRAS is a gene that acts as an on/off switch in cell signaling. In some embodiments, a compound of the disclosure is used in combination with a KRAS inhibitor. In some embodiments, a compound of the disclosure is used in combination with a wild type KRAS inhibitor. In some embodiments, a compound of the disclosure is used in combination with a mutated KRAS inhibitor (e.g., a G12C mutated KRAS). In some embodiments, the KRAS inhibitor is sotorasib (AMG-510), COTI-219, ARS-3248, WDB-178, BI-3406, BI-1701963, SML-8-73-1 (G12C), Compound 3144 (G12D), Kobe0065, Kobe/2602, (Ras GTP), RT11, or adagrasib (MRTX-849).

[0219] **BTK inhibitors**: Bruton's tyrosine kinase (BTK) is a non-receptor tyrosine kinase of the Tec kinase family that is involved in B-cell receptor signaling. In some embodiments, a compound of the disclosure is used in combination with a BTK inhibitor. In some embodiments, a compound of the disclosure is used in combination with a BTK inhibitor, such as ibrutinib or acalabrutinib.

[0220] **CDK inhibitors**: CDK4 and CDK6 are cyclin-dependent kinases that control the transition between the G1 and S phases of the cell cycle. CDK4/CDK6 activity is deregulated and overactive in

cancer cells. Selective CDK4/CDK6 inhibitors can block cell-cycle progression in the mid-G1 phase of the cell cycle, causing arrest and preventing the proliferation of cancer cells. In some embodiments, a compound of the disclosure is used in combination with a CDK4/CDK6 inhibitor. In some embodiments, a compound of the disclosure is used in combination with a CDK4/CDK6 inhibitor, such as palbociclib (Ibrance®), ribociclib, trilaciclib, seliciclib, dinaciclib, milciclib, roniciclib, atuveciclib, briciclib, riviciclib, voruciclib, or abemaciclib. In some embodiments, a compound of the disclosure is used in combination with palbociclib. In some embodiments, a compound of the disclosure is used in combination with ribociclib. In some embodiments, a compound of the disclosure is used in combination with abemaciclib.

[0221] In some examples, a compound of the disclosure is used in combination with an inhibitor of CDK4 and/or CDK6 and with an agent that reinforces the cytostatic activity of CDK4/6 inhibitors and/or with an agent that converts reversible cytostasis into irreversible growth arrest or cell death. Examples of cancer subtypes include NSCLC, melanoma, neuroblastoma, glioblastoma, liposarcoma, and mantle cell lymphoma. In some examples, a compound of the disclosure is used in combination with at least one additional pharmaceutically active agent that alleviates CDKN2A (cyclin-dependent kinase inhibitor 2A) deletion. In some examples, a compound of the disclosure is used in combination with at least one additional pharmaceutically active agent that alleviates CDK9 (cyclin-dependent kinase 9) abnormality.

[0222] In some embodiments, a compound of the disclosure is used in combination with a CDK2, CDK7, and/or CDK9 inhibitor. In some embodiments, a compound of the disclosure is used in combination with a CDK2, CDK7, or CDK9 inhibitor, such as seliciclib, voruciclib, or milciclib. In some embodiments, a compound of the disclosure is used in combination with a CDK inhibitor, such as dinaciclib, roniciclib (Kisqali®), or briciclib. In some examples, a compound of the disclosure is used in combination with at least one additional pharmaceutically-active agent that alleviates CDKN2A (cyclin-dependent kinase inhibitor 2A) deletion.

[0223] **ATM regulators**: A compound of the disclosure can be used in combination with one or more anti-cancer agent that regulates the ATM (upregulate or downregulate). In some embodiments the compounds described herein can synergize with one or more ATM regulators. In some embodiments one or more of the compounds described herein can synergize with all ATM regulators.

[0224] **AKT inhibitors**: In some embodiments, a compound of the disclosure is used in combination with one or more anti-cancer agent that inhibits the AKT (protein kinase B (PKB)). In some embodiments the compounds described herein can synergize with one or more AKT inhibitors.

n. Combination treatment with other anti-cancer agents

[0225] In some examples, a compound of the disclosure is used in combination with at least one anti-cancer agent that alleviates PTEN (phosphatase and tensin homolog) deletion. In some examples, a compound of the disclosure is used in combination with at least one anti-cancer agent that alleviates Wip-1Alpha over expression. In some examples, a compound of the disclosure is used in combination with at least one anti-cancer agent that is a Nucleoside metabolic inhibitor. Examples of nucleoside metabolic inhibitors include capecitabine, gemcitabine and cytarabine (Arac).

[0226] The table below lists suitable anti-cancer agents for use with the methods described herein.

Cancer Type	Drug name	Brand name
ALL	ABT-199	none
ALL	clofarabine	Clofarex
ALL	cyclophosphamide	Clafen, Cytoxan, Neosar
ALL	cytarabine	Cytosar-U, Tarabine PFS
ALL	doxorubicin	Adriamycin
ALL	imatinib mesylate	Gleevec
ALL	methotrexate	Abitrexate, Mexate, Folex
ALL	prednisone	Deltasone, Medicorten
ALL	romidepsin	Istodax
ALL	vincristine	Vincasar
AML	ABT-199	none
AML	azacitadine	Vidaza
AML	cyclophosphamide	Clafen, Cytoxan, Neosar
AML	cytarabine	Cytosar-U, Tarabine PFS
AML	decitabine	Dacogen
AML	doxorubicin	Adriamycin
AML	etoposide	Etopophos, Vepesid
AML	vincristine	Vincasar
bone	doxorubicin	Adriamycin
bone	methotrexate	Abitrexate, Mexate, Folex
breast	capecitabine	Xeloda
breast	cyclophosphamide	Clafen, Cytoxan, Neosar
breast	docetaxel	Taxotere
breast	doxorubicin	Adriamycin
breast	eribulin mesylate	Haliben
breast	everolimus	Afinitor
breast	exemestane	Aromasin
breast	fluorouracil	Adrucil, Efudex
breast	fulvestrant	Faslofex
breast	gemcitabine	Gemzar
breast	goserelin acetate	Zoladex
breast	letrozole	Femara
breast	megestrol acetate	Megace
breast	methotrexate	Abitrexate, Mexate, Folex

Cancer Type	Drug name	Brand name
breast	paclitaxel	Abraxane®, Taxol
breast	palbociclib	Ibrance
breast	pertuzumab	Perjeta
breast	tamoxifen citrate	Nolvadex
breast	trastuzumab	Herceptin, Kadcyla
colon	capecitabine	Xeloda
colon	cetuximab	Erbitux
colon	fluorouracil	Adrucil, Efudex
colon	irinotecan	camptosar
colon	ramucirumab	Cyramza
endometrial	carboplatin	Paraplatin, Paraplat
endometrial	cisplatin	Platinol
endometrial	doxorubicin	Adriamycin
endometrial	megestrol acetate	Megace
endometrial	paclitaxel	Abraxane®, Taxol
gastric	docetaxel	Taxotere
gastric	doxorubicin	Adriamycin
gastric	fluorouracil	Adrucil, Efudex
gastric	ramucirumab	Cyramza
gastric	trastuzumab	Herceptin
kidney	axitinib	Inlyta
kidney	everolimus	Afinitor
kidney	pazopanib	Votrient
kidney	sorafenib tosylate	Nexavar
liver	sorafenib tosylate	Nexavar
melanoma	dacarbazine	DTIC, DTIC-Dome
melanoma	paclitaxel	Abraxane®, Taxol
melanoma	trametinib	Mekinist
melanoma	vemurafenib	Zelboraf
melanoma	dabrafenib	Taflinar
mesothelioma	cisplatin	Platinol
mesothelioma	pemetrexed	Alimta
NHL	ABT-199	none
NHL	bendamustine	Treanda
NHL	bortezomib	Velcade

Cancer Type	Drug name	Brand name
NHL	brentuximab vedotin	Adcetris
NHL	chlorambucil	Ambochlorin, Leukeran, Linfolizin
NHL	cyclophosphamide	Clafen, Cytoxan, Neosar
NHL	dexamethasone	Decadrone, Dexasone
NHL	doxorubicin	Adriamycin
NHL	Ibrutinib	Imbruvica
NHL	lenalidomide	Revlimid
NHL	methotrexate	Abitrexate, Mexate, Folex
NHL	obinutuzumab	Gazyva
NHL	prednisone	Deltasone, Medicorten
NHL	romidepsin	Istodax
NHL	rituximab	Rituxan
NHL	vincristine	Vincasar
NSCLC	afatinib Dimaleate	Gilotrif
NSCLC	carboplatin	Paraplatin, Paraplat
NSCLC	cisplatin	Platinol
NSCLC	crizotinib	Xalkori
NSCLC	docetaxel	Taxotere
NSCLC	erlotinib	Tarceva
NSCLC	gemcitabine	Gemzar
NSCLC	methotrexate	Abitrexate, Mexate, Folex
NSCLC	paclitaxel	Abraxane®, Taxol
NSCLC	palbociclib	Ibrance
NSCLC	pemetrexed	Alimta
NSCLC	ramucirumab	Cyramza
ovarian	carboplatin	Paraplatin, Paraplat
ovarian	cisplatin	Platinol
ovarian	cyclophosphamide	Clafen, Cytoxan, Neosar
ovarian	gemcitabine	Gemzar
ovarian	olaparib	Lynparza
ovarian	paclitaxel	Abraxane®, Taxol
ovarian	topotecan	Hycamtin
prostate	abiraterone	Zytiga
prostate	cabazitaxel	Jevtana
prostate	docetaxel	Taxotere

Cancer Type	Drug name	Brand name
prostate	enzalutamide	Xtandi
prostate	goserelin acetate	Zoladex
prostate	prednisone	Deltasone, Medicorten
soft tissue sarcoma	doxorubicin	Adriamycin
soft tissue sarcoma	imatinib mesylate	Gleevec
soft tissue sarcoma	pazopanib	Votrient
T-cell lymphoma	romidepsin	Istodax

Administration of Combination Treatment of Compound of Disclosure and Anti-Cancer Agent

[0227] A compound of the disclosure or a pharmaceutical composition comprising a compound of the disclosure and at least one anti-cancer agent as disclosed herein can be administered simultaneously (i.e., simultaneous administration) or sequentially (i.e., sequential administration).

[0228] In some embodiments, a compound of the disclosure and the at least one anti-cancer agent described herein are administered simultaneously, either in the same composition or in separate compositions. When the drugs are administered simultaneously, the compound and the at least one anti-cancer agent described herein, may be contained in the same composition (*e.g.*, a composition comprising both the compound and the at least one anti-cancer agent) or in separate compositions (*e.g.*, the compound is contained in one composition and the at least one anti-cancer agent is contained in another composition).

[0229] In some embodiments, the compound and the at least one anti-cancer agent are administered sequentially, *i.e.*, the compound is administered either prior to or after the administration of the anti-cancer agent. In some embodiments, the compound is administered before the anti-cancer agent. In some embodiments, the anti-cancer agent described herein is administered before the compound. The compound and the anti-cancer agent described herein are contained in separate compositions, which may be contained in the same or different packages.

[0230] In some embodiments, the administration of the compound and the anti-cancer agent described herein are concurrent, *i.e.*, the administration period of the compounds and that of the anti-cancer agent overlap with each other. In some embodiments, the administration of the compounds and the anti-cancer agent described herein are non-concurrent. For example, in some embodiments, the administration of the compound is terminated before the anti-cancer agent described herein is administered. In some embodiments, the administration of the anti-cancer agent described herein is terminated before the compound is administered. The time period between these two non-concurrent administrations can range from being hours apart to being days apart to being weeks apart.

[0231] The dosing frequency of the compound and the at least one anti-cancer agent described herein may be adjusted over the course of the treatment, based on the judgment of the administering physician. When administered separately, the compound and the at least one anti-cancer agent described herein can be administered at different dosing frequency or intervals. For example, the compound can be

administered weekly, while the at least one anti-cancer agent described herein can be administered more or less frequently. Or, the compound can be administered twice weekly, while the at least one anti-cancer agent described herein can be administered more or less frequently. In addition, the compound and the at least one anti-cancer agent described herein can be administered using the same route of administration or using different routes of administration.

[0232] A therapeutically-effective amount of a compound and/or the anti-cancer agent described herein for use in therapy can vary with the nature of the condition being treated, the length of treatment time desired, the age and the condition of the patient, and can be determined by the attending physician.

[0233] In some embodiments, when a compound of the disclosure is administered in combination with at least one anti-cancer agent described herein, the dosage of the compound can be given a lower dosage than when the compound is administered alone. . In some embodiments, the dosage of a compound of the disclosure in combination therapy can be from about 1 mg/kg to about 20 mg/kg. In some embodiments, the dosage of a compound of the disclosure in combination therapy can be from about 5 mg/kg to about 10 mg/kg..

[0234] In some embodiments, the dosage of a compound of the disclosure in combination therapy can be in an amount of about 0.5 mg/kg; about 1 mg/kg; about 2 mg/kg; about 3 mg/kg; about 4 mg/kg; about 5 mg/kg; about 6 mg/kg; about 7 mg/kg; about 8 mg/kg; about 9 mg/kg; or about 10 mg/kg..

[0235] In some embodiments, the dosage of the compound of the disclosure in combination therapy with at least one additional therapeutic agent can be at least 5% less than the dose of the compound of the disclosure administered alone, or at least 10% less, at least 15% less, at least 20% less, at least 25% less, at least 30% less, at least 35% less, at least 40% less, at least 45% less, at least 50% less, at least 55% less, at least 60% less, at least 65% less, at least 70% less, or at least 75% less than the dose of the compound of the disclosure administered alone.

[0236] In some embodiments, when a compound of the disclosure is administered in combination with at least one anti-cancer agent described herein, the dosage of the at least one additional anti-cancer agent can be given a lower dosage than when the anti-cancer agent is administered alone. In some embodiments, the dosage of the at least one anti-cancer agent in combination therapy can be from about 50 μg to about 100 μg; from about 100 μg to about 150 μg; from about 150 μg to about 200 μg; from about 200 μg to about 250 μg; from about 250 μg to about 300 μg; from about 300 μg to about 350 μg; from about 350 μg to about 400 μg; from about 400 μg to about 450 μg; from about 450 μg to about 500 μg; from about 500 μg to about 600 μg; from about 600 μg to about 700 μg; from about 700 μg to about 800 μg; from about 800 μg to about 900 μg; or from about 900 μg to about 1000 μg. In some embodiments, the dosage of the at least one anti-cancer agent in combination therapy can be from about 100 μg to about 150 μg. In some embodiments, the dosage of the at least one anti-cancer agent in combination therapy can be from about 150 μg to about 200 μg. In some embodiments, the dosage of the at least one additional anti-cancer agent in combination therapy can be from about 200 μg to about 250 μg.

[0237] In some embodiments, the dosage of the at least one anti-cancer agent in combination therapy can be in an amount of about 50 μg; about 100 μg; about 150 μg; about 200 μg; about 250 μg; about 300 μg;

about 350 μg; about 400 μg; about 450 μg; or about 500 μg. In some embodiments, the dosage of the at least one anti-cancer agent in combination therapy can be in an amount of about 200 μg.

[0238] In some embodiments, the dosage of the at least one anti-cancer agent in combination therapy can be from about 1 mg/kg to about 5 mg/kg; from about 5 mg/kg to about 25 mg/kg; from about 25 mg/kg to about 50 mg/kg; from about 50 mg/kg to about 75 mg/kg; from about 75 mg/kg to about 100 mg/kg; from about 100 mg/kg to about 150 mg/kg; from about 150 mg/kg to about 200 mg/kg; from about 200 mg/kg to about 250 mg/kg; from about 250 mg/kg to about 300 mg/kg; from about 300 mg/kg to about 350 mg/kg; from about 350 mg/kg to about 400 mg/kg; from about 400 mg/kg to about 450 mg/kg; from about 450 mg/kg to about 500 mg/kg; from about 500 mg/kg to about 600 mg/kg; from about 600 mg/kg to about 700 mg/kg; from about 700 mg/kg to about 800 mg/kg; from about 800 mg/kg to about 900 mg/kg; or from about 900 mg/kg to about 1000 mg/kg. In some embodiments, the dosage of the at least one anti-cancer agent in combination therapy can be from about 1 mg/kg to about 5 mg/kg. In some embodiments, the dosage of the at least one anti-cancer agent in combination therapy can be from about 100 mg/kg to about 150 mg/kg. In some embodiments, the dosage of the at least one additional therapeutic agent in combination therapy can be from about 200 mg/kg to about 250 mg/kg.

[0239] In some embodiments, the dosage of the at least one anti-cancer agent in combination therapy can be at least 5% less than the dose of the at least one anti-cancer agent administered alone, or at least 10% less, at least 15% less, at least 20% less, at least 25% less, at least 30% less, at least 35% less, at least 40% less, at least 45% less, at least 50% less, at least 55% less, at least 60% less, at least 65% less, at least 70% less, or at least 75% less than the dose of the at least one anti-cancer agent administered alone.

[0240] In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be from about 1 mg/kg to about 20 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy can be from about 1 mg/kg to about 500 mg/kg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be from about 5 mg/kg to about 10 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy can be from about 1 mg/kg to about 250 mg/kg.

[0241] In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be about 1 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy can about 5 mg/kg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be about 2 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy can about 5 mg/kg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be about 4 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy can about 5 mg/kg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be about 6 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy can about 5 mg/kg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be about 8 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy can about 5 mg/kg.

[0242] In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be from about 1 mg/kg to about 20 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy can be from about 100 μg to about 500 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be from about 5 mg/kg to about 10 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy can be from about 100 μg to about 500 μg.

[0243] In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be about 1 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 2 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 4 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 6 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 8 mg/kg; and the dosage of the at least one anti-cancer agent in combination therapy is about 200 μg.

[0244] In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be from about 1 mg/kg to about 20 mg/kg; and the dosage of anti-PD-1 agent as an anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be from about 5 mg/kg to about 10 mg/kg; and the dosage of anti-PD-1 agent as an anti-cancer agent in combination therapy is about 200 μg.

[0245] In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 1 mg/kg or about 100 mg; and the dosage of anti-PD-1 agent as an anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 2 mg/kg or about 150 mg; and the dosage of anti-PD-1 agent as an anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 4 mg/kg or about 300 mg; and the dosage of anti-PD-1 agent as an anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 6 mg/kg or about 400 mg; and the dosage of anti-PD-1 agent as an anti-cancer agent in combination therapy is about 200 μg. . In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 8 mg/kg or about 500 mg; and the dosage of anti-PD-1 agent as an anti-cancer agent in combination therapy is about 200 μg.

[0246] In some embodiments, the dosage of the compound of the disclosure administered in combination therapy can be from about 1 mg/kg to about 20 mg/kg; and the dosage of anti-CD20 agent as an anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound

of the disclosure administered in combination therapy can be from about 5 mg/kg to about 10 mg/kg; and the dosage of anti- CD20 agent as an anti-cancer agent in combination therapy is about 200 μg.

[0247] In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 1 mg/kg; and the dosage of anti- CD20 agent as an anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 2 mg/kg; and the dosage of anti- CD20 agent as an anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 4 mg/kg; and the dosage of anti- CD20 agent as an anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 6 mg/kg; and the dosage of anti- CD20 agent as an anti-cancer agent in combination therapy is about 200 μg. In some embodiments, the dosage of the compound of the disclosure administered in combination therapy is about 8 mg/kg; and the dosage of anti- CD20 agent as an anti-cancer agent in combination therapy is about 200 μg

[0248] In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject once a day. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject twice a day. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject three times a day.

[0249] In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day once every 1, 2, 3, 4, 5, 6, or 7 days. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject once a day once every 3 days. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject twice a day once every 3 days. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day once every 7 days. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject once a day once every 7 days. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject twice a day once every 7 days.

[0250] In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day once every 1, 2, 3, 4, 5, 6, or 7 days for 1 to 50 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day once every 1, 2, 3, 4, 5, 6, or 7 days for about 5 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day once every 1, 2, 3, 4, 5, 6, or 7 days for about 10 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day once every 1, 2, 3, 4, 5, 6, or 7 days for about 15 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can

be administered to a subject 1, 2, 3, 4, or 5 times a day once every 1, 2, 3, 4, 5, 6, or 7 days for about 20 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day once every 1, 2, 3, 4, 5, 6, or 7 days for about 25 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day once every 1, 2, 3, 4, 5, 6, or 7 days for about 30 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject 1, 2, 3, 4, or 5 times a day once every 1, 2, 3, 4, 5, 6, or 7 days for about 35 doses.

[0251] In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject once a day every 7 days for about 5 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject once a day every 7 days for about 10 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject twice a day every 7 days for about 15 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject once a day every 3 days for about 20 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject once a day every 3 days for about 35 doses.

[0252] In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject twice a day every 7 days for about 5 doses. In some embodiments, a pharmaceutically-acceptable amount of a compound of the disclosure can be administered to a subject twice a day every 7 days for about 15 doses.

Pharmaceutical compositions for combination treatment

[0253] According to certain embodiments, the compounds and the anti-cancer agent described herein are administered within a single pharmaceutical composition. In some embodiments, the compounds of the disclosure and the anti-cancer agent described herein can be provided in a single unit dosage form for being taken together. According to some embodiments, the pharmaceutical composition further comprises a pharmaceutically-acceptable diluent or carrier. According to certain embodiments, the compounds of the disclosure and the anti-cancer agent described herein are administered within different pharmaceutical compositions. In some embodiments, the compounds of the disclosure and the anti-cancer agent described herein can be provided in a single unit dosage as separate entities (e.g., in separate containers) to be administered simultaneously or with a certain time difference.

[0254] In some embodiments, the compounds of the disclosure and the anti-cancer agent described herein can be administered via the same route of administration. In some embodiments, the compounds of the disclosure and the anti-cancer agent described herein can be administered via the different route of administration. In some embodiments, a compound of the disclosure and the anti-cancer agent are administered orally. In some embodiments, a compound of the disclosure is administered orally, and the anti-cancer agent is not administered orally. In some embodiments, a compound of the disclosure is not administered orally, and the anti-cancer agent is administered orally.

[0255] Treatment of a condition by administering a compound of the disclosure in combination with an anti-cancer agent can increase a median survival time of a subject compared to subjects who do not receive the combination therapy. In some embodiments, a median survival time of a first patient population receiving the combination therapy can be greater than a median survival time of a second patient population that does not receive any cancer therapy. In some embodiments, a median survival time of a first patient population receiving the combination therapy can be greater than a median survival time of a second patient population that receives therapy with a compound of the disclosure alone. In some embodiments, a median survival time of a first patient population receiving the combination therapy can be greater than a median survival time of a second patient population that receives therapy with the anti-cancer agent alone.

[0256] In some embodiments, a median survival time of a first patient population receiving the combination therapy can be greater than a median survival time of a second patient population not receiving the combination therapy (e.g., no therapy, a compound of the disclosure alone, or the anti-cancer agent alone) by at least about 50%, about 60%, about 70%, about 80%, about 90%, about 100%, about 110%, about 120%, about 130%, about 140%, about 150%, about 160%, about 170%, about 180%, about 190%, about 200%, about 210%, about 220%, about 230%, about 240%, about 250%, about 260%, about 270%, about 280%, about 290%, about 300%, about 310%, about 320%, about 330%, about 340%, about 350%, about 360%, about 370%, about 380%, about 390%, about 400%, about 410%, about 420%, about 430%, about 440%, about 450%, about 460%, about 470%, about 480%, about 490%, or about 500%. In some embodiments, a median survival time of a first patient population receiving the combination therapy can be greater than a median survival time of a second patient population not receiving the combination therapy by at least about 50%. In some embodiments, a median survival time of a first patient population receiving the combination therapy can be greater than a median survival time of a second patient population not receiving the combination therapy by at least about 100%. In some embodiments, a median survival time of a first patient population receiving the combination therapy can be greater than a median survival time of a second patient population not receiving the combination therapy by at least about 150%. In some embodiments, a median survival time of a first patient population receiving the combination therapy can be greater than a median survival time of a second patient population not receiving the combination therapy by at least about 200%.

Methods of treatment

[0257] Provided herein is a method of treating cancer in a subject in need thereof, the method comprising: (i) administering to the subject a therapeutically-effective amount of a compound that blocks SUMOylation in the subject; and (ii) administering to the subject a therapeutically-effective amount of an anti-cancer agent that functions through a pathway other than SUMOylation. In some embodiments, a compound of the disclosure comprises a substituted 4,5,6,7-tetrahydrothieno[2,3-c]pyridine group, wherein the compound blocks SUMOylation. In some embodiments, the compound binds to Uba2. In some embodiments, the compound has an inhibitory effect on activating enzymes (E1) of SUMO.

[0258] In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is breast

cancer. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is AML. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is a lymphoma. In some embodiments, the subject is human.

[0259] In some embodiments, the administering of the compound is oral. In some embodiments, the administering of the compound is subcutaneous. In some embodiments, the administering of the compound is topical.

[0260] In some embodiments, the therapeutically-effective amount of the compound is from about 1 mg/kg to about 20 mg/kg. In some embodiments, the therapeutically-effective amount of the compound is from about 5 mg to about 10 mg.. In some embodiments, the therapeutically-effective amount of the compound is about 50 mg, about 5100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, or about 500 mg. In some embodiments, the therapeutically-effective amount of the compound is about 150 mg. In some embodiments, the therapeutically-effective amount of the compound is about 200 mg. In some embodiments, the therapeutically-effective amount of the compound is about 300 mg. In some embodiments, the therapeutically-effective amount of the compound is about 400 mg.

[0261] In some embodiments, the anti-cancer agent is a small molecule. In some embodiments, the anti-cancer agent is an antibody.

[0262] In some embodiments, the anti-cancer agent is an immune checkpoint inhibitor. In some embodiments, the immune checkpoint inhibitor is an anti-PD-1 agent. In some embodiments, the anti-PD-1 agent is nivolumab. In some embodiments, the anti-PD-1 agent is pembrolizumab. In some embodiments, the anti-PD-1 agent is cemiplimab. In some embodiments, the immune checkpoint inhibitor is an anti-PD-L1 agent. In some embodiments, the anti-PD-L1 agent is atezolizumab. In some embodiments, the anti-PD-L1 agent is avelumab. In some embodiments, the anti-PD-L1 agent is durvalumab. In some embodiments, the administering of the anti-cancer agent is oral. In some embodiments, the administering of the anti-cancer agent is subcutaneous. In some embodiments, the administering of the anti-cancer agent is topical. In some embodiments, the therapeutically-effective amount of the anti-cancer agent is from about 5 mg/kg to about 500 mg/kg. In some embodiments, the therapeutically-effective amount of the anti-cancer agent is from about 10 μg to about 500 μg. In some embodiments, the therapeutically-effective amount of the anti-cancer agent is about 200 μg.

[0263] In some embodiments, the anti-cancer agent is an anti-CD20 antibody. Such anti-CD-20 antibodies include rituximab (Mabthera®/ Rituxan®), obinutuzumab (Gazyva®), ibritumomab tiuxetan, tositumomab, ofatumumab (Genmab®), ocaratuzumab, ocrelizumab, TRU-015, and veltuzumab. In some cases, the anti-cancer agent is rituximab. In some embodiments, the therapeutically-effective amount of the anti-CD20 antibody is from about 5 mg/kg to about 500 mg/kg. In some embodiments, the therapeutically-effective amount of the anti-CD20 antibody is from about 10 μg to about 500 μg.

[0264] In some embodiments, the anti-cancer agent is a hypomethylating agent (HMA). In some embodiments, a compound of the disclosure is used in combination with a HMA, such as azacitidine (Vidaza®, Azadine®) or decitabine (Dacogen®). In some embodiments, the therapeutically-effective

amount of the HMA is from about 5 mg/kg to about 500 mg/kg. In some embodiments, the therapeutically-effective amount of the HMA is from about 0.005 μM to about 0.500 μM.

[0265] Each patent, publication, and non-patent literature cited in this disclosure is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

EXAMPLES

EXAMPLE 1: *Compounds of the disclosure*

[0266] SUMO inhibitors were prepared as described in PCT publication WO2020191151, WO2021150918 and PCT application PCT/US22/73985 and are shown in **TABLE A**. For the examples below, Compound A is (S,E)-6-(4-(dimethylamino)but-2-enoyl)-4-(2-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-3-fluorophenyl)-3-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-2-carbonitrile.

EXAMPLE 2: *Combination of Compound A and anti-CD-20 agents [rituximab] in subcutaneous mouse lymphoma xenograft model [Raji human B cell]*

[0267] The anti-tumor efficacy of Compound A in combination with rituximab was evaluated in the subcutaneous Raji human lymphoma xenograft model in female CB17 SCID mice. The overall dosing regimen is included in Table 1. The Raji tumor cells (ATCC, Cat# CCL-86) were maintained in vitro as a suspension culture in RPMI 1640 medium supplemented with 10% heat inactivated fetal bovine serum, 100 U/mL penicillin and 100 μg/mL streptomycin at 37°C in an atmosphere of 5% CO2 in air. The tumor cells were routinely subcultured twice weekly. The cells growing to a confluency around 70% - 80% were harvested and counted for tumor inoculation. 75 CB17 SCID mice [female, 6-8 weeks old, 18-20g weight] were inoculated subcutaneously at the right flanks with Raji cells for tumor development. The mice were kept in individual ventilation cages at constant temperature and humidity with 4 animals in each cage [temperature 20-26 C and 40-70% humidity]. Fourteen days after tumor inoculation, 48 mice with tumor sizes ranging from 65-268 mm^3 (average tumor size 147.16 mm3) were selected and assigned into 6 groups using stratified randomization with 8 mice in each group based upon their tumor volumes. The treatments were started from the day of randomization (defined as PG-D1) and mice were treated as follows: Group 1: Vehicle control, p.o., (BIW on D1/4/8/11/14); Group 2: Compound A, 50 mg/kg, p.o., (BIW on D1/4/8/11/14/17); Group 3: Rituximab, 20 mg/kg, i.p., (BIW on D1/4/8/11/14); Group 4: Compound A, 50 mg/kg, p.o.,+ Rituximab, 20 mg/kg, i.p., (BIW on D1/4/8/11/14/17); Group 5: Compound A, 50 mg/kg, p.o., (QD x 17 days); and Group 6: SUMO comparator, 15 mg/kg, i.v., (BIW on D1/4/8/11/14/17). The entire study was terminated on day 17 and plasma samples were collected for analysis. Dosing was QD: daily, Q2D: once every 2 days, QW: once weekly. BIW: twice weekly. BID: twice daily. All the treatments groups showed significant statistically difference on tumor growth inhibition ($p<0.0001$ vs. vehicle control via Two-way RM ANOVA). P values represent statistical significance compared to the vehicle control group. COMPOUND A inhibits the growth of lymphoma tumors in vivo.

Table 1

Group	n	Treatment	Dose (mg/kg)	Dosing Volume (mL/kg)	Dosing Route	Schedule
1	8	Vehicle control	--	10	p.o.	D1/4/8/11/14
2	8	CPD A	50	10	p.o.	D1/4/8/11/14/17
3	8	Rituximab	20	10	i.p.	D1/4/8/11/14
4	8	CPD A	50	10	p.o.	D1/4/8/11/14/17
		Rituximab	20	10	i.p.	D1/4/8/11/14/17
5	8	CPD A	50	10	p.o.	QD x17 days

[0268] Body weights were measured at days 1, 4, 8, 11 and 14 after the start of treatment. No obvious body weight loss was observed during the dosing period, all the treatments were tolerated well. Relative change of body Weight (RCBW) of each mouse was calculated according to the following formula: RCBW (%) = (BWTreatment_DayN - BWTreatment_Day0)/ BWTreatment_Day0×100%. Weight change of less than 5% was observed. See Figure 2.

[0269] Tumor Measurements and Endpoints - The major endpoint is to see if the tumor growth can be delayed or mice can be cured. Tumor sizes were measured two times a week in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: $V = 0.5\ a \times b^2$ where a and b are the long and short diameters of the tumor, respectively. The tumor sizes were used for the calculations of both tumor growth inhibition (TGI) values. TGI is calculated for each group using the formula: TGI (%) = [1-(TVTreatment_DayN- TVTreatment_Day0)/ (TVVehicle_DayN - TVVehicle_Day0)] ×100%; TVTreatment_DayN is the average tumor volume of a treatment group on a given day, TVTreatment_Day0 is the average tumor volume of the treatment group on the first day of treatment, TVVehicle_DayN is the average tumor volume of the vehicle control group on a given day, and TVVehicle_Day0 is the average tumor volume of the vehicle group on the first day of treatment. Mean tumor volumes over time are shown in Table 2 and tumor growth curves are shown in Figure 1. Tumor growth inhibition values are shown in Table 3.

Table 2. Tumor Volume over Time

Days	G1: Vehicle, p.o., (BIW D1/4/8/11/14)	G2: CPD A, 50mg/kg, p.o., (BIW on D1/4/8/11/14/17)	G3: Rituximab 20mg/kg, i.p., BIW on D1/4/8/11/14	G4: CPD A, 50mg/kg, p.o.,+ Rituximab, 20mg/kg, i.p., BIW on D1/4/8/11/14/17	G5: CPD A, 50mg/kg, p.o. QD x 17 days
1	148±20	150±19	145±19	144±19	148±23
4	285±48	240±32	248±52	193±30	226±35
8	577±136	342±53	357±80	184±21	275±45
11	822±186	385±68	410±106	151±23	306±60
14	1267±260	361±67	446±125	113±16	306±64
17	-	380±70	554±147	80±5	363±68

Table 3. Tumor Growth Inhibition Parameters Based on TV Measurements on Day 14

Treatment	Tumor Size (mm^3)	TGI (%)	*P value a*
Group 1	1267±260	-	-
Group 2	361±67	81.12	< 0.0001
Group 3	446±125	73.09	< 0.0001
Group 4	113±16	102.81	< 0.0001
Group 5	306±64	85.88	< 0.0001
Group 6	416±46	76.01	< 0.0001

EXAMPLE 3: *Combination of Compound A and a hypomethylating agent (HMA) in AML cell line model [GDM-1 cells and MV4-11]*

[0270] Assay Principle - This cellular assay measures the viability of leukemia cell lines upon treatment with a SUMO E1 inhibitor, Compound A, and a hypomethylating agent (HMA), decitabine, as single agents, as well as in combination. Cell viability was measured using the Promega CellTiter-Glo Luminescent Cell Viability Assay, which determines the number of viable cells based on the quantitation of ATP (as an indicator of metabolically active cells). Three acute myeloid leukemia (AML) cell lines, including GDM-1, and MV4-11, were first treated with Compound A or decitabine as single treatments to establish single agent IC50s to describe the quantity of compound needed to inhibit 50% of cell viability. Next, cells were treated with both Compound A and decitabine, with 4 to 5 decreasing doses of each compound, to generate a matrix of 25 combinations. Dose response curves and IC50 values were generated, and Zero interaction potency (ZIP) synergy scores were calculated using SynergyFinder 3.0 (https://synergyfinder.fimm.fi/synergy/2022070121520519 3938/). The ZIP model determines whether combination treatments result in synergistic or additive effects by comparing the potency at specific dose levels between single and combination treatments. Overall, the cell viability of three different AML cells lines were evaluated during single and combination treatment with Compound A and decitabine to determine the efficacy of combination therapy.

[0271] GDM-1 and MV4-11 cells were plated overnight in white-walled 96-well plates (10,000 cells/well in 100ul total volume). The next day, compounds were diluted in cell culture media and cells were treated with 4 to 5 different doses of Compound A and decitabine (either as single treatment or in combination). Cells were then incubated for 72 hrs. At 72 hrs post-treatment, cells were lysed with the CellTiter-Glo 2.0 reagent, and luminescence signal was read using the Glomax Discover Promega plate reader (program CellTiter-Glo). The raw data were analyzed in Excel to calculate percent inhibition compared to a DMSO control and the obtained values were plotted using GraphPad Prism 9 (ver. 9.4.0) to derive dose response curves and IC_{50} values. Zero interaction potency (ZIP) synergy scores were calculated using SynergyFinder 3.0 (https://synergyfinder.fimm.fi/synergy/2022 0701215205193938/).

[0272] Two different AML cell lines were tested to determine whether the efficacy of Compound A could be enhanced by combining with the chemotherapeutic compound decitabine. Cells were treated with 4 to 5 different doses of Compound A in combination with 4 to 5 doses of decitabine, and cell viability was measured at 72 hrs post-treatment. Figure 3A shows cell viability dose response curves of Compound

A alone, along with the combination of escalating doses with decitabine in GDM-1 and MV-411 cells. The IC_{50} values from each curve, along with the calculated ZIP score are found in Table 4. For all three cell lines, the combination of Compound A and decitabine impacted cell viability, as seen in the shift in the dose response curves (Figure 3A) and in the reduction in the IC_{50} values compared to treatment with Compound A alone (Table 4). In addition, all three cell lines exhibited an additive effect when the two drugs were combined, as shown by calculated ZIP values (between -10 and 10) using SynergyFinder 3.0 (Table 4). This additive effect can also be seen in Figure 3B, where combination treatment led to a greater % inhibition when compared to single treatment with Compound A or decitabine. As seen in Figure 3B, single treatment of MV-411 cells with the indicated doses of Compound A or decitabine resulted in between 40-80% inhibition, but that the combination of both compounds resulted in 100% inhibition. Overall, these data indicate that the efficacy of Compound A and was increased upon combination with decitabine.

[0273] Compound A alone inhibited GDM-1 cell growth with an IC_{50} of 0.209 μM, and addition of decitabine caused left-shifted IC_{50} curves (left graph), and decreasing IC_{50} values for Compound A (right table) indicating enhanced anti-tumor activity.

[0274] Compound A (0.167μM) or decitabine (0.167μM) as single agents inhibited MV4-11 cell growth, but the combination of the two agents resulted in greater inhibition of tumor cell growth (left graph). In dose response format, Compound A inhibited the growth of MV4-11 cells with an IC_{50} of 0.16 μM, and this decreased with increasing concentrations of decitabine (right table).

Table 4. Tumor Growth Inhibition over Time

CELLS	**Concentrations**	**CPD IC50** (μM)
GDM-1	Compound A	0.209
	CPD A and 0.1234 μM decitabine	0.124
	CPD A and 0.0370 μM decitabine	0.078
	CPD A and 0.1111 μM decitabine	nd
	CPD A and 0.3333 μM decitabine	nd
	CPD A and 1.0 μM decitabine	nd
MV4-11	Compound A	0.16
	CPD A and 0.006 μM decitabine	0.098
	CPD A and 0.0185 μM decitabine	0.148
	CPD A and 0.056 μM decitabine	0.115
	CPD A and 0.167 μM decitabine	0.1453

EXAMPLE 4: *Combination of Compound A and anti-PD-1 agent in a mouse colon cancer model*

[0275] The combinations of the present invention are evaluated in CT26 model of syngeneic colon cancer. See Sato, Y., Fu, Y., Liu, H. *et al.* Tumor-immune profiling of CT-26 and Colon 26 syngeneic mouse models reveals mechanism of anti-PD-1 response. *BMC Cancer* **21**, 1222 (2021). For

the CT26 tumor study, BALB/c mice are injected subcutaneously with 1 x 10^5 CT26 cells on Day 0. Beginning day 5, mice are treated with Compound A [50 mpk]. and 250 pg of anti-PD-1 (BioXcell, Clone RMP1-14) or isotype control (BioXcell, Clone 2A3). Subsequently, all mice were continued on study the assigned combination therapy on days 12, 15, and 19.

[0276] Tumor volume is assessed using the formula TV = 0.5 x (L x W^2) where length (L) is the longest dimension of the tumor and width (W) is the longest dimension perpendicular to the length. Statistical significance of treatment is assessed using Prism V8.0 software (GraphPad Software, San Diego, CA).

[0277] Administration of Compound A results in dose responsive anti-tumor effect with tumor grow delay. Combination therapy with anti-PD-1 significantly improves the anti-tumor effect demonstrating regression, cures, and a significant increase in median survival time at the highest dose level.

EMBODIMENTS

[0278] The following non-limiting embodiments provide illustrative examples of the invention, but do not limit the scope of the invention.

[0279] Embodiment 1. A method of treating a cancer in a subject in need thereof, the method comprising:
(i) administering to the subject a therapeutically-effective amount of a compound that blocks SUMOylation in the subject; and
(ii) administering to the subject a therapeutically-effective amount of an anti-cancer agent that functions through a pathway other than SUMOylation.

[0280] Embodiment 2. The method of embodiment 1, wherein the compound binds to Uba2.

[0281] Embodiment 3. The method of embodiment 1, wherein the compound has an inhibitory effect on activating enzymes (E1) of SUMO.

[0282] Embodiment 4. The method of embodiment 1, wherein the cancer is selected from acute myeloid leukemia, large B-cell lymphoma, lung squamous cell carcinoma, pancreatic adenocarcoma, esophegeal carcinoma, cervical squamous cell carcinoma, endocervical adenocarcoma, stomach adenocarcinomathymoma, renal cell carcinoma, head and neck squamous cell carcinoma, bladder carcinoma, ovarian cystadenocarcinoma, multiple myeloma, non-Hodgkin's lymphoma (NHL), and mesothelioma.

[0283] Embodiment 5. The method of embodiment 1, wherein the cancer is selected from head and neck squamous cell carcinoma (HNSCC), non-squamous non-small cell lung cancer (NSCLC), cervical cancer, colorectal cancer (CRC), cutaneous melanoma, squamous NSCLC, and small cell lung cancer.

[0284] Embodiment 6. The method of embodiment 1, wherein the cancer is B Cell Lymphoma.

[0285] Embodiment 7. The method of embodiment 1, wherein the cancer is acute myeloid leukemia.

[0286] Embodiment 8. The method of embodiment 1, wherein the cancer is colon cancer.

[0287] Embodiment 9. The method of embodiment 1, wherein the administering of the compound is oral.

[0288] Embodiment 10. The method of embodiment 1, wherein the subject is human

[0289] Embodiment 11. The method of embodiment 1, wherein the therapeutically-effective amount of the compound is from about 100 mg to about 500 mg.

[0290] Embodiment 12. The method of any one of embodiments 1-12, wherein the therapeutically-

effective amount of the compound is from about 200 mg to about 400 mg.

[0291] Embodiment 13. The method of any one of embodiments 1-13, wherein the therapeutically-effective amount of the compound is about 300 mg.

[0292] Embodiment 14. The method of any one of embodiments 1-13, wherein the therapeutically-effective amount of the compound is about 200 mg.

[0293] Embodiment 15. The method of any one of embodiments 1-13, wherein the therapeutically-effective amount of the compound is about 400 mg.

[0294] Embodiment 18. The method of any one of embodiments 1-17, wherein the anti-cancer agent is a small molecule.

[0295] Embodiment 19. The method of any one of embodiments 1-17, wherein the anti-cancer agent is an antibody.

[0296] Embodiment 20. The method of any one of embodiments 1-17, wherein the anti-cancer agent is an immune checkpoint inhibitor.

[0297] Embodiment 21. The method of any one of embodiments 1-17 or 20, wherein the immune checkpoint inhibitor is an anti-PD-1 agent.

[0298] Embodiment 22. The method of any one of embodiments 1-17, 20, or 21, wherein the anti-PD-1 agent is nivolumab.

[0299] Embodiment 23. The method of any one of embodiments 1-17, 20, or 21, wherein the anti-PD-1 agent is pembrolizumab.

[0300] Embodiment 24. The method of any one of embodiments 1-17, 20, or 21, wherein the anti-PD-1 agent is cemiplimab.

[0301] Embodiment 25. The method of any one of embodiments 1-17 or 20, wherein the immune checkpoint inhibitor is an anti-PD-L1 agent.

[0302] Embodiment 26. The method of any one of embodiments 1-17, 20, or 25, wherein the anti-PD-L1 agent is atezolizumab.

[0303] Embodiment 27. The method of any one of embodiments 1-17, 20, or 25, wherein the anti-PD-L1 agent is avelumab.

[0304] Embodiment 28. The method of any one of embodiments 1-17, 20, or 25, wherein the anti-PD-L1 agent is durvalumab.

[0305] Embodiment 29. The method of any one of embodiments 1-28, wherein the administering of the anti-cancer agent is oral.

[0306] Embodiment 30. The method of any one of embodiments 1-28, wherein the administering of the anti-cancer agent is subcutaneous.

[0307] Embodiment 31. The method of any one of embodiments 1-28, wherein the administering of the anti-cancer agent is topical.

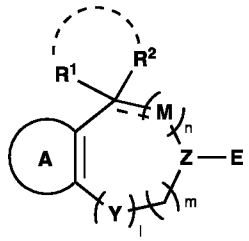
[0308] Embodiment 32. The method of any one of embodiments 1-31, wherein the therapeutically-effective amount of the anti-cancer agent is from about 1 mg/kg to about 20 mg/kg.

[0309] Embodiment 33. The method of any one of embodiments 1-31, wherein the therapeutically-

effective amount of the anti-cancer agent is from about 10 μg to about 500 μg.

[0310] Embodiment 34. The method of any one of embodiments 1-31 or 33, wherein the therapeutically-effective amount of the anti-cancer agent is about 200 μg.

[0311] Embodiment 35. The method of any one of embodiments 1-34, wherein the compound is of the formula:



(I)

wherein ==== is a single bond or double bond;

wherein l, m, n are each independently an integer from 0 to 2;

wherein M is selected from CR^3R^4, NR^5, C=O, O, S=O, O=S=O, and S;

wherein Y is selected from CR^6R^7, NR^8, C=O, O, S=O, O=S=O, and S;

wherein Z is CR^9, or N;

wherein ring A is selected from

a) 5- or 6-membered partially saturated heterocyclyl,

b) 5- or 6-membered aryl or heteroaryl,

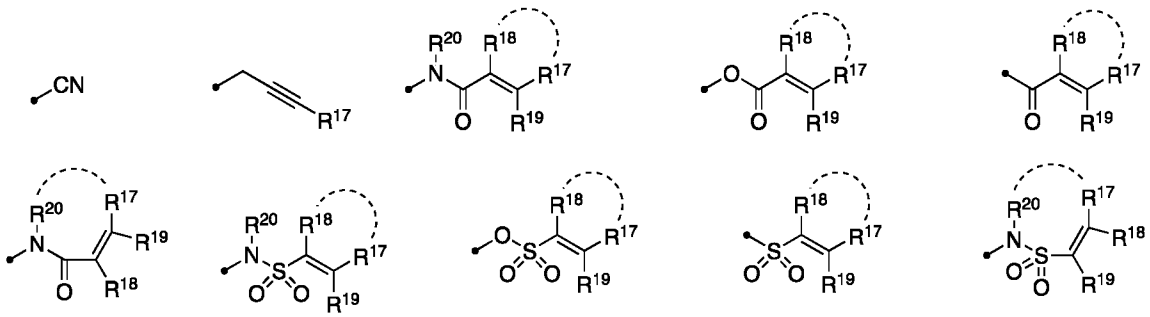
c) 9-, 10- or 11-membered fused partially saturated heterocyclyl,

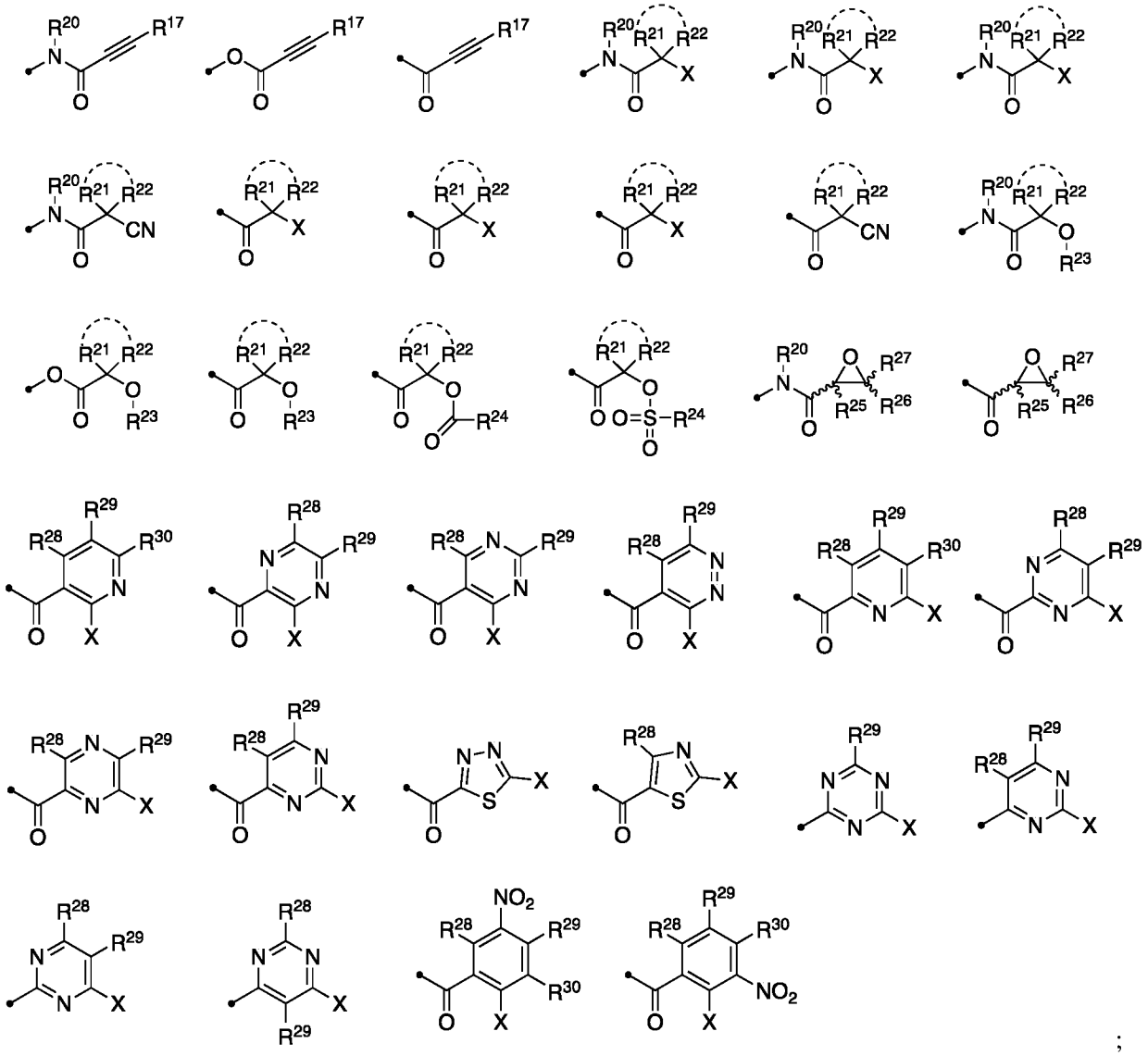
d) 9- or 10-membered fused heteroaryl,

e) naphthyl, and

f) 4-, 5- or 6-membered cycloalkenyl;

wherein E is an electrophilic moiety, selected from:





;

Wherein R^1 is selected from hydrogen, halogen, $-C(X^1)_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-NHNR^{1A}R^{1B}$, $-C(O)R^{1A}$, $-C(O)-OR^{1A}$, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHNR^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$, $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, 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;

Wherein R^2 is selected from hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHNR^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHNR^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$, $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, 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; R^1 and R^2 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

Wherein R^3 is selected from hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHNR^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, 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;

Wherein R^4 is selected from hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHNR^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHNR^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, 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^3 and R^3 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

Wherein R^5 is selected from hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHNR^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHNR^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, 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;

Wherein R^6 is selected from hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-NHNR^{6A}R^{6B}$, $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHNR^{6A}R^{6B}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, 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;

Wherein R^7 is selected from hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHNR^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHNR^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, 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;

Wherein R^8 is selected from hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, -CN, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}8^{7B}$, $-NHNR^{8A}R^{8B}$, $-C(O)R^{8A}$, $-C(O)-OR^{8A}$, $-C(O)NR^{8A}R^{8B}$, $-C(O)NHNR^{8A}R^{8B}$,

$-OR^{8A}$, $-NR^{8A}SO_2R^{8B}$, $-NR^{8A}C(O)R^{8B}$, $-NR^{8A}C(O)OR^{8B}$, $-NR^{8A}OR^{8B}$, $-N_3$, 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;

Wherein R^9 is selected from hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHNR^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)$-OR^{9A}, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHNR^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, 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;

Wherein R^{10} is selected from hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNR^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)$-OR^{10A}, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNR^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, 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;

Wherein R^{11} is selected from hydrogen, halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, -CN, $-SO_{n11}R^{11A}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-NHNR^{11A}R^{11B}$, $-C(O)R^{11A}$, $-C(O)$-OR^{11A}, $-C(O)NR^{11A}R^{11B}$, $-C(O)NHNR^{11A}R^{11B}$, $-OR^{11A}$, $-NR^{11A}SO_2R^{11B}$, $-NR^{11A}C(O)R^{11B}$, $-NR^{11A}C(O)OR^{11B}$, $-NR^{11A}OR^{11B}$, $-N_3$, 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;

Wherein R^{12} is selected from hydrogen, halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, -CN, $-SO_{n12}R^{12A}$, $-SO_{v12}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m12}$, $-NR^{12A}R^{12B}$, $-NHNR^{12A}R^{12B}$, $-C(O)R^{12A}$, $-C(O)$-OR^{12A}, $-C(O)NR^{12A}R^{12B}$, $-C(O)NHNR^{12A}R^{12B}$, $-OR^{12A}$, $-NR^{12A}SO_2R^{12B}$, $-NR^{12A}C(O)R^{12B}$, $-NR^{12A}C(O)OR^{12B}$, $-NR^{12A}OR^{12B}$, $-N_3$, 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;

Wherein R^{13} is selected from hydrogen, halogen, $-CX^{13}_3$, $-CHX^{13}_2$, $-CH_2X^{13}$, $-OCX^{13}_3$, $-OCH_2X^{13}$, $-OCHX^{13}_2$, -CN, $-SO_{n13}R^{13A}$, $-SO_{v13}NR^{13A}R^{13B}$, $-NHC(O)NR^{13A}R^{13B}$, $-N(O)_{m13}$, $-NR^{13A}R^{13B}$, $-NHNR^{13A}R^{13B}$, $-C(O)R^{13A}$, $-C(O)$-OR^{13A}, $-C(O)NR^{13A}R^{13B}$, $-C(O)NHNR^{13A}R^{13B}$, $-OR^{13A}$, $-NR^{13A}SO_2R^{13B}$, $-NR^{13A}C(O)R^{13B}$, $-NR^{13A}C(O)OR^{13B}$, $-NR^{13A}OR^{13B}$, $-N_3$, 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;

Wherein R^{14} is selected from hydrogen, halogen, $-CX^{14}_3$, $-CHX^{14}_2$, $-CH_2X^{14}$, $-OCX^{14}_3$, $-OCH_2X^{14}$, $-OCHX^{14}_2$, -CN, $-SO_{n14}R^{14A}$, $-SO_{v14}NR^{14A}R^{14B}$, $-NHC(O)NR^{14A}R^{14B}$, $-N(O)_{m14}$, $-NR^{14A}R^{14B}$, $-NHNR^{14A}R^{14B}$, $-C(O)R^{14A}$, $-C(O)-OR^{14A}$, $-C(O)NR^{14A}R^{14B}$, $-C(O)NHNR^{14A}R^{14B}$, $-OR^{14A}$, $-NR^{14A}SO_2R^{14B}$, $-NR^{14A}C(O)R^{14B}$, $-NR^{14A}C(O)OR^{14B}$, $-NR^{14A}OR^{14B}$, $-N_3$, 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;

Wherein R^{15} is selected from hydrogen, halogen, $-CX^{15}_3$, $-CHX^{15}_2$, $-CH_2X^{15}$, $-OCX^{15}_3$, $-OCH_2X^{15}$, $-OCHX^{15}_2$, -CN, $-SO_{n15}R^{15A}$, $-SO_{v15}NR^{15A}R^{15B}$, $-NHC(O)NR^{15A}R^{15B}$, $-N(O)_{m15}$, $-NR^{15A}R^{15B}$, $-NHNR^{15A}R^{15B}$, $-C(O)R^{15A}$, $-C(O)-OR^{15A}$, $-C(O)NR^{15A}R^{15B}$, $-C(O)NHNR^{15A}R^{15B}$, $-OR^{15A}$, $-NR^{15A}SO_2R^{15B}$, $-NR^{15A}C(O)R^{15B}$, $-NR^{15A}C(O)OR^{15B}$, $-NR^{15A}OR^{15B}$, $-N_3$, 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;

R^{16} is selected from hydrogen, halogen, $-CX^{16}_3$, $-CHX^{16}_2$, $-CH_2X^{16}$, $-OCX^{16}_3$, $-OCH_2X^{16}$, $-OCHX^{16}_2$, -CN, $-SO_{n16}R^{16A}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-NHNR^{16A}R^{16B}$, $-C(O)R^{16A}$, $-C(O)-OR^{16A}$, $-C(O)NR^{16A}R^{16B}$, $-C(O)NHNR^{16A}R^{16B}$, $-OR^{16A}$, $-NR^{16A}SO_2R^{16B}$, $-NR^{16A}C(O)R^{16B}$, $-NR^{16A}C(O)OR^{16B}$, $-NR^{16A}OR^{16B}$, $-N_3$, 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;

R^{17} is selected from hydrogen, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-CH_2X^{17}$, $-OCX^{17}_3$, $-OCH_2X^{17}$, $-OCHX^{17}_2$, -CN, $-SO_{n17}R^{17A}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-C(O)R^{17A}$, $-C(O)-OR^{17A}$, $-C(O)NR^{17A}R^{17B}$, $-C(O)NHNR^{17A}R^{17B}$, $-OR^{17A}$, $-NR^{17A}SO_2R^{17B}$, $-NR^{17A}C(O)R^{17B}$, $-NR^{17A}C(O)OR^{17B}$, $-NR^{17A}OR^{17B}$, $-N_3$, 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;

R^{18} is selected from hydrogen, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-OCX^{18}_3$, $-OCH_2X^{18}$, $-OCHX^{18}_2$, -CN, $-SO_{n18}R^{18A}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-NHNR^{18A}R^{18B}$, $-C(O)R^{18A}$, $-C(O)-OR^{18A}$, $-C(O)NR^{18A}R^{18B}$, $-C(O)NHNR^{18A}R^{18B}$, $-OR^{18A}$, $-NR^{18A}SO_2R^{18B}$, $-NR^{18A}C(O)R^{18B}$, $-NR^{18A}C(O)OR^{18B}$, $-NR^{18A}OR^{18B}$, $-N_3$, 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; R^{17} and R^{18} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{19} is selected from hydrogen, halogen, $-CX^{19}_3$, $-CHX^{19}_2$, $-CH_2X^{19}$, $-OCX^{19}_3$, $-OCH_2X^{19}$, $-OCHX^{19}_2$, -CN, $-SO_{n19}R^{19A}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-NHNR^{19A}R^{19B}$, $-C(O)R^{19A}$, $-C(O)-OR^{19A}$, $-C(O)NR^{19A}R^{19B}$, $-C(O)NHNR^{19A}R^{19B}$, $-OR^{19A}$, $-NR^{19A}SO_2R^{19B}$, $-NR^{19A}C(O)R^{19B}$, $-NR^{19A}C(O)OR^{19B}$, $-NR^{19A}OR^{19B}$, $-N_3$, 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;

R^{20} is selected from hydrogen, halogen, $-CX^{20}_3$, $-CHX^{20}_2$, $-CH_2X^{20}$, $-OCX^{20}_3$, $-OCH_2X^{20}$, $-OCHX^{20}_2$, -CN, $-SO_{n20}R^{20A}$, $-SO_{v20}NR^{20A}R^{20B}$, $-NHC(O)NR^{20A}R^{20B}$, $-N(O)_{m20}$, $-NR^{20A}R^{20B}$, $-NHNR^{20A}R^{20B}$, $-C(O)R^{20A}$, $-C(O)-OR^{20A}$, $-C(O)NR^{20A}R^{20B}$, $-C(O)NHNR^{20A}R^{20B}$, $-OR^{20A}$, $-NR^{20A}SO_2R^{20B}$, $-NR^{20A}C(O)R^{20B}$, $-NR^{20A}C(O)OR^{20B}$, $-NR^{20A}OR^{20B}$, $-N_3$, 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; R^{17} and R^{20} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{21} is selected from hydrogen, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, -CN, $-SO_{n21}R^{21A}$, $-SO_{v21}NR^{21A}R^{21B}$, $-NHC(O)NR^{21A}R^{21B}$, $-N(O)_{m21}$, $-NR^{21A}R^{21B}$, $-NHNR^{21A}R^{21B}$, $-C(O)R^{21A}$, $-C(O)-OR^{21A}$, $-C(O)NR^{21A}R^{21B}$, $-C(O)NHNR^{21A}R^{21B}$, $-OR^{21A}$, $-NR^{21A}SO_2R^{21B}$, $-NR^{21A}C(O)R^{21B}$, $-NR^{21A}C(O)OR^{21B}$, $-NR^{21A}OR^{21B}$, $-N_3$, 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;

R^{22} is selected from hydrogen, halogen, $-CX^{22}_3$, $-CHX^{22}_2$, $-CH_2X^{22}$, $-OCX^{22}_3$, $-OCH_2X^{22}$, $-OCHX^{22}_2$, -CN, $-SO_{n22}R^{22A}$, $-SO_{v22}NR^{22A}R^{22B}$, $-NHC(O)NR^{22A}R^{22B}$, $-N(O)_{m22}$, $-NR^{22A}R^{22B}$, $-NHNR^{22A}R^{22B}$, $-C(O)R^{22A}$, $-C(O)-OR^{22A}$, $-C(O)NR^{22A}R^{22B}$, $-C(O)NHNR^{22A}R^{22B}$, $-OR^{22A}$, $-NR^{22A}SO_2R^{22B}$, $-NR^{22A}C(O)R^{22B}$, $-NR^{22A}C(O)OR^{22B}$, $-NR^{22A}OR^{22B}$, $-N_3$, 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; R^{21} and R^{22} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

wherein R^{23} is selected from hydrogen, halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-CH_2X^{23}$, $-OCX^{23}_3$, $-OCH_2X^{23}$, $-OCHX^{23}_2$, -CN, $-SO_{n23}R^{23A}$, $-SO_{v23}NR^{23A}R^{23B}$, $-NHC(O)NR^{23A}R^{23B}$, $-N(O)_{m23}$, $-NR^{23A}R^{23B}$, $-NHNR^{23A}R^{23B}$, $-C(O)R^{23A}$, $-C(O)-OR^{23A}$, $-C(O)NR^{23A}R^{23B}$, $-C(O)NHNR^{23A}R^{23B}$, $-OR^{23A}$, $-NR^{23A}SO_2R^{23B}$, $-NR^{23A}C(O)R^{23B}$, $-NR^{23A}C(O)OR^{23B}$, $-NR^{23A}OR^{23B}$, $-N_3$, 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;

wherein R^{24} is selected from hydrogen, halogen, $-CX^{24}_3$, $-CHX^{24}_2$, $-CH_2X^{24}$, $-OCX^{24}_3$, $-OCH_2X^{24}$, $-OCHX^{24}_2$, -CN, $-SO_{n24}R^{24A}$, $-SO_{v24}NR^{24A}R^{24B}$, $-NHC(O)NR^{24A}R^{24B}$, $-N(O)_{m24}$, $-NR^{24A}R^{24B}$, $-NHNR^{24A}R^{24B}$, $-C(O)R^{24A}$, $-C(O)-OR^{24A}$, $-C(O)NR^{24A}R^{24B}$, $-C(O)NHNR^{24A}R^{24B}$, $-OR^{24A}$, $-NR^{24A}SO_2R^{24B}$, $-NR^{24A}C(O)R^{24B}$, $-NR^{24A}C(O)OR^{24B}$, $-NR^{24A}OR^{24B}$, $-N_3$, 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;

wherein R^{25} is selected from hydrogen, halogen, $-CX^{25}_3$, $-CHX^{25}_2$, $-CH_2X^{25}$, $-OCX^{25}_3$, $-OCH_2X^{25}$, $-OCHX^{25}_2$, -CN, $-SO_{n25}R^{25A}$, $-SO_{v25}NR^{25A}R^{25B}$, $-NHC(O)NR^{25A}R^{25B}$, $-N(O)_{m25}$, $-NR^{25A}R^{25B}$, $-NHNR^{25A}R^{25B}$, $-C(O)R^{25A}$, $-C(O)-OR^{25A}$, $-C(O)NR^{25A}R^{25B}$, $-C(O)NHNR^{25A}R^{25B}$, $-OR^{25A}$, $-NR^{25A}SO_2R^{25B}$, $-NR^{25A}C(O)R^{25B}$, $-NR^{25A}C(O)OR^{25B}$, $-NR^{25A}OR^{25B}$, $-N_3$, 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;

wherein R^{26} is selected from hydrogen, halogen, $-CX^{26}_3$, $-CHX^{26}_2$, $-CH_2X^{26}$, $-OCX^{26}_3$, $-OCH_2X^{26}$, $-OCHX^{26}_2$, -CN, $-SO_{n26}R^{26A}$, $-SO_{v26}NR^{26A}R^{26B}$, $-NHC(O)NR^{26A}R^{26B}$, $-N(O)_{m26}$, $-NR^{26A}R^{26B}$, $-NHNR^{26A}R^{26B}$, $-C(O)R^{26A}$, $-C(O)-OR^{26A}$, $-C(O)NR^{26A}R^{26B}$, $-C(O)NHNR^{26A}R^{26B}$, $-OR^{26A}$, $-NR^{26A}SO_2R^{26B}$, $-NR^{26A}C(O)R^{26B}$, $-NR^{26A}C(O)OR^{26B}$, $-NR^{26A}OR^{26B}$, $-N_3$, 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;

wherein R^{27} is selected from hydrogen, halogen, $-CX^{27}_3$, $-CHX^{27}_2$, $-CH_2X^{27}$, $-OCX^{27}_3$, $-OCH_2X^{27}$, $-OCHX^{27}_2$, -CN, $-SO_{n27}R^{27A}$, $-SO_{v27}NR^{27A}R^{27B}$, $-NHC(O)NR^{27A}R^{27B}$, $-N(O)_{m27}$, $-NR^{27A}R^{27B}$, $-NHNR^{27A}R^{27B}$, $-C(O)R^{27A}$, $-C(O)-OR^{27A}$, $-C(O)NR^{27A}R^{27B}$, $-C(O)NHNR^{27A}R^{27B}$, $-OR^{27A}$, $-NR^{27A}SO_2R^{27B}$, $-NR^{27A}C(O)R^{27B}$, $-NR^{27A}C(O)OR^{27B}$, $-NR^{27A}OR^{27B}$, $-N_3$, 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;

Wherein R^{28} is selected from hydrogen, halogen, $-CX^{28}_3$, $-CHX^{28}_2$, $-CH_2X^{28}$, $-OCX^{28}_3$, $-OCH_2X^{28}$, $-OCHX^{28}_2$, -CN, $-SO_{n28}R^{28A}$, $-SO_{v28}NR^{28A}R^{28B}$, $-NHC(O)NR^{28A}R^{28B}$, $-N(O)_{m28}$, $-NR^{28A}R^{28B}$, $-NHNR^{28A}R^{28B}$, $-C(O)R^{28A}$, $-C(O)-OR^{28A}$, $-C(O)NR^{28A}R^{28B}$, $-C(O)NHNR^{28A}R^{28B}$, $-OR^{28A}$, $-NR^{28A}SO_2R^{28B}$, $-NR^{28A}C(O)R^{28B}$, $-NR^{28A}C(O)OR^{28B}$, $-NR^{28A}OR^{28B}$, $-N_3$, 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;

Wherein R^{29} is selected from hydrogen, halogen, $-CX^{29}_3$, $-CHX^{29}_2$, $-CH_2X^{29}$, $-OCX^{29}_3$, $-OCH_2X^{29}$, $-OCHX^{29}_2$, -CN, $-SO_{n29}R^{29A}$, $-SO_{v29}NR^{29A}R^{29B}$, $-NHC(O)NR^{29A}R^{29B}$, $-N(O)_{m29}$, $-NR^{29A}R^{29B}$, $-NHNR^{29A}R^{29B}$, $-C(O)R^{29A}$, $-C(O)-OR^{29A}$, $-C(O)NR^{29A}R^{29B}$,

-C(O)NHNR^{29A}R^{29B}, -OR^{29A}, -NR^{29A}SO$_2$R^{29B}, -NR^{29A}C(O)R^{29B}, -NR^{29A}C(O)OR^{29B}, -NR^{29A}OR^{29B}, -N$_3$, 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;

R^{30} is selected from hydrogen, halogen, -CX$^{30}_3$, -CHX$^{30}_2$, -CH$_2$X^{30}, -OCX$^{30}_3$, -OCH$_2$X^{30}, -OCHX$^{30}_2$, -CN, -SO$_{n30}$R^{30A}, -SO$_{v30}$NR^{30A}R^{30B}, -NHC(O)NR^{30A}R^{30B}, -N(O)$_{m30}$, -NR^{30A}R^{30B}, -NHNR^{30A}R^{30B}, -C(O)R^{30A}, -C(O)-OR^{30A}, -C(O)NR^{30A}R^{30B}, -C(O)NHNR^{30A}R^{30B}, -OR^{30A}, -NR^{30A}SO$_2$R^{30B}, -NR^{30A}C(O)R^{30B}, -NR^{30A}C(O)OR^{30B}, -NR^{30A}OR^{30B}, -N$_3$, 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;

Each R^{1A}, R^{1B}, R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{6A}, R^{6B}, R^{7A}, R^{7B}, R^{8A}, R^{8B}, R^{9A}, R^{9B}, R^{10A}, R^{10B}, R^{11A}, R^{11B}, R^{12A}, R^{12B}, R^{13A}, R^{13B}, R^{14A}, R^{14B}, R^{15A}, R^{15B}, R^{16A}, R^{16B}, R^{17A}, R^{17B}, R^{18A}, R^{18B}, R^{19A}, R^{19B}, R^{20A}, R^{20B}, R^{21A}, R^{21B}, R^{22A}, R^{22B}, R^{23A}, R^{23B}, R^{24A}, R^{24B}, R^{25A}, R^{25B}, R^{26A}, R^{26B}, R^{27A}, R^{27B}, R^{28A}, R^{28B}, R^{29A}, R^{29B}, R^{30A}, R^{30B} is independently selected from hydrogen, -CX$_3$, -CHX$_2$, -CH$_2$X, -C(O)OH, -C(O)NH$_2$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -NO$_2$, -SH, -SO$_3$H, -SO$_4$H, -SO$_2$NH$_2$, -NHNH$_2$, -ONH$_2$, -NHC=(O)NHNH$_2$, -NHC=(O)NH$_2$, -NHSO$_2$H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX$_3$, -OCHX$_2$, -OCH$_2$X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

wherein R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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^{5A} and R^{5B} 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^{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; 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; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{11A} and R^{11B} substituents bonded to

the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{12A} and R^{12B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{13A} and R^{13B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{14A} and R^{14B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{20A} and R^{20B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{21A} and R^{21B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{22A} and R^{22B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{23A} and R^{23B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{24A} and R^{24B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{25A} and R^{25B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{26A} and R^{26B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{27A} and R^{27B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{28A} and R^{28B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{29A} and R^{29B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{30A} and R^{30B} substituents bonded to

the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

Wherein each m1, m2, m3, m4, m5, m6, m7, m8, m9, m10, m11, m12, m13, m14, m15, m16, m17, m18, m19, m20, m21, m22, m23, m24, m25, m26, m27, m28, m29, and m30 are independently 1 or 2;

wherein each v1, v2, v3, v4, v5, v6, v7, v8, v9, v10, v11, v12, v13, v14, v15, v16, v17, v18, v19, v20, v21, v22, v23, v24, v25, v26, v27, v28, v29 and v30 are independently 1 or 2;

wherein each n1, n2, n3, n4, n5, n6, n7, n8, n9, n10, n11, n12, n13, n14, n15, n16, n17, n18, n19, n20, n21, n22, n23, n24, n25, n26, n27, n28, n29 and n30 are independently an integer from 0 to 2; and

wherein each X, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, X^{16}, X^{17}, X^{18}, X^{19}, X^{20}, X^{21}, X^{22}, X^{23}, X^{24}, X^{25}, X^{26}, X^{27}, X^{28}, X^{29} and X^{30} are independently -Cl, -Br, -I or –F.

[0312] Embodiment 36. The method of embodiment 35 wherein l is 1; m is 0; and n is 1.

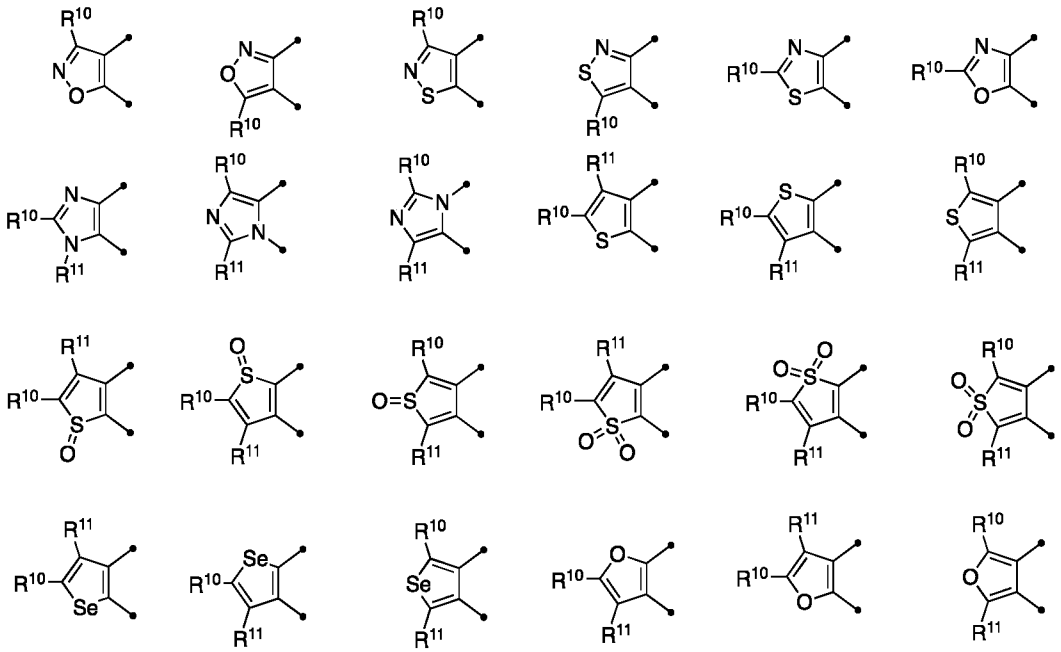
[0313] Embodiment 37. The method of embodiment 35 wherein Z is N.

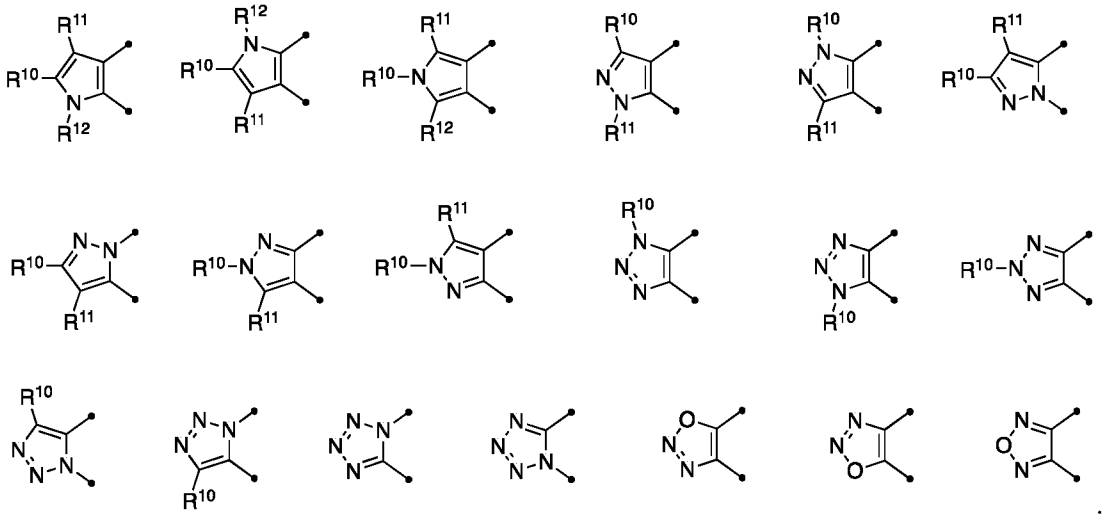
[0314] Embodiment 38. The method of embodiment 35 wherein ring A is selected from 5-membered heteroaryl, wherein ring A is optionally substituted with one or more substituent groups.

[0315] Embodiment 39. The method of embodiment 35 R^2 is selected from substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0316] Embodiment 40. The method of embodiment 38 ring A is selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl, wherein ring A is optionally substituted with one or more substituent groups

[0317] Embodiment 41. The method of embodiment 40 wherein ring A is selected from



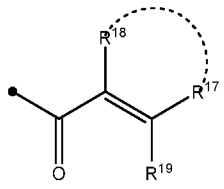


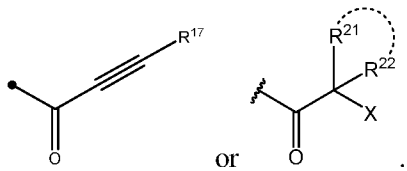
[0318] Embodiment 42. The method of embodiment 39 wherein R^2 is selected from substituted or unsubstituted phenyl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted 5- or 6-membered heteroaryl

[0319] Embodiment 43. The method of embodiment 42, wherein R^2 is selected from substituted or unsubstituted phenyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl and substituted or unsubstituted pyridyl

[0320] Embodiment 44. The method of embodiment 35 wherein E is selected from -C(=O)CH=CH_2, -C(=O)-ethynyl, -C(=O)CH=$CHCF_3$, -C(=O)CH=$CHCHF_2$, -C(=O)CH=$CHCH_2F$, 4-(dimethylamino)but-2-en-1-one and -C(=O)CH_2Br.

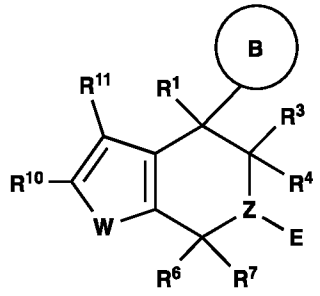
[0321] Embodiment 45. The method of embodiment 35 wherein M is CR^3R^4.

[0322] Embodiment 46. The method of embodiment 35 wherein E is  ,



[0323] Embodiment 47. The method of embodiment 35 wherein Y is CR^6R^7.

[0324] Embodiment 48. The method of any one of embodiments 1-34, wherein the compound is of the formula:



(VIII).

wherein

Z is N, or CR^9;

W is selected from NR^{12}, O, S, S=O, O=S=O, and Se;

ring B is selected from

a) 5- or 6-membered cycloalkyl, saturated or partially saturated heterocyclyl,

b) 5- or 6-membered aryl or heteroaryl,

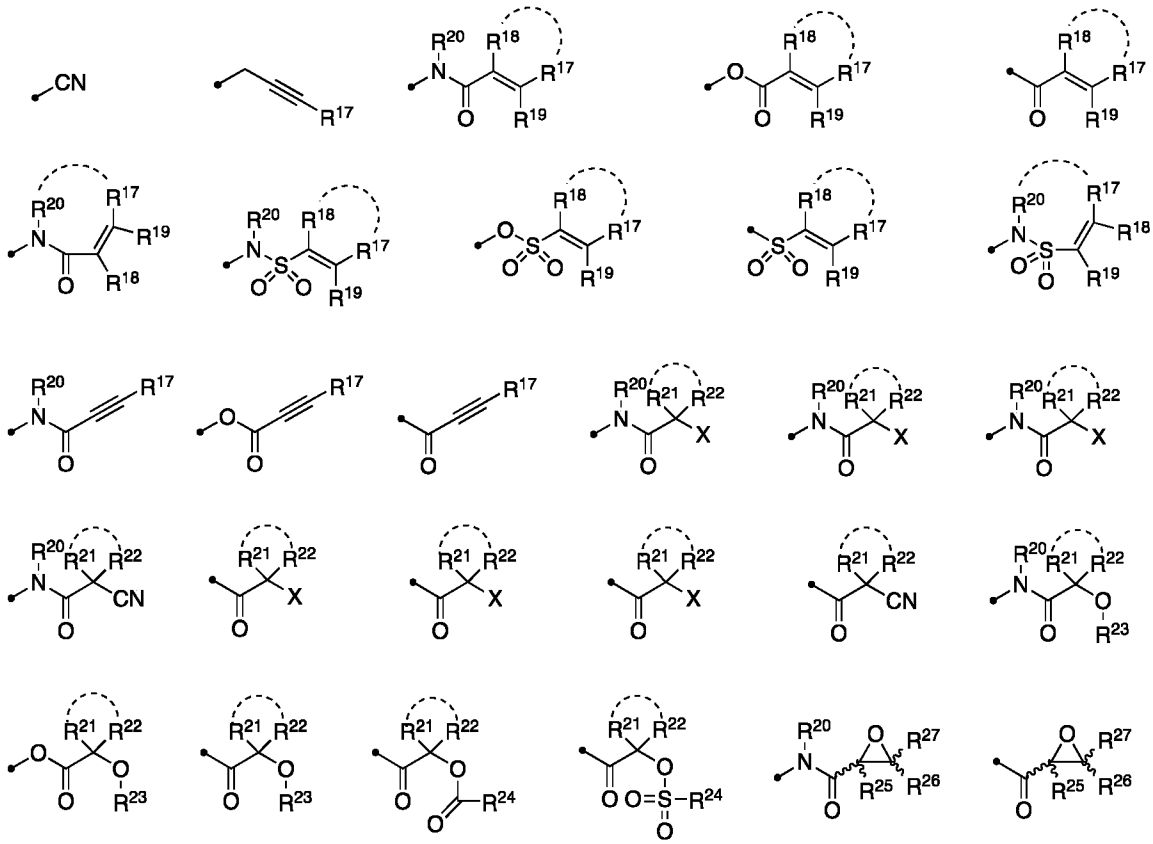
c) 9-, 10- or 11-membered fused partially saturated heterocyclyl,

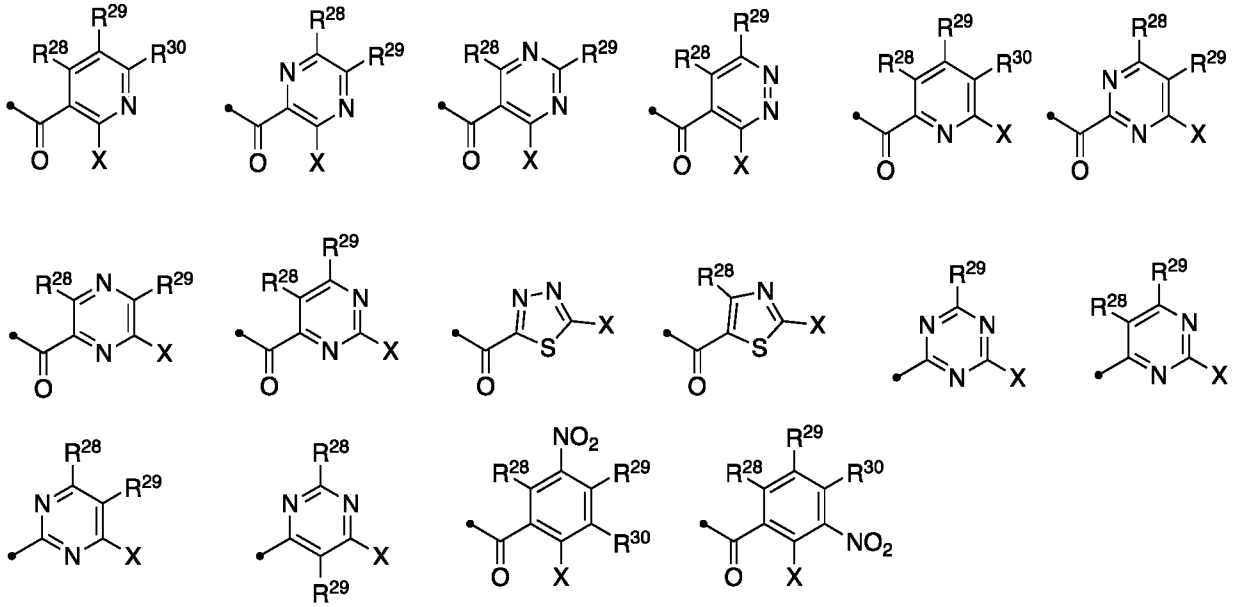
d) 9- or 10-membered fused heteroaryl,

e) naphthyl, and

f) 4-, 5- or 6-membered cycloalkenyl;

E is selected from an electrophilic moiety, selected from





;

R^1 is selected from hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-NHNR^{1A}R^{1B}$, $-C(O)R^{1A}$, $-C(O)-OR^{1A}$, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHNR^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$, $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, rand substituted or unsubstituted heteroaryl;

R^3 is selected from hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHNR^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, 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;

R^4 is selected from hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHNR^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHNR^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, 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; R^3 and R^3 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^6 is selected from hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-NHNR^{6A}R^{6B}$, $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHNR^{6A}R^{6B}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, 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;

R^7 is selected from hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHNR^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHNR^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, 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;

R^9 is selected from hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHNR^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHNR^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, 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;

R^{10} is selected from hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNR^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNR^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, 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;

R^{11} is selected from hydrogen, halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, -CN, $-SO_{n11}R^{11A}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-NHNR^{11A}R^{11B}$, $-C(O)R^{11A}$, $-C(O)-OR^{11A}$, $-C(O)NR^{11A}R^{11B}$, $-C(O)NHNR^{11A}R^{11B}$, $-OR^{11A}$, $-NR^{11A}SO_2R^{11B}$, $-NR^{11A}C(O)R^{11B}$, $-NR^{11A}C(O)OR^{11B}$, $-NR^{11A}OR^{11B}$, $-N_3$, 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;

R^{12} is selected from hydrogen, halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, -CN, $-SO_{n12}R^{12A}$, $-SO_{v12}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m12}$, $-NR^{12A}R^{12B}$, $-NHNR^{12A}R^{12B}$, $-C(O)R^{12A}$, $-C(O)-OR^{12A}$, $-C(O)NR^{12A}R^{12B}$, $-C(O)NHNR^{12A}R^{12B}$, $-OR^{12A}$, $-NR^{12A}SO_2R^{12B}$, $-NR^{12A}C(O)R^{12B}$, $-NR^{12A}C(O)OR^{12B}$, $-NR^{12A}OR^{12B}$, $-N_3$, 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;

R^{17} is selected from hydrogen, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-CH_2X^{17}$, $-OCX^{17}_3$, $-OCH_2X^{17}$, $-OCHX^{17}_2$, -CN, $-SO_{n17}R^{17A}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-C(O)R^{17A}$, $-C(O)-OR^{17A}$, $-C(O)NR^{17A}R^{17B}$, $-C(O)NHNR^{17A}R^{17B}$, $-OR^{17A}$, $-NR^{17A}SO_2R^{17B}$, $-NR^{17A}C(O)R^{17B}$, $-NR^{17A}C(O)OR^{17B}$, $-NR^{17A}OR^{17B}$, $-N_3$, 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;

R^{18} is selected from hydrogen, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-OCX^{18}_3$, $-OCH_2X^{18}$, $-OCHX^{18}_2$, -CN, $-SO_{n18}R^{18A}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-NHNR^{18A}R^{18B}$, $-C(O)R^{18A}$, $-C(O)-OR^{18A}$, $-C(O)NR^{18A}R^{18B}$, $-C(O)NHNR^{18A}R^{18B}$, $-OR^{18A}$, $-NR^{18A}SO_2R^{18B}$, $-NR^{18A}C(O)R^{18B}$, $-NR^{18A}C(O)OR^{18B}$, $-NR^{18A}OR^{18B}$, $-N_3$, 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; R^{16} and R^{18} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{19} is selected from hydrogen, halogen, $-CX^{19}_3$, $-CHX^{19}_2$, $-CH_2X^{19}$, $-OCX^{19}_3$, $-OCH_2X^{19}$, $-OCHX^{19}_2$, -CN, $-SO_{n19}R^{19A}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-NHNR^{19A}R^{19B}$, $-C(O)R^{19A}$, $-C(O)-OR^{19A}$, $-C(O)NR^{19A}R^{19B}$, $-C(O)NHNR^{19A}R^{19B}$, $-OR^{19A}$, $-NR^{19A}SO_2R^{19B}$, $-NR^{19A}C(O)R^{19B}$, $-NR^{19A}C(O)OR^{19B}$, $-NR^{19A}OR^{19B}$, $-N_3$, 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; R^{16} and R^{19} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{20} is selected from hydrogen, halogen, $-CX^{20}_3$, $-CHX^{20}_2$, $-CH_2X^{20}$, $-OCX^{20}_3$, $-OCH_2X^{20}$, $-OCHX^{20}_2$, -CN, $-SO_{n20}R^{20A}$, $-SO_{v20}NR^{20A}R^{20B}$, $-NHC(O)NR^{20A}R^{20B}$, $-N(O)_{m20}$, $-NR^{20A}R^{20B}$, $-NHNR^{20A}R^{20B}$, $-C(O)R^{20A}$, $-C(O)-OR^{20A}$, $-C(O)NR^{20A}R^{20B}$, $-C(O)NHNR^{20A}R^{20B}$, $-OR^{20A}$, $-NR^{20A}SO_2R^{20B}$, $-NR^{20A}C(O)R^{20B}$, $-NR^{20A}C(O)OR^{20B}$, $-NR^{20A}OR^{20B}$, $-N_3$, 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;

R^{21} is selected from hydrogen, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, -CN, $-SO_{n21}R^{21A}$, $-SO_{v21}NR^{21A}R^{21B}$, $-NHC(O)NR^{21A}R^{21B}$, $-N(O)_{m21}$, $-NR^{21A}R^{21B}$, $-NHNR^{21A}R^{21B}$, $-C(O)R^{21A}$, $-C(O)-OR^{21A}$, $-C(O)NR^{21A}R^{21B}$, $-C(O)NHNR^{21A}R^{21B}$, $-OR^{21A}$, $-NR^{21A}SO_2R^{21B}$, $-NR^{21A}C(O)R^{21B}$, $-NR^{21A}C(O)OR^{21B}$, $-NR^{21A}OR^{21B}$, $-N_3$, 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; R^{20} and R^{21} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{22} is selected from hydrogen, halogen, $-CX^{22}_3$, $-CHX^{22}_2$, $-CH_2X^{22}$, $-OCX^{22}_3$, $-OCH_2X^{22}$, $-OCHX^{22}_2$, -CN, $-SO_{n22}R^{22A}$, $-SO_{v22}NR^{22A}R^{22B}$, $-NHC(O)NR^{22A}R^{22B}$, $-N(O)_{m22}$, $-NR^{22A}R^{22B}$, $-NHNR^{22A}R^{22B}$, $-C(O)R^{22A}$, $-C(O)-OR^{22A}$, $-C(O)NR^{22A}R^{22B}$, $-C(O)NHNR^{22A}R^{22B}$, $-OR^{22A}$, $-NR^{22A}SO_2R^{22B}$, $-NR^{22A}C(O)R^{22B}$, $-NR^{22A}C(O)OR^{22B}$, $-NR^{22A}OR^{22B}$, $-N_3$, 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;

R^{23} is selected from hydrogen, halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-CH_2X^{23}$, $-OCX^{23}_3$, $-OCH_2X^{23}$, $-OCHX^{23}_2$, -CN, $-SO_{n23}R^{23A}$, $-SO_{v23}NR^{23A}R^{23B}$, $-NHC(O)NR^{23A}R^{23B}$, $-N(O)_{m23}$, $-NR^{23A}R^{23B}$, $-NHNR^{23A}R^{23B}$, $-C(O)R^{23A}$, $-C(O)-OR^{23A}$, $-C(O)NR^{23A}R^{23B}$, $-C(O)NHNR^{23A}R^{23B}$, $-OR^{23A}$, $-NR^{23A}SO_2R^{23B}$, $-NR^{23A}C(O)R^{23B}$, $-NR^{23A}C(O)OR^{23B}$, $-NR^{23A}OR^{23B}$, $-N_3$, 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;

R^{24} is selected from hydrogen, halogen, $-CX^{24}_3$, $-CHX^{24}_2$, $-CH_2X^{24}$, $-OCX^{24}_3$, $-OCH_2X^{24}$, $-OCHX^{24}_2$, -CN, $-SO_{n24}R^{24A}$, $-SO_{v24}NR^{24A}R^{24B}$, $-NHC(O)NR^{24A}R^{24B}$, $-N(O)_{m24}$, $-NR^{24A}R^{24B}$, $-NHNR^{24A}R^{24B}$, $-C(O)R^{24A}$, $-C(O)-OR^{24A}$, $-C(O)NR^{24A}R^{24B}$, $-C(O)NHNR^{24A}R^{24B}$, $-OR^{24A}$, $-NR^{24A}SO_2R^{24B}$, $-NR^{24A}C(O)R^{24B}$, $-NR^{24A}C(O)OR^{24B}$, $-NR^{24A}OR^{24B}$, $-N_3$, 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;

R^{25} is selected from hydrogen, halogen, $-CX^{25}_3$, $-CHX^{25}_2$, $-CH_2X^{25}$, $-OCX^{25}_3$, $-OCH_2X^{25}$, $-OCHX^{25}_2$, -CN, $-SO_{n25}R^{25A}$, $-SO_{v25}NR^{25A}R^{25B}$, $-NHC(O)NR^{25A}R^{25B}$, $-N(O)_{m25}$, $-NR^{25A}R^{25B}$, $-NHNR^{25A}R^{25B}$, $-C(O)R^{25A}$, $-C(O)-OR^{25A}$, $-C(O)NR^{25A}R^{25B}$, $-C(O)NHNR^{25A}R^{25B}$, $-OR^{25A}$, $-NR^{25A}SO_2R^{25B}$, $-NR^{25A}C(O)R^{25B}$, $-NR^{25A}C(O)OR^{25B}$, $-NR^{25A}OR^{25B}$, $-N_3$, 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;

R^{26} is selected from hydrogen, halogen, $-CX^{26}_3$, $-CHX^{26}_2$, $-CH_2X^{26}$, $-OCX^{26}_3$, $-OCH_2X^{26}$, $-OCHX^{26}_2$, -CN, $-SO_{n26}R^{26A}$, $-SO_{v26}NR^{26A}R^{26B}$, $-NHC(O)NR^{26A}R^{26B}$, $-N(O)_{m26}$, $-NR^{26A}R^{26B}$, $-NHNR^{26A}R^{26B}$, $-C(O)R^{26A}$, $-C(O)-OR^{26A}$, $-C(O)NR^{26A}R^{26B}$, $-C(O)NHNR^{26A}R^{26B}$, $-OR^{26A}$, $-NR^{26A}SO_2R^{26B}$, $-NR^{26A}C(O)R^{26B}$, $-NR^{26A}C(O)OR^{26B}$, $-NR^{26A}OR^{26B}$, $-N_3$, 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;

R^{27} is selected from hydrogen, halogen, $-CX^{27}_3$, $-CHX^{27}_2$, $-CH_2X^{27}$, $-OCX^{27}_3$, $-OCH_2X^{27}$, $-OCHX^{27}_2$, -CN, $-SO_{n27}R^{27A}$, $-SO_{v27}NR^{27A}R^{27B}$, $-NHC(O)NR^{27A}R^{27B}$, $-N(O)_{m27}$, $-NR^{27A}R^{27B}$, $-NHNR^{27A}R^{27B}$, $-C(O)R^{27A}$, $-C(O)-OR^{27A}$, $-C(O)NR^{27A}R^{27B}$, $-C(O)NHNR^{27A}R^{27B}$, $-OR^{27A}$, $-NR^{27A}SO_2R^{27B}$, $-NR^{27A}C(O)R^{27B}$, $-NR^{27A}C(O)OR^{27B}$, $-NR^{27A}OR^{27B}$, $-N_3$, 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;

R^{28} is selected from hydrogen, halogen, $-CX^{28}_3$, $-CHX^{28}_2$, $-CH_2X^{28}$, $-OCX^{28}_3$, $-OCH_2X^{28}$, $-OCHX^{28}_2$, -CN, $-SO_{n28}R^{28A}$, $-SO_{v28}NR^{28A}R^{28B}$, $-NHC(O)NR^{28A}R^{28B}$, $-N(O)_{m28}$, $-NR^{28A}R^{28B}$, $-NHNR^{28A}R^{28B}$, $-C(O)R^{28A}$, $-C(O)-OR^{28A}$, $-C(O)NR^{28A}R^{28B}$, $-C(O)NHNR^{28A}R^{28B}$, $-OR^{28A}$, $-NR^{28A}SO_2R^{28B}$, $-NR^{28A}C(O)R^{28B}$, $-NR^{28A}C(O)OR^{28B}$, $-NR^{28A}OR^{28B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted and unsubstituted heteroaryl;

R^{29} is selected from hydrogen, halogen, $-CX^{29}_3$, $-CHX^{29}_2$, $-CH_2X^{29}$, $-OCX^{29}_3$, $-OCH_2X^{29}$, $-OCHX^{29}_2$, -CN, $-SO_{n29}R^{29A}$, $-SO_{v29}NR^{29A}R^{29B}$, $-NHC(O)NR^{29A}R^{29B}$, $-N(O)_{m29}$, $-NR^{29A}R^{29B}$, $-NHNR^{29A}R^{29B}$, $-C(O)R^{29A}$, $-C(O)-OR^{29A}$, $-C(O)NR^{29A}R^{29B}$, $-C(O)NHNR^{29A}R^{29B}$, $-OR^{29A}$, $-NR^{29A}SO_2R^{29B}$, $-NR^{29A}C(O)R^{29B}$, $-NR^{29A}C(O)OR^{29B}$, $-NR^{29A}OR^{29B}$, $-N_3$, 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;

R^{30} is selected from hydrogen, halogen, $-CX^{30}_3$, $-CHX^{30}_2$, $-CH_2X^{30}$, $-OCX^{30}_3$, $-OCH_2X^{30}$, $-OCHX^{30}_2$, -CN, $-SO_{n30}R^{30A}$, $-SO_{v30}NR^{30A}R^{30B}$, $-NHC(O)NR^{30A}R^{30B}$, $-N(O)_{m30}$, $-NR^{30A}R^{30B}$, $-NHNR^{30A}R^{30B}$, $-C(O)R^{30A}$, $-C(O)\text{-}OR^{30A}$, $-C(O)NR^{30A}R^{30B}$, $-C(O)NHNR^{30A}R^{30B}$, $-OR^{30A}$, $-NR^{30A}SO_2R^{30B}$, $-NR^{30A}C(O)R^{30B}$, $-NR^{30A}C(O)OR^{30B}$, $-NR^{30A}OR^{30B}$, $-N_3$, 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;

R^{31} is selected from hydrogen, halogen, $-CX^{31}_3$, $-CHX^{31}_2$, $-CH_2X^{31}$, $-OCX^{31}_3$, $-OCH_2X^{31}$, $-OCHX^{31}_2$, -CN, $-SO_{n31}R^{31A}$, $-SO_{v31}NR^{31A}R^{31B}$, $-NHC(O)NR^{31A}R^{31B}$, $-N(O)_{m31}$, $-NR^{31A}R^{31B}$, $-NHNR^{31A}R^{31B}$, $-C(O)R^{31A}$, $-C(O)\text{-}OR^{31A}$, $-C(O)NR^{31A}R^{31B}$, $-C(O)NHNR^{31A}R^{31B}$, $-OR^{31A}$, $-NR^{31A}SO_2R^{31B}$, $-NR^{31A}C(O)R^{31B}$, $-NR^{31A}C(O)OR^{31B}$, $-NR^{31A}OR^{31B}$, $-N_3$, 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;

R^{32} is selected from hydrogen, halogen, $-CX^{32}_3$, $-CHX^{32}_2$, $-CH_2X^{32}$, $-OCX^{32}_3$, $-OCH_2X^{32}$, $-OCHX^{32}_2$, -CN, $-SO_{n32}R^{32A}$, $-SO_{v32}NR^{32A}R^{32B}$, $-NHC(O)NR^{32A}R^{32B}$, $-N(O)_{m32}$, $-NR^{32A}R^{32B}$, $-NHNR^{32A}R^{32B}$, $-C(O)R^{32A}$, $-C(O)\text{-}OR^{32A}$, $-C(O)NR^{32A}R^{32B}$, $-C(O)NHNR^{32A}R^{32B}$, $-OR^{32A}$, $-NR^{32A}SO_2R^{32B}$, $-NR^{32A}C(O)R^{32B}$, $-NR^{32A}C(O)OR^{32B}$, $-NR^{32A}OR^{32B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted and unsubstituted heteroaryl;

R^{33} is selected from hydrogen, halogen, $-CX^{33}_3$, $-CHX^{33}_2$, $-CH_2X^{33}$, $-OCX^{33}_3$, $-OCH_2X^{33}$, $-OCHX^{33}_2$, -CN, $-SO_{n33}R^{33A}$, $-SO_{v33}NR^{33A}R^{33B}$, $-NHC(O)NR^{33A}R^{33B}$, $-N(O)_{m33}$, $-NR^{33A}R^{33B}$, $-NHNR^{33A}R^{33B}$, $-C(O)R^{33A}$, $-C(O)\text{-}OR^{33A}$, $-C(O)NR^{33A}R^{33B}$, $-C(O)NHNR^{33A}R^{33B}$, $-OR^{33A}$, $-NR^{33A}SO_2R^{33B}$, $-NR^{33A}C(O)R^{33B}$, $-NR^{33A}C(O)OR^{33B}$, $-NR^{33A}OR^{33B}$, $-N_3$, 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;

R^{34} is selected from hydrogen, halogen, $-CX^{34}_3$, $-CHX^{34}_2$, $-CH_2X^{34}$, $-OCX^{34}_3$, $-OCH_2X^{34}$, $-OCHX^{34}_2$, -CN, $-SO_{n34}R^{34A}$, $-SO_{v34}NR^{34A}R^{34B}$, $-NHC(O)NR^{34A}R^{34B}$, $-N(O)_{m34}$, $-NR^{34A}R^{34B}$, $-NHNR^{34A}R^{34B}$, $-C(O)R^{34A}$, $-C(O)\text{-}OR^{34A}$, $-C(O)NR^{34A}R^{34B}$, $-C(O)NHNR^{34A}R^{34B}$, $-OR^{34A}$, $-NR^{34A}SO_2R^{34B}$, $-NR^{34A}C(O)R^{34B}$, $-NR^{34A}C(O)OR^{34B}$, $-NR^{34A}OR^{34B}$, $-N_3$, 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;

R^{35} is selected from hydrogen, halogen, $-CX^{35}_3$, $-CHX^{35}_2$, $-CH_2X^{35}$, $-OCX^{35}_3$, $-OCH_2X^{35}$, $-OCHX^{35}_2$, -CN, $-SO_{n35}R^{35A}$, $-SO_{v35}NR^{35A}R^{35B}$, $-NHC(O)NR^{35A}R^{35B}$, $-N(O)_{m35}$, $-NR^{35A}R^{35B}$, $-NHNR^{35A}R^{35B}$, $-C(O)R^{35A}$, $-C(O)\text{-}OR^{35A}$, $-C(O)NR^{35A}R^{35B}$, $-C(O)NHNR^{35A}R^{35B}$, $-OR^{35A}$, $-NR^{35A}SO_2R^{35B}$, $-NR^{35A}C(O)R^{35B}$, $-NR^{35A}C(O)OR^{35B}$, $-NR^{35A}OR^{35B}$, $-N_3$, 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;

Each R^{1A}, R^{1B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{6A}, R^{6B}, R^{7A}, R^{7B}, R^{9A}, R^{9B}, R^{10A}, R^{10B}, R^{11A}, R^{11B}, R^{17A}, R^{17B}, R^{18A}, R^{18B}, R^{19A}, R^{19B}, R^{20A}, R^{20B}, R^{21A}, R^{21B}, R^{22A}, R^{22B}, R^{23A}, R^{23B}, R^{24A}, R^{24B}, R^{25A}, R^{25B}, R^{26A}, R^{26B}, R^{27A}, R^{27B},

R^{28A}, R^{28B}, R^{29A}, R^{29B}, R^{30A}, R^{30B}, R^{31A}, R^{31B}, R^{32A}, R^{32B}, R^{33A}, R^{33B}, R^{34A}, R^{34B}, R^{35A}, R^{35B}, is independently selected from hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, -C(O)OH, $-C(O)NH_2$, -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, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, 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^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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^{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; R^{13A} and R^{13B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{14A} and R^{14B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{20A} and R^{20B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{21A} and R^{21B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{22A} and R^{22B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{23A} and R^{23B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{24A} and R^{24B} substituents bonded to the same

nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{25A} and R^{25B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{26A} and R^{26B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{27A} and R^{27B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{28A} and R^{28B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{29A} and R^{29B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{30A} and R^{30B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

Each m1, m3, m4, m6, m7, m9, m10, m11, m17, m18, m19, m20, m21, m22, m23, m24, m25, m26, m27, m28, m29, m30, m31, m32, m33, m34 and m35 is independently 1 or 2;

Each v1, v3, v4, v6, v7, v9, v10, v11, v17, v18, v19, v20, v21, v22, v23, v24, v25, v26, v27, v28, v29, v30, v31, v32, v33, v34 and v35 is independently 1 or 2;

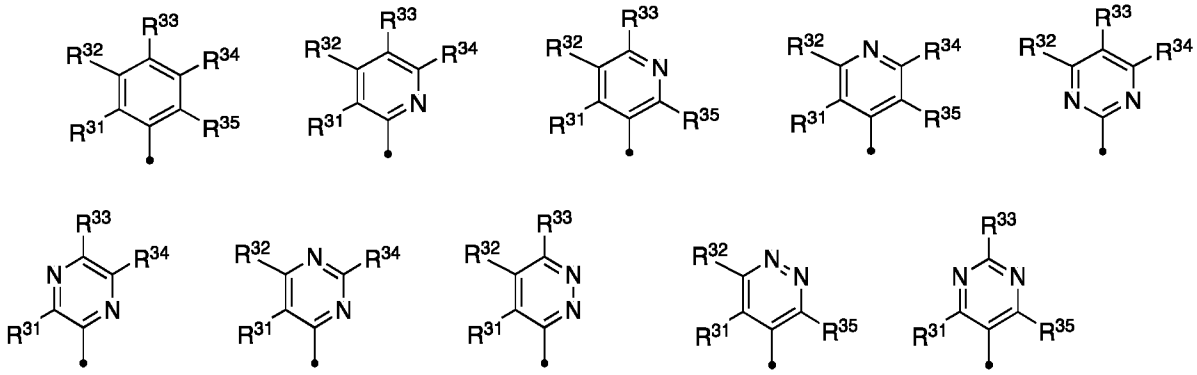
Each n1, n3, n4, n6, n7, n9, n10, n11, n17, n18, n19, n20, n21, n22, n23, n24, n25, n26, n27, n28, n29, n30, n31, n32, n33, n34 and n35 is independently an integer from 0 to 2; and

Each X^1, X^3, X^4, X^6, X^7, X^9, X^{10}, X^{11}, X^{17}, X^{18}, X^{19}, X^{20}, X^{21}, X^{22}, X^{23}, X^{24}, X^{25}, X^{26}, X^{27}, X^{28}, X^{29}, X^{30}, X^{31}, X^{32}, X^{33}, X^{34}, and X^{35} is independently -Cl, -Br, -I or –F.

[0325] Embodiment 49. The method of embodiment 48 wherein ring B is selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl, wherein Ring B is optionally substituted with one or more substituents.

[0326] Embodiment 50. The method of embodiment 48 wherein ring B is selected from phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl, wherein ring B is optionally substituted with one or more substituent groups.

[0327] Embodiment 51. The method of embodiment 50 wherein ring B is selected from



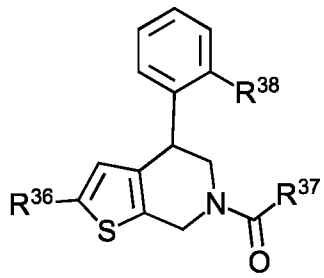
[0328] Embodiment 52. The method of embodiment 48 wherein E is selected from -C(=O)CH=CH_2, -C(=O)-ethynyl, -C(=O)CH=$CHCF_3$, -C(=O)CH=$CHCHF_2$, -C(=O)CH=$CHCH_2F$, 4-(dimethylamino)but-

2-en-1-one and -C(=O)CH_2Br.

[0329] Embodiment 53. The method of embodiment 48 wherein W is S.

[0330] Embodiment 54. The method of embodiment 48 wherein R^{10} is selected from hydrogen, fluoro, chloro, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, substituted or unsubstituted 6-10 membered aryl, and substituted or unsubstituted 5-10 membered heteroaryl; and R^{11} is selected from hydrogen, fluoro, chloro, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} heteroalkyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, substituted or unsubstituted 6-10 membered aryl, and substituted or unsubstituted 5-10 membered heteroaryl.

[0331] Embodiment 55. The method of any one of embodiments 1-34, wherein the compound is of the formula:



[XIA]

wherein R^{36} is H, halo, C_1-C_4 alkyl, C_2-C_4 alkenyl or C_3-C_6 cycloalkyl;

R^{37} is substituted or unsubstituted C_2-C_4 alkenyl or C_2-C_4 alkynyl; and

R^{38} is selected from substituted or unsubstituted nitrogen containing 5-membered heteroaryl, substituted or unsubstituted nitrogen containing 5- or 6- membered partially unsaturated heterocyclyl and substituted or unsubstituted nitrogen containing 6-10 membered heteroaryl; provided R^{38} is not 4-pyridyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof.

[0332] Embodiment 56. The method of embodiment 55 wherein R^{38} is selected from substituted or unsubstituted nitrogen containing 5-membered heteroaryl selected from pyrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, thiazolyl, triazolyl and imidazolyl; substituted or unsubstituted nitrogen containing 6- membered heteroaryl selected from pyridinyl, pyrimidinyl and pyrazinyl; substituted or unsubstituted nitrogen containing 5-membered partially unsaturated heterocyclyl selected from pyrrolinyl, and imidazolidinyl; and substituted or unsubstituted dihydropyridinyl;.

[0333] Embodiment 57. The method of embodiment 55 wherein R^{36} is selected from chloro, methyl, ethyl, isopropyl, allylyl, and cyclopropyl;.

[0334] Embodiment 58. The method of embodiment 55 wherein R^{38} is selected from substituted 5-pyrazolyl, substituted 4-pyrazolyl, substituted 1-pyrazolyl, substituted or unsubstituted 4-isoxazolyl, substituted or unsubstituted 4-isothiazolyl, substituted or unsubstituted 3-pyrrolyl, substituted or

unsubstituted 5-thiazolyl, substituted or unsubstituted 5-imidazolyl, substituted or unsubstituted 1-imidazolyl, substituted or unsubstituted [1,2,4]triazol-5-yl, substituted or unsubstituted 3-pyridyl, and substituted or unsubstituted 5-pyrimidinyl;.

[0335] Embodiment 59. The method of embodiment 58 wherein R^{38} is selected from 3-trifluoromethyl-pyrazol-4-yl, 1-isopropyl-3-trifluoromethyl-pyrazol-4-yl, 1-ethyl-3-trifluoromethyl-pyrazol-4-yl, 1-methyl-3-difluoromethyl-pyrazol-4-yl, 1-butyl-3-trifluoromethyl-pyrazol-4-yl, 1-methoxymethyl-3-trifluoromethyl-pyrazol-4-yl, 1-propyl-3-trifluoromethyl-pyrazol-4-yl, 1,3-dimethyl-pyrazol-4-yl, 1,3,5-trimethyl-pyrazol-4-yl, 1-methyl-3-cyclopropyl-pyrazol-4-yl, 1-methyl-3-trifluoromethyl-pyrazol-4-yl, 1-ethyl-3-amino-pyrazol-4-yl, 1-ethyl-3-methoxy-pyrazol-4-yl, 1-hydroxyethyl-3-trifluoromethyl-pyrazol-4-yl, 1-[2-hydroxypropyl]-3-trifluoromethyl-pyrazol-4-yl, 1-[2-hydroxyisobutyl]-3-trifluoromethyl-pyrazol-4-yl, 1-methoxyethyl-3-trifluoromethyl-pyrazol-4-yl, 1-[N,N-dimethylaminoethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-[N-methylaminocarbonylmethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-[N-methylaminocarbonylethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-[N,N-dimethylaminocarbonylmethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-aminocarbonylmethyl-3-trifluoromethyl-pyrazol-4-yl, 1-methylcarbonylaminoethyl-3-trifluoromethyl-pyrazol-4-yl, 1-methylcarbonylaminobutyl-3-trifluoromethyl-pyrazol-4-yl, 1-aminocarbonylethyl-3-trifluoromethyl-pyrazol-4-yl, 1-aminocarbonylpropyl-3-trifluoromethyl-pyrazol-4-yl, 1-aminocarbonylisopropyl-3-trifluoromethyl-pyrazol-4-yl, 1-cyanopropyl-3-trifluoromethyl-pyrazol-4-yl, 1-[N,N-dimethylaminocarbonylethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-carboxyethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-carboxymethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-methoxycarbonylmethyl]-3-trifluoromethyl-pyrazol-4-yl, 1-ethyl-3-carboxy-pyrazol-4-yl, 1-ethyl-5-carboxy-pyrazol-4-yl, 1-ethyl-3-methylaminocarbonyl-pyrazol-4-yl, 1-ethyl-3-[N,N-dimethylaminocarbonyl]-pyrazol-4-yl, 1-ethyl-5-methylaminocarbonyl-pyrazol-4-yl, 1-ethyl-5-[N,N-dimethylaminocarbonyl]-pyrazol-4-yl, 1-benzyl-3-methyl-pyrazol-4-yl, 1-(cyclopropylmethyl)-3-trifluoromethyl-pyrazol-4-yl, 1-cyclopropyl-3-trifluoromethyl-pyrazol-4-yl, 1-[1-methylazetidin-3-yl]-3-trifluoromethyl-pyrazol-4-yl, 1-[1-methylpyrrolidin-3-yl]-3-trifluoromethyl-pyrazol-4-yl, 1-[1-methylpiperidin-3-yl]-3-trifluoromethyl-pyrazol-4-yl, 1-[1-methylpiperidin-4-yl]-3-trifluoromethyl-pyrazol-4-yl, 1-(3-pyridinylmethyl)-3-methyl-pyrazol-4-yl, 1-(2-pyridinylmethyl)-3-methyl-pyrazol-4-yl, 1-[2-pyridyl]-3-methyl-pyrazol-4-yl, 1-methyl-5-pyrazolyl, 1-ethyl-5-trifluoromethylpyrazol-4-yl, 1,3-dimethyl-5-pyrazolyl, 1-methyl-3-cyclopropyl-pyrazol-5-yl, 1-methyl-4-pyrazolyl, 1-ethyl-3-methylpyrazol-4-yl, 1,5-dimethyl-4-pyrazolyl, 1,3,5-trimethyl-4-pyrazolyl, 1-methyl-3-pyrazolyl, 4-methyl-3-pyrazolyl, 1-methyl-[1,2,4]triazol-3-yl, 4-bromo-2-methyl-[1,2,4]triazol-5-yl, 4-bromo-2-ethyl-[1,2,4]triazol-5-yl, 1-methyl-[1,2,4]triazol-5-yl, 4-isothiazolyl, 4-methyl-2-oxazolyl, isoxazol-4-yl, 2,4-dimethylthiazol-5-yl, 3,5-dimethylisoxazol-4-yl, 2-methyl-5-thiazolyl and 4-methyl-5-thiazolyl.

[0336] Embodiment 60. The method of embodiment 59 wherein R^{38} is selected from 5-pyrimidinyl, 2-methyl-5-pyrimidinyl, 4-methyl-5-pyrimidinyl, 4,6-dimethoxy-5-pyrimidinyl, 4,6-dimethyl-5-pyrimidinyl, 4-triflouromethyl-5-pyrimidinyl, 4-pyrimidinyl, 2-methyl-4-pyrimidinyl, 4-methyl-6-pyrimidinyl, 2,4-

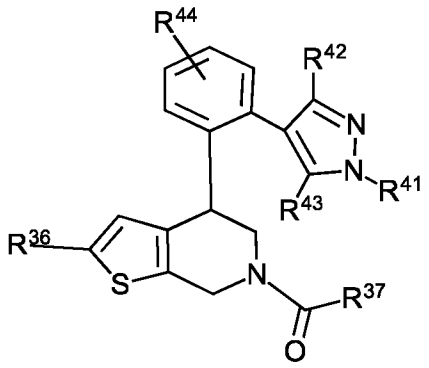
dimethyl-6-pyrimidinyl, 3-pyridinyl, 2-pyridinyl, 4-methyl-2-pyridinyl, 2-triflouromethyl-3-pyridinyl, 4-triflouromethyl-3-pyridinyl, 2-methyl-3-pyridinyl, 2,5-dimethyl-3-pyridinyl, 2,6-dimethyl-3-pyridinyl, 2,4-dimethyl-3-pyridinyl, 2-ethyl-3-pyridinyl, 5-methyl-3-pyridinyl, 2-ethoxy-3-pyridinyl, 2-ethoxy-5-methyl-3-pyridinyl, 2-methoxy-3-pyridinyl, 2-methoxy-6-methyl-3-pyridinyl, 2-ethoxy-6-methyl-3-pyridinyl, 2-isopropoxy-3-pyridinyl, 2-(3-pentoxy)-3-pyridinyl, 2-methoxyethoxy-3-pyridinyl, 2-cyclopropoxy-3-pyridinyl, 2-cyclopentyloxy-3-pyridinyl, 2-cyclohexloxy-3-pyridinyl, 2-fluoro-3-pyridinyl, 2-chloro-3-pyridinyl, 2-phenyl-3-pyridinyl, 2-flouro-3-methyl-5-pyridinyl, 2-flouro-3-chloro-5-pyridinyl, 3-fluoro-5-pyridinyl, 3-chloro-5-pyridinyl, 2-chloro-4-methyl-5-pyridinyl, 2-methoxy-5-pyridinyl, 3-methoxy-5-pyridinyl, 2-ethoxy-5-pyridinyl, 3-ethoxy-5-pyridinyl, 3-triflouromethyl-5-pyridinyl, 3-ethyl-5-pyridinyl, 2,3-dimethyl-5-pyridinyl, 2-(2-hydroxymethylpyrrolidin-1-yl)-5-pyridinyl, 2-(morpholin-1-yl)-3-chloro-5-pyridinyl, 2-(dimethylaminoethoxy)-5-pyridinyl, 2-(2-dimethylaminomethylpyrrolidin-1-yl)-5-pyridinyl, 2-phenyl-5-pyridinyl, 2-methyl-6-pyridinyl, 2,4-dimethyl-6-pyridinyl and 2-ethyl-6-pyridinyl.

[0337] Embodiment 61. The method of embodiment 55 wherein R^{38} is selected from substituted or unsubstituted tetrahydroquinolinyl, substituted or unsubstituted 1-pyrrolin-3-yl, substituted or unsubstituted 1-imidazolidinyl, and substituted or unsubstituted dihydropyridin-3-yl;.

[0338] Embodiment 62. The method of embodiment 61 wherein R^{38} is selected from 4-isoquinolinyl, 1-methoxy-4-isoquinolinyl, 1-chloro-4-isoquinolinyl, 6-methyl-4-isoquinolinyl, 1-oxo-2-methyl-4-isoquinolinyl, 3-quinolinyl, 4-quinolinyl, 5-pyrrolopyridinyl, [1,3,3a]-triazainden-5-yl, 1-ethyl-3-pyrrolopyridinyl, and 1-methyl-5-pyrrolopyridinyl;

[0339] Embodiment 63. The method of embodiment 55 wherein R^{37} is selected from ethenyl, fluoroethenyl, propynyl, dialkylaminopropenyl, alkylaminopropenyl, aminopropenyl and nitrogen-containing heterocyclyl-propenyl.

[0340] Embodiment 64. The method of any one of embodiments 1-34 wherein the compound is of the formula:



XIV

wherein R^{36} is selected from H, halo, C_1-C_4 alkyl, C_2-C_4 alkenyl and C_3-C_6 cycloalkyl;
R^{37} is substituted or unsubstituted C_2-C_4 alkenyl, or C_2-C_4 alkynyl; and

R^{41} is selected from H, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylamino-C_{1-6} alkyl, C_{1-6} alkylaminocarbonyl-C_{1-6} alkyl, aminocarbonyl-C_{1-6} alkyl, C_{1-6} alkoxycarbonyl-C_{1-6} alkyl, carboxy-C_{1-6} alkyl, C_{1-6} alkylcarbonylamino-C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, aryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heteroaryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heterocyclyl and substituted or unsubstituted 5 or 6 membered heteroaryl;

R^{42} is selected from H, carboxy, amino, C_{1-6} alkyl, C_{1-3} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylaminocarbonyl, and C_{3-6} cycloalkyl;

R^{43} is selected from H, carboxy, C_{1-4} alkyl, C_{1-3} haloalkyl, and C_{1-6} alkylaminocarbonyl; or an isomer or stereoisomer of any of the foregoing, and

R^{44} is one or more substituents selected from H, halo, alkoxy and hydroxy; or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0341] Embodiment 65. The method of embodiment 64, wherein R^{41} is selected from H, ethyl, isopropyl, butyl, propyl, methyl, D_3-methyl, 1-hydroxyethyl, 2-hydroxymethylethyl, 1-hydroxy-2,2-dimethylethyl, 2-hydroxypropyl, 2-hydroxy-2-methylpropyl, methoxymethyl, methoxyethyl, dimethylaminoethyl, carboxymethyl, carboxyethyl, methoxycarbonylmethyl, dimethylaminocarbonylmethyl, dimethylaminocarbonylethyl, methylaminocarbonylethyl, methylaminocarbonylmethyl, aminocarbonylmethyl, aminocarbonylethyl, aminocarbonyl-1,1-dimethylmethyl, methylcarbonylaminoethyl, 1-methylcarbonylamino-2.2-dimethylethyl, 2-cyano-2-methylethyl, cyanomethyl, cyanoethyl, cyclopropyl, cyclopropylmethyl, benzyl, 3-pyridinylmethyl, 2-pyridinylmethyl, 4-oxazolylmethyl, oxadiazol-5-ylmethyl, 1-methylazetidin-3-yl, 1-methylpyrrolidin-3-yl, 1-methylpiperidin-4-yl, 1-methylpiperidin-3-yl, 3,5-difluoro-4-pyridyl, 3-chloro-4-pyridyl, 4-pyridyl and 2-pyridyl; or an isomer or a pharmaceutically acceptable salt thereof.

[0342] Embodiment 66. The method of embodiment 64, wherein R^{36} is H, chloro, methyl, ethyl, isopropyl, propenyl, trifluoromethyl, 2-furyl, 2-pyridinyl, or cyclopropyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0343] Embodiment 67. The method of embodiment 64, wherein R^{37} is selected from ethenyl, fluoroethenyl, fluoropropenyl, propynyl, dialkylaminopropenyl, alkylaminopropenyl, aminopropenyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-ethenyl and substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-propenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

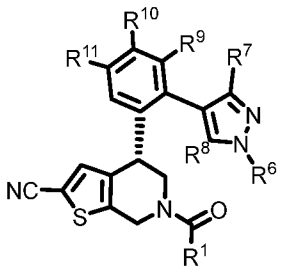
[0344] Embodiment 68. The method of embodiment 64, wherein, R^{37} is azetidin-1-ylpropenyl, 1-methylpyrrolidin-2-ylethenyl, dimethylaminopropenyl, methylaminopropenyl, piperidin-1-ylpropenyl, 4-hydroxy-piperidin-1-ylpropenyl, pyrrolidin-1-ylpropenyl, 3-hydroxypyrrolidin-1-ylpropenyl, morpholin-1-ylpropenyl, or aminopropenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0345] Embodiment 69. The method of embodiment 64, wherein R^{42} is selected from H, trifluoromethyl, difluoromethyl, methyl, ethyl, methoxy, amino, dimethylamino, carboxy. methylaminocarbonyl, dimethylaminocarbonyl, and cyclopropyl; or an isomer or a pharmaceutically acceptable salt thereof.

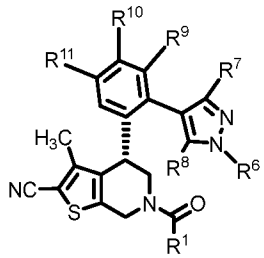
[0346] Embodiment 70. The method of embodiment 64, wherein R^{43} is selected from H, trifluoromethyl, methyl, ethyl, carboxy, cyano and methylaminocarbonyl; or an isomer or a pharmaceutically acceptable salt thereof.

[0347] Embodiment 71. The method of embodiment 64, wherein R^{44} is one or more substituents selected from H, hydroxy, fluoro and methoxyl; or an isomer or a pharmaceutically acceptable salt thereof.

[0348] Embodiment 72. The method of any one of embodiments 1-34 wherein the compound is of the formula:



IV or



V

wherein

R^1 is substituted or unsubstituted C_2-C_6 alkenyl, or substituted or unsubstituted C_2-C_6 alkynyl;

R^6 is selected from H, C_{1-6} alkyl, C_{2-4} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylamino-C_{1-6} alkyl, C_{1-6} alkylaminocarbonyl-C_{1-6} alkyl, aminocarbonyl-C_{1-6} alkyl, C_{1-6} alkoxycarbonyl-C_{1-6} alkyl, carboxy-C_{1-6} alkyl, C_{1-6} alkylcarbonylamino-C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{1-6} alkylsulfonyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, aryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heteroaryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heterocyclyl and substituted or unsubstituted 5 or 6 membered heteroaryl;

R^7 is selected from H, carboxy, amino, C_{1-6} alkyl, C_{1-3} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylaminocarbonyl, and C_{3-6} cycloalkyl;

R^8 is selected from H, carboxy, cyano, C_{1-4} alkyl, C_{1-3} haloalkyl, and C_{1-6} alkylaminocarbonyl;

R^9 is selected from H, halo, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, amino, C_{1-3} alkylcarbonylamino, C_{1-3} alkylsulfonylamino, and C_{1-3} alkylaminocarbonylamino;

R^{10} is selected from H, halo, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, amino, C_{1-3} alkylcarbonylamino, C_{1-3} alkylsulfonylamino, and C_{1-3} alkylaminocarbonylamino; and

R^{11} is selected from H, halo, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, amino, C_{1-3} alkylcarbonylamino, C_{1-3} alkylsulfonylamino, and C_{1-3} alkylaminocarbonylamino;

or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0349] Embodiment 73. The method of embodiment 72, wherein R^1 is selected from C_2-C_6 alkenyl, halo-substituted C_2-C_6 alkenyl; alkoxy substituted C_2-C_6 alkenyl; dialkylamino substituted C_2-C_6 alkenyl,

alkylamino substituted C_2-C_6 alkenyl, amino substituted C_2-C_6 alkenyl, hydroxy substituted amino-C_2-C_6 alkenyl, phenyl substituted amino-C_2-C_6 alkenyl, amino substituted C_2-C_6 alkynyl, dialkylamino substituted C_2-C_6 alkynyl, alkylamino substituted C_2-C_6 alkynyl, alkoxy substituted C_2-C_6 alkynyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl- substituted C_2-C_6 alkynyl, substituted or unsubstituted 3-7 membered cycloalkyl- substituted C_2-C_6 alkenyl, substituted or unsubstituted 3-7 membered oxygen-containing heterocyclyl- substituted C_2-C_6 alkenyl, substituted or unsubstituted 3-7 membered oxygen-containing heterocyclyl- substituted C_2-C_6 alkynyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl- substituted C_2-C_6 alkenyl, and substituted or unsubstituted 3-7 membered cycloalkyl- substituted C_2-C_6 alkynyl; .

[0350] . Embodiment 74. The method of embodiment 73, wherein R^1 is selected from ethenyl, fluoropropenyl, 3,3-difluoropropenyl, 3,3,3-trifluoropropenyl, 3,3,3-trifluoroprop-1-enyl, alkoxypropenyl, dialkylaminopropenyl, alkylaminopropenyl, aminopropenyl, 3-amino-4-hydroxy-butenyl, 3-amino-4-phenyl-butenyl, dialkylaminobutenyl, alkylaminobutenyl, aminobutenyl, dialkylaminopentenyl, alkylaminopentenyl, aminopentenyl, aminopropynyl, dialkylaminopropynyl, alkylaminopropynyl, methoxypropynyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-propynyl, substituted or unsubstituted 3-7 membered cycloalkyl-ethenyl, substituted or unsubstituted 3-7 membered cycloalkyl-propenyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-ethynyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-propynyl, substituted or unsubstituted 3-7 membered oxygen-containing heterocyclyl-ethenyl, substituted or unsubstituted 3-7 membered oxygen-containing heterocyclyl-propenyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-ethenyl, substituted or unsubstituted 3-7 membered nitrogen-containing heterocyclyl-propenyl, substituted or unsubstituted 3-7 membered cycloalkyl-ethynyl, substituted or unsubstituted 3-7 membered cycloalkyl-propynyl, substituted or unsubstituted 3-7 membered cycloalkyl-ethynyl, and substituted or unsubstituted 3-7 membered cycloalkyl-propynyl;

[0351] Embodiment 75. The method of embodiment 74, wherein R^1 is selected from ethenyl, fluoropropenyl, 3,3-difluoropropenyl, 3,3,3-trifluoropropenyl, 3,3,3-trifluoroprop-1-enyl, methoxypropenyl, ethoxypropenyl, aminopropenyl, 3-amino-butenyl, 3-methylamino-butenyl, 3-amino-4-hydroxy-butenyl, 3-methylamino-4-methoxy-butenyl, 3-amino-4-phenyl-butenyl, 3-amino-pentenyl, aminopropynyl, methoxypropynyl, dimethylaminopropenyl, di(d1,d2,d3-methyl)aminopropenyl, diethylaminopropenyl, 3-(N,N-dimethylamino)-3-phenyl-propenyl, 3-(N,N-dimethylamino)-3-cyclopropyl-propenyl, (cyclopropylamino)propenyl, bicyclo[1.1.1]pent-1-ylamino, (1-methylcyclopropylamino)propenyl, (3-methyloxetan-3-yl)aminopropenyl, (3-methyltetrahydrofur-3-yl)aminopropenyl, (4-methyl-tetrahydropyran-4-yl)aminopropenyl, methylaminopropenyl, N-benzyl-N-methylaminopropenyl, N-(tert-butyl)aminopropenyl, N-sec-butylaminopropenyl, N-butylaminopropenyl, N-(isopropyl)aminopropenyl, N-(d2-isopropyl)aminopropenyl, ethylaminopropenyl, N-[3,3-difluorocyclobutyl]aminopropenyl, 1-hydroxymethyl-1-methyl-ethylaminopropenyl, 3-dimethylamino-butenyl, 3-(N-methylamino)-butenyl, methylaminobutenyl, N,N-dimethylaminobutenyl, piperidin-2-

ylpropenyl, pyrrolidin-1-ylpropenyl, 3-methyl-oxetan-3-ylpropenyl, 4-methyl-tetrahydropyran-4-ylpropenyl, piperidin-2-ylethenyl, pyrrolidin-2-ylethenyl, azetidin-2-ylethenyl, morpholin-3-ylethenyl, 1-methylpyrrolidin-2-ylethenyl, 3-methylpyrrolidin-5-ylethenyl, 3-ethylpyrrolidin-5-ylethenyl, 2-methylpyrrolidin-5-ylethenyl, 2,2-dimethylpyrrolidin-5-ylethenyl, 3-methoxypyrrolidin-5-ylethenyl, 3-fluoropyrrolidin-5-ylethenyl, 3,3-difluoropyrrolidin-5-ylethenyl, 5-azaspiro[2.4]heptan-6-ylethenyl, 2-azabicyclo[3.1.0]hexan-3-ylethenyl, 3,3-dimethylpyrrolidin-5-ylethenyl, 3-methylpyrrolidin-1-ylpropenyl, 2-methylpyrrolidin-1-ylpropenyl, 1-methylcarbonylpyrrolidin-3-ylethenyl, 2-carboxypyrrolidin-1-ylpropenyl, 3-carboxypyrrolidin-1-ylpropenyl, tetrahydrofur-3-ylpropenyl, dimethylaminopropynyl, methylaminopropynyl, 2-amino-2-methylbutynyl, 2-(1-amino-cyclopropyl)-ethynyl, 2-(1-amino-cyclobutyl)-ethynyl, 2-(1-amino-cyclopentyl)-ethynyl, azetidin-2-ylethynyl, pyrrolidin-2-ylethynyl, pyrrolidin-3-ylethynyl, 2-methyl-pyrrolidin-2-ylethynyl, 4-methyl-piperazin-1-ylpropynyl, and piperidin-3-ylethynyl;

[0352] Embodiment 76. The method of embodiment 72, wherein R^6 is selected from H, ethyl, isopropyl, butyl, propyl, methyl, propynyl, 1-hydroxyethyl, 2-hydroxymethylethyl, 1-hydroxy-2,2-dimethylethyl, 2-hydroxypropyl, 2-hydroxy-2-methylpropyl, methoxymethyl, methoxyethyl, dimethylaminoethyl, carboxymethyl, carboxyethyl, carboxypropyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, ethoxycarbonylpropyl, dimethylaminocarbonylmethyl, dimethylaminocarbonyl-1-ethyl, methylaminocarbonyl-1-ethyl, methylaminocarbonylethyl, methylaminocarbonylmethyl, aminocarbonylmethyl, aminocarbonylethyl, 1-aminocarbonylethyl, aminocarbonyl-1,1-dimethylmethyl, methylcarbonylaminoethyl, 1-methylcarbonylamino-2,2-dimethylethyl, 2-cyano-2-methylethyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methylsulfonyl, cyclopropyl, cyclopropylmethyl, benzyl, 4-pyridinylethyl, 2-pyridinylethyl, 3-pyridinylmethyl, 2-pyridinylmethyl, 4-oxazolylmethyl, 1,3,4-oxadiazol-2-yl]methyl, 1,2,4-oxadiazol-2-yl]methyl 1-methylazetidin-3-yl, 1-methylpyrrolidin-3-yl, 1-methylpiperidin-4-yl, 1-methylpiperidin-3-yl, 5-methoxypyrimidin-4-yl, 2-amino-4-pyridyl, 3-chloro-5-fluoro-4-pyridyl, 3,5-difluoro-4-pyridyl, 3-fluoro-2-pyridyl, 3-methoxy-2-pyridyl, 3-fluoro-4-pyridyl, 3-chloro-4-pyridyl, 4-pyridyl and 2-pyridyl;

[0353] Embodiment 77. The method of embodiment 72, wherein R^7 is selected from H, trifluoromethyl, difluoromethyl, 1,1-difluoroethyl, methyl, ethyl, methoxy, amino, dimethylamino, carboxy. methylaminocarbonyl, dimethylaminocarbonyl, and cyclopropyl;

[0354] Embodiment 78. The method of embodiment 72, wherein R^8 is selected from H, trifluoromethyl, methyl, ethyl, carboxy, cyano and methylaminocarbonyl;

[0355] Embodiment 79. The method of embodiment 72, wherein R^9 is selected from H, fluoro, chloro, methyl, and cyano;

[0356] Embodiment 80. The method of embodiment 72, wherein R^{10} is selected from H, fluoro, methylcarbonylamino, chloro, amino, hydroxy, methyl, difluoromethyl, methylsulfonylamino, and methylaminocarbonylamino;

[0357] Embodiment 81. The method of embodiment 72, wherein R^{11} is H or fluoro;

[0358] Embodiment 82. The method of embodiment 72, wherein R^6 is ethyl; R^7 is trifluoromethyl; and R^8 is H;

[0359] Embodiment 83. The method of embodiment 72, wherein R^6 is methyl; R^7 is trifluoromethyl; and R^8 is H;

[0360] Embodiment 84. The method of embodiment 72, wherein R^6 is H; R^7 is trifluoromethyl; and R^8 is H;

[0361] Embodiment 85. The method of embodiment 72, wherein R^6 is 3,5-difluoropyridin-4-yl; R^7 is trifluoromethyl; and R^8 is H;

[0362] Embodiment 86. The method of embodiment 72, wherein R^1 is substituted ethenyl;.

[0363] Embodiment 87. The method of embodiment 72, wherein R^1 is dimethylaminopropenyl;.

[0364] Embodiment 88. The method of embodiment 72, wherein R^1 is methylaminopropenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0365] Embodiment 89. The method of embodiment 72, wherein R^1 is 3,3-difluoropropenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0366] Embodiment 90. The method of embodiment 72, wherein R^1 is 2-(azetin-2-yl)ethenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0367] Embodiment 91. The method of embodiment 72, wherein R^1 is 2-(2-methyl-pyrrolidiny-5-yl)ethenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0368] Embodiment 92. The method of embodiment 72, wherein R^1 is 3-(methylamino)butenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0369] Embodiment 93. The method of embodiment 72, wherein R^1 is ethylaminopropenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0370] Embodiment 94. The method of embodiment 72, wherein R^1 is 2-(3-methoxypyrrolidiny-5-yl)ethenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0371] Embodiment 95. The method of embodiment 72, wherein R^1 is 2-(3-fluoropyrrolidiny-5-yl)ethenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0372] Embodiment 96. The method of embodiment 72, wherein R^1 is 2-(pyrrolidiny-2-yl)ethenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0373] Embodiment 97. The method of embodiment 72, wherein R^1 is aminopropenyl; or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0374] Embodiment 98. The method of embodiment 72, wherein R^9 is fluoro; R^{10} is H; and R^{11} is H; an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

[0375] Embodiment 99. The method of any one of embodiments 1-34 wherein the compound is a compound of Table A.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a cancer in a subject in need thereof, the method comprising:

(i) administering to the subject a therapeutically-effective amount of a compound that blocks SUMOylation in the subject; and

(ii) administering to the subject a therapeutically-effective amount of an anti-cancer agent that functions through a pathway other than SUMOylation.

2. The method of claim 1, wherein the compound binds to Uba2.

3. The method of claim 1 or 2, wherein the compound has an inhibitory effect on activating enzymes (E1) of SUMO.

4. The method of claim 1, 2, or 3, wherein the cancer is selected from acute myeloid leukemia, large B-cell lymphoma, lung squamous cell carcinoma, pancreatic adenocarcoma, esophegeal carcinoma, cervical squamous cell carcinoma, endocervical adenocarcoma, stomach adenocarcinomathymoma, renal cell carcinoma, head and neck squamous cell carcinoma, bladder carcinoma, ovarian cystadenocarcinoma, multiple myeloma, non-Hodgkin's lymphoma (NHL), and mesothelioma.

5. The method of claim 1, 2, or 3, wherein the cancer is selected from head and neck squamous cell carcinoma (HNSCC), non-squamous non-small cell lung cancer (NSCLC), cervical cancer, colorectal cancer (CRC), cutaneous melanoma, squamous NSCLC, and small cell lung cancer.

6. The method of claim 1, 2, or 3, wherein the cancer is B Cell Lymphoma.

7. The method of claim 1, 2, or 3, wherein the cancer is acute myeloid leukemia.

8. The method of claim 1, 2, or 3, wherein the cancer is colon cancer.

9. The method of anyone of claims 1-8, wherein the administering of the compound is oral.

10. The method of any one of claims 1-9, wherein the therapeutically-effective amount of the compound is from about 100 mg to about 500 mg.

11. The method of any one of claims 1-10, wherein the subject is human.

12. The method of any one of claims 1-11, wherein the anti-cancer agent is a hypomethylating agent.

13. The method of any one of claims 1-12, wherein the anti-cancer agent is an anti-CD20 antibody.

14. The method of any one of claims 1-12, wherein the anti-cancer agent is an immune checkpoint inhibitor.

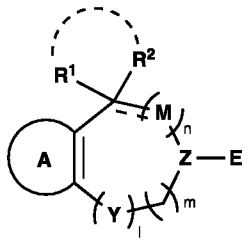
15. The method of claim 14, wherein the immune checkpoint inhibitor is an anti-PD-1 agent.

16. The method of claim 14, wherein the immune checkpoint inhibitor is an anti-PD-L1 agent.

17. The method of any one of claims 1-16, wherein the therapeutically-effective amount of the anti-cancer agent is from about 5 mg/kg to about 500 mg/kg.

18. The method of any one of claims 1-16, wherein the therapeutically-effective amount of the anti-cancer agent is from about 10 μg to about 500 μg.

19. The method of any one of claims 1-18, wherein the compound is of the formula:



(I)

wherein ==== is a single bond or double bond;

wherein l, m, n are each independently an integer from 0 to 2;

wherein M is selected from CR^3R^4, NR^5, C=O, O, S=O, O=S=O, and S;

wherein Y is selected from CR^6R^7, NR^8, C=O, O, S=O, O=S=O, and S;

wherein Z is CR^9, or N;

wherein ring A is selected from

a) 5- or 6-membered partially saturated heterocyclyl,

b) 5- or 6-membered aryl or heteroaryl,

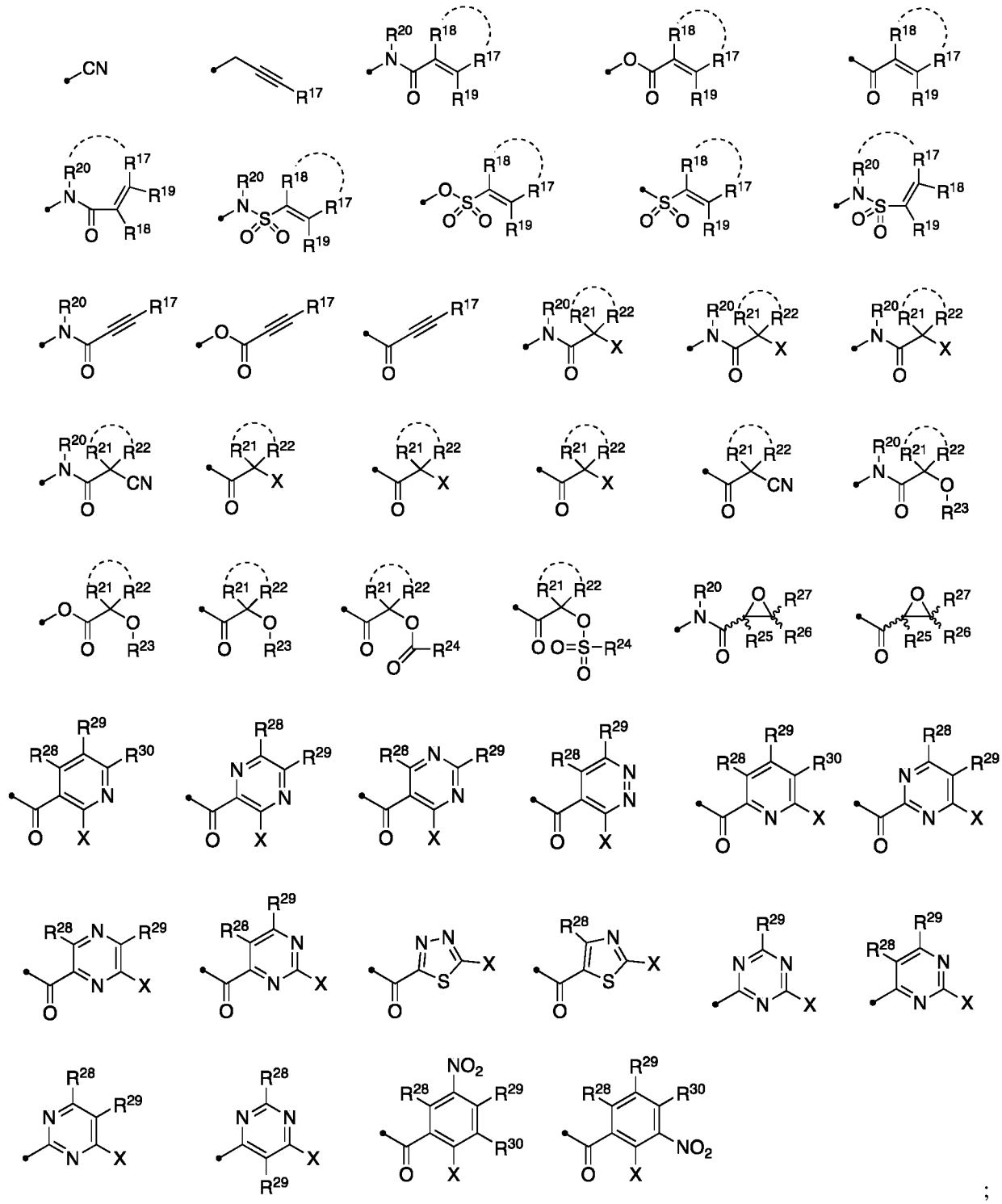
c) 9-, 10- or 11-membered fused partially saturated heterocyclyl,

d) 9- or 10-membered fused heteroaryl,

e) naphthyl, and

f) 4-, 5- or 6-membered cycloalkenyl;

wherein E is an electrophilic moiety, selected from:



;

Wherein R^1 is selected from hydrogen, halogen, $-C(X^1)_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-NHNR^{1A}R^{1B}$, $-C(O)R^{1A}$, $-C(O)-OR^{1A}$, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHNR^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$, $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, 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;

Wherein R^2 is selected from hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHNR^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHNR^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$, $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, 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; R^1 and R^2 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

Wherein R^3 is selected from hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHNR^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, 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;

Wherein R^4 is selected from hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHNR^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHNR^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, 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^3 and R^3 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

Wherein R^5 is selected from hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHNR^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHNR^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, 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;

Wherein R^6 is selected from hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-NHNR^{6A}R^{6B}$, $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHNR^{6A}R^{6B}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, 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;

Wherein R^7 is selected from hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHNR^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHNR^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, 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;

Wherein R^8 is selected from hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, -CN, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}8^{7B}$, $-NHNR^{8A}R^{8B}$, $-C(O)R^{8A}$, $-C(O)-OR^{8A}$, $-C(O)NR^{8A}R^{8B}$, $-C(O)NHNR^{8A}R^{8B}$, $-OR^{8A}$, $-NR^{8A}SO_2R^{8B}$, $-NR^{8A}C(O)R^{8B}$, $-NR^{8A}C(O)OR^{8B}$, $-NR^{8A}OR^{8B}$, $-N_3$, 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;

Wherein R^9 is selected from hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHNR^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHNR^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, 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;

Wherein R^{10} is selected from hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNR^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNR^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, 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;

Wherein R^{11} is selected from hydrogen, halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, -CN, $-SO_{n11}R^{11A}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-NHNR^{11A}R^{11B}$, $-C(O)R^{11A}$, $-C(O)-OR^{11A}$, $-C(O)NR^{11A}R^{11B}$, $-C(O)NHNR^{11A}R^{11B}$, $-OR^{11A}$, $-NR^{11A}SO_2R^{11B}$, $-NR^{11A}C(O)R^{11B}$, $-NR^{11A}C(O)OR^{11B}$, $-NR^{11A}OR^{11B}$, $-N_3$, 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;

Wherein R^{12} is selected from hydrogen, halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, -CN, $-SO_{n12}R^{12A}$, $-SO_{v12}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m12}$,

$-NR^{12A}R^{12B}$, $-NHNR^{12A}R^{12B}$, $-C(O)R^{12A}$, $-C(O)\text{-}OR^{12A}$, $-C(O)NR^{12A}R^{12B}$, $-C(O)NHNR^{12A}R^{12B}$, $-OR^{12A}$, $-NR^{12A}SO_2R^{12B}$, $-NR^{12A}C(O)R^{12B}$, $-NR^{12A}C(O)OR^{12B}$, $-NR^{12A}OR^{12B}$, $-N_3$, 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;

Wherein R^{13} is selected from hydrogen, halogen, $-CX^{13}_3$, $-CHX^{13}_2$, $-CH_2X^{13}$, $-OCX^{13}_3$, $-OCH_2X^{13}$, $-OCHX^{13}_2$, -CN, $-SO_{n13}R^{13A}$, $-SO_{v13}NR^{13A}R^{13B}$, $-NHC(O)NR^{13A}R^{13B}$, $-N(O)_{m13}$, $-NR^{13A}R^{13B}$, $-NHNR^{13A}R^{13B}$, $-C(O)R^{13A}$, $-C(O)\text{-}OR^{13A}$, $-C(O)NR^{13A}R^{13B}$, $-C(O)NHNR^{13A}R^{13B}$, $-OR^{13A}$, $-NR^{13A}SO_2R^{13B}$, $-NR^{13A}C(O)R^{13B}$, $-NR^{13A}C(O)OR^{13B}$, $-NR^{13A}OR^{13B}$, $-N_3$, 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;

Wherein R^{14} is selected from hydrogen, halogen, $-CX^{14}_3$, $-CHX^{14}_2$, $-CH_2X^{14}$, $-OCX^{14}_3$, $-OCH_2X^{14}$, $-OCHX^{14}_2$, -CN, $-SO_{n14}R^{14A}$, $-SO_{v14}NR^{14A}R^{14B}$, $-NHC(O)NR^{14A}R^{14B}$, $-N(O)_{m14}$, $-NR^{14A}R^{14B}$, $-NHNR^{14A}R^{14B}$, $-C(O)R^{14A}$, $-C(O)\text{-}OR^{14A}$, $-C(O)NR^{14A}R^{14B}$, $-C(O)NHNR^{14A}R^{14B}$, $-OR^{14A}$, $-NR^{14A}SO_2R^{14B}$, $-NR^{14A}C(O)R^{14B}$, $-NR^{14A}C(O)OR^{14B}$, $-NR^{14A}OR^{14B}$, $-N_3$, 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;

Wherein R^{15} is selected from hydrogen, halogen, $-CX^{15}_3$, $-CHX^{15}_2$, $-CH_2X^{15}$, $-OCX^{15}_3$, $-OCH_2X^{15}$, $-OCHX^{15}_2$, -CN, $-SO_{n15}R^{15A}$, $-SO_{v15}NR^{15A}R^{15B}$, $-NHC(O)NR^{15A}R^{15B}$, $-N(O)_{m15}$, $-NR^{15A}R^{15B}$, $-NHNR^{15A}R^{15B}$, $-C(O)R^{15A}$, $-C(O)\text{-}OR^{15A}$, $-C(O)NR^{15A}R^{15B}$, $-C(O)NHNR^{15A}R^{15B}$, $-OR^{15A}$, $-NR^{15A}SO_2R^{15B}$, $-NR^{15A}C(O)R^{15B}$, $-NR^{15A}C(O)OR^{15B}$, $-NR^{15A}OR^{15B}$, $-N_3$, 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;

R^{16} is selected from hydrogen, halogen, $-CX^{16}_3$, $-CHX^{16}_2$, $-CH_2X^{16}$, $-OCX^{16}_3$, $-OCH_2X^{16}$, $-OCHX^{16}_2$, -CN, $-SO_{n16}R^{16A}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-NHNR^{16A}R^{16B}$, $-C(O)R^{16A}$, $-C(O)\text{-}OR^{16A}$, $-C(O)NR^{16A}R^{16B}$, $-C(O)NHNR^{16A}R^{16B}$, $-OR^{16A}$, $-NR^{16A}SO_2R^{16B}$, $-NR^{16A}C(O)R^{16B}$, $-NR^{16A}C(O)OR^{16B}$, $-NR^{16A}OR^{16B}$, $-N_3$, 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;

R^{17} is selected from hydrogen, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-CH_2X^{17}$, $-OCX^{17}_3$, $-OCH_2X^{17}$, $-OCHX^{17}_2$, -CN, $-SO_{n17}R^{17A}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-C(O)R^{17A}$, $-C(O)\text{-}OR^{17A}$, $-C(O)NR^{17A}R^{17B}$, $-C(O)NHNR^{17A}R^{17B}$, $-OR^{17A}$, $-NR^{17A}SO_2R^{17B}$, $-NR^{17A}C(O)R^{17B}$, $-NR^{17A}C(O)OR^{17B}$, $-NR^{17A}OR^{17B}$, $-N_3$, 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;

R^{18} is selected from hydrogen, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-OCX^{18}_3$, $-OCH_2X^{18}$, $-OCHX^{18}_2$, -CN, $-SO_{n18}R^{18A}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-NHNR^{18A}R^{18B}$, $-C(O)R^{18A}$, $-C(O)-OR^{18A}$, $-C(O)NR^{18A}R^{18B}$, $-C(O)NHNR^{18A}R^{18B}$, $-OR^{18A}$, $-NR^{18A}SO_2R^{18B}$, $-NR^{18A}C(O)R^{18B}$, $-NR^{18A}C(O)OR^{18B}$, $-NR^{18A}OR^{18B}$, $-N_3$, 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; R^{17} and R^{18} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{19} is selected from hydrogen, halogen, $-CX^{19}_3$, $-CHX^{19}_2$, $-CH_2X^{19}$, $-OCX^{19}_3$, $-OCH_2X^{19}$, $-OCHX^{19}_2$, -CN, $-SO_{n19}R^{19A}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-NHNR^{19A}R^{19B}$, $-C(O)R^{19A}$, $-C(O)-OR^{19A}$, $-C(O)NR^{19A}R^{19B}$, $-C(O)NHNR^{19A}R^{19B}$, $-OR^{19A}$, $-NR^{19A}SO_2R^{19B}$, $-NR^{19A}C(O)R^{19B}$, $-NR^{19A}C(O)OR^{19B}$, $-NR^{19A}OR^{19B}$, $-N_3$, 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;

R^{20} is selected from hydrogen, halogen, $-CX^{20}_3$, $-CHX^{20}_2$, $-CH_2X^{20}$, $-OCX^{20}_3$, $-OCH_2X^{20}$, $-OCHX^{20}_2$, -CN, $-SO_{n20}R^{20A}$, $-SO_{v20}NR^{20A}R^{20B}$, $-NHC(O)NR^{20A}R^{20B}$, $-N(O)_{m20}$, $-NR^{20A}R^{20B}$, $-NHNR^{20A}R^{20B}$, $-C(O)R^{20A}$, $-C(O)-OR^{20A}$, $-C(O)NR^{20A}R^{20B}$, $-C(O)NHNR^{20A}R^{20B}$, $-OR^{20A}$, $-NR^{20A}SO_2R^{20B}$, $-NR^{20A}C(O)R^{20B}$, $-NR^{20A}C(O)OR^{20B}$, $-NR^{20A}OR^{20B}$, $-N_3$, 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; R^{17} and R^{20} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{21} is selected from hydrogen, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, -CN, $-SO_{n21}R^{21A}$, $-SO_{v21}NR^{21A}R^{21B}$, $-NHC(O)NR^{21A}R^{21B}$, $-N(O)_{m21}$, $-NR^{21A}R^{21B}$, $-NHNR^{21A}R^{21B}$, $-C(O)R^{21A}$, $-C(O)-OR^{21A}$, $-C(O)NR^{21A}R^{21B}$, $-C(O)NHNR^{21A}R^{21B}$, $-OR^{21A}$, $-NR^{21A}SO_2R^{21B}$, $-NR^{21A}C(O)R^{21B}$, $-NR^{21A}C(O)OR^{21B}$, $-NR^{21A}OR^{21B}$, $-N_3$, 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;

R^{22} is selected from hydrogen, halogen, $-CX^{22}_3$, $-CHX^{22}_2$, $-CH_2X^{22}$, $-OCX^{22}_3$, $-OCH_2X^{22}$, $-OCHX^{22}_2$, -CN, $-SO_{n22}R^{22A}$, $-SO_{v22}NR^{22A}R^{22B}$, $-NHC(O)NR^{22A}R^{22B}$, $-N(O)_{m22}$, $-NR^{22A}R^{22B}$, $-NHNR^{22A}R^{22B}$, $-C(O)R^{22A}$, $-C(O)-OR^{22A}$, $-C(O)NR^{22A}R^{22B}$, $-C(O)NHNR^{22A}R^{22B}$, $-OR^{22A}$, $-NR^{22A}SO_2R^{22B}$, $-NR^{22A}C(O)R^{22B}$, $-NR^{22A}C(O)OR^{22B}$,

$-NR^{22A}OR^{22B}$, $-N_3$, 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; R^{21} and R^{22} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

wherein R^{23} is selected from hydrogen, halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-CH_2X^{23}$, $-OCX^{23}_3$, $-OCH_2X^{23}$, $-OCHX^{23}_2$, -CN, $-SO_{n23}R^{23A}$, $-SO_{v23}NR^{23A}R^{23B}$, $-NHC(O)NR^{23A}R^{23B}$, $-N(O)_{m23}$, $-NR^{23A}R^{23B}$, $-NHNR^{23A}R^{23B}$, $-C(O)R^{23A}$, $-C(O)-OR^{23A}$, $-C(O)NR^{23A}R^{23B}$, $-C(O)NHNR^{23A}R^{23B}$, $-OR^{23A}$, $-NR^{23A}SO_2R^{23B}$, $-NR^{23A}C(O)R^{23B}$, $-NR^{23A}C(O)OR^{23B}$, $-NR^{23A}OR^{23B}$, $-N_3$, 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;

wherein R^{24} is selected from hydrogen, halogen, $-CX^{24}_3$, $-CHX^{24}_2$, $-CH_2X^{24}$, $-OCX^{24}_3$, $-OCH_2X^{24}$, $-OCHX^{24}_2$, -CN, $-SO_{n24}R^{24A}$, $-SO_{v24}NR^{24A}R^{24B}$, $-NHC(O)NR^{24A}R^{24B}$, $-N(O)_{m24}$, $-NR^{24A}R^{24B}$, $-NHNR^{24A}R^{24B}$, $-C(O)R^{24A}$, $-C(O)-OR^{24A}$, $-C(O)NR^{24A}R^{24B}$, $-C(O)NHNR^{24A}R^{24B}$, $-OR^{24A}$, $-NR^{24A}SO_2R^{24B}$, $-NR^{24A}C(O)R^{24B}$, $-NR^{24A}C(O)OR^{24B}$, $-NR^{24A}OR^{24B}$, $-N_3$, 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;

wherein R^{25} is selected from hydrogen, halogen, $-CX^{25}_3$, $-CHX^{25}_2$, $-CH_2X^{25}$, $-OCX^{25}_3$, $-OCH_2X^{25}$, $-OCHX^{25}_2$, -CN, $-SO_{n25}R^{25A}$, $-SO_{v25}NR^{25A}R^{25B}$, $-NHC(O)NR^{25A}R^{25B}$, $-N(O)_{m25}$, $-NR^{25A}R^{25B}$, $-NHNR^{25A}R^{25B}$, $-C(O)R^{25A}$, $-C(O)-OR^{25A}$, $-C(O)NR^{25A}R^{25B}$, $-C(O)NHNR^{25A}R^{25B}$, $-OR^{25A}$, $-NR^{25A}SO_2R^{25B}$, $-NR^{25A}C(O)R^{25B}$, $-NR^{25A}C(O)OR^{25B}$, $-NR^{25A}OR^{25B}$, $-N_3$, 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;

wherein R^{26} is selected from hydrogen, halogen, $-CX^{26}_3$, $-CHX^{26}_2$, $-CH_2X^{26}$, $-OCX^{26}_3$, $-OCH_2X^{26}$, $-OCHX^{26}_2$, -CN, $-SO_{n26}R^{26A}$, $-SO_{v26}NR^{26A}R^{26B}$, $-NHC(O)NR^{26A}R^{26B}$, $-N(O)_{m26}$, $-NR^{26A}R^{26B}$, $-NHNR^{26A}R^{26B}$, $-C(O)R^{26A}$, $-C(O)-OR^{26A}$, $-C(O)NR^{26A}R^{26B}$, $-C(O)NHNR^{26A}R^{26B}$, $-OR^{26A}$, $-NR^{26A}SO_2R^{26B}$, $-NR^{26A}C(O)R^{26B}$, $-NR^{26A}C(O)OR^{26B}$, $-NR^{26A}OR^{26B}$, $-N_3$, 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;

wherein R^{27} is selected from hydrogen, halogen, $-CX^{27}_3$, $-CHX^{27}_2$, $-CH_2X^{27}$, $-OCX^{27}_3$, $-OCH_2X^{27}$, $-OCHX^{27}_2$, -CN, $-SO_{n27}R^{27A}$, $-SO_{v27}NR^{27A}R^{27B}$, $-NHC(O)NR^{27A}R^{27B}$, $-N(O)_{m27}$, $-NR^{27A}R^{27B}$, $-NHNR^{27A}R^{27B}$, $-C(O)R^{27A}$, $-C(O)-OR^{27A}$, $-C(O)NR^{27A}R^{27B}$, $-C(O)NHNR^{27A}R^{27B}$, $-OR^{27A}$, $-NR^{27A}SO_2R^{27B}$, $-NR^{27A}C(O)R^{27B}$, $-NR^{27A}C(O)OR^{27B}$, $-NR^{27A}OR^{27B}$, $-N_3$, 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;

Wherein R^{28} is selected from hydrogen, halogen, $-CX^{28}_3$, $-CHX^{28}_2$, $-CH_2X^{28}$, $-OCX^{28}_3$, $-OCH_2X^{28}$, $-OCHX^{28}_2$, -CN, $-SO_{n28}R^{28A}$, $-SO_{v28}NR^{28A}R^{28B}$, $-NHC(O)NR^{28A}R^{28B}$, $-N(O)_{m28}$, $-NR^{28A}R^{28B}$, $-NHNR^{28A}R^{28B}$, $-C(O)R^{28A}$, $-C(O)-OR^{28A}$, $-C(O)NR^{28A}R^{28B}$, $-C(O)NHNR^{28A}R^{28B}$, $-OR^{28A}$, $-NR^{28A}SO_2R^{28B}$, $-NR^{28A}C(O)R^{28B}$, $-NR^{28A}C(O)OR^{28B}$, $-NR^{28A}OR^{28B}$, $-N_3$, 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;

Wherein R^{29} is selected from hydrogen, halogen, $-CX^{29}_3$, $-CHX^{29}_2$, $-CH_2X^{29}$, $-OCX^{29}_3$, $-OCH_2X^{29}$, $-OCHX^{29}_2$, -CN, $-SO_{n29}R^{29A}$, $-SO_{v29}NR^{29A}R^{29B}$, $-NHC(O)NR^{29A}R^{29B}$, $-N(O)_{m29}$, $-NR^{29A}R^{29B}$, $-NHNR^{29A}R^{29B}$, $-C(O)R^{29A}$, $-C(O)-OR^{29A}$, $-C(O)NR^{29A}R^{29B}$, $-C(O)NHNR^{29A}R^{29B}$, $-OR^{29A}$, $-NR^{29A}SO_2R^{29B}$, $-NR^{29A}C(O)R^{29B}$, $-NR^{29A}C(O)OR^{29B}$, $-NR^{29A}OR^{29B}$, $-N_3$, 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;

R^{30} is selected from hydrogen, halogen, $-CX^{30}_3$, $-CHX^{30}_2$, $-CH_2X^{30}$, $-OCX^{30}_3$, $-OCH_2X^{30}$, $-OCHX^{30}_2$, -CN, $-SO_{n30}R^{30A}$, $-SO_{v30}NR^{30A}R^{30B}$, $-NHC(O)NR^{30A}R^{30B}$, $-N(O)_{m30}$, $-NR^{30A}R^{30B}$, $-NHNR^{30A}R^{30B}$, $-C(O)R^{30A}$, $-C(O)-OR^{30A}$, $-C(O)NR^{30A}R^{30B}$, $-C(O)NHNR^{30A}R^{30B}$, $-OR^{30A}$, $-NR^{30A}SO_2R^{30B}$, $-NR^{30A}C(O)R^{30B}$, $-NR^{30A}C(O)OR^{30B}$, $-NR^{30A}OR^{30B}$, $-N_3$, 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;

Each R^{1A}, R^{1B}, R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{5A}, R^{5B}, R^{6A}, R^{6B}, R^{7A}, R^{7B}, R^{8A}, R^{8B}, R^{9A}, R^{9B}, R^{10A}, R^{10B}, R^{11A}, R^{11B}, R^{12A}, R^{12B}, R^{13A}, R^{13B}, R^{14A}, R^{14B}, R^{15A}, R^{15B}, R^{16A}, R^{16B}, R^{17A}, R^{17B}, R^{18A}, R^{18B}, R^{19A}, R^{19B}, R^{20A}, R^{20B}, R^{21A}, R^{21B}, R^{22A}, R^{22B}, R^{23A}, R^{23B}, R^{24A}, R^{24B}, R^{25A}, R^{25B}, R^{26A}, R^{26B}, R^{27A}, R^{27B}, R^{28A}, R^{28B}, R^{29A}, R^{29B}, R^{30A}, R^{30B} is independently selected from hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, -C(O)OH, $-C(O)NH_2$, -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, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, 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;

wherein R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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^{5A} and R^{5B} 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^{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; 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; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{11A} and R^{11B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{12A} and R^{12B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{13A} and R^{13B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{14A} and R^{14B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{20A}

and R^{20B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{21A} and R^{21B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{22A} and R^{22B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{23A} and R^{23B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{24A} and R^{24B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{25A} and R^{25B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{26A} and R^{26B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{27A} and R^{27B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{28A} and R^{28B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{29A} and R^{29B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{30A} and R^{30B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

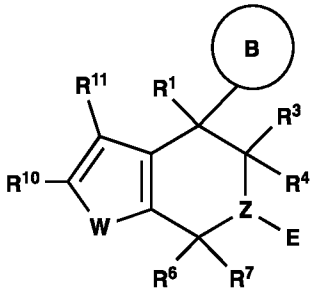
Wherein each m1, m2, m3, m4, m5, m6, m7, m8, m9, m10, m11, m12, m13, m14, m15, m16, m17, m18, m19, m20, m21, m22, m23, m24, m25, m26, m27, m28, m29, and m30 are independently 1 or 2;

wherein each v1, v2, v3, v4, v5, v6, v7, v8, v9, v10, v11, v12, v13, v14, v15, v16, v17, v18, v19, v20, v21, v22, v23, v24, v25, v26, v27, v28, v29 and v30 are independently 1 or 2;

wherein each n1, n2, n3, n4, n5, n6, n7, n8, n9, n10, n11, n12, n13, n14, n15, n16, n17, n18, n19, n20, n21, n22, n23, n24, n25, n26, n27, n28, n29 and n30 are independently an integer from 0 to 2; and

wherein each X, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, X^{16}, X^{17}, X^{18}, X^{19}, X^{20}, X^{21}, X^{22}, X^{23}, X^{24}, X^{25}, X^{26}, X^{27}, X^{28}, X^{29} and X^{30} are independently -Cl, -Br, -I or –F.

20. The method of any one of claims 1-18, wherein the compound is of the formula:



(VIII).

wherein

Z is N, or CR^9;

W is selected from NR^{12}, O, S, S=O, O=S=O, and Se;

ring B is selected from

a) 5- or 6-membered cycloalkyl, saturated or partially saturated heterocyclyl,

b) 5- or 6-membered aryl or heteroaryl,

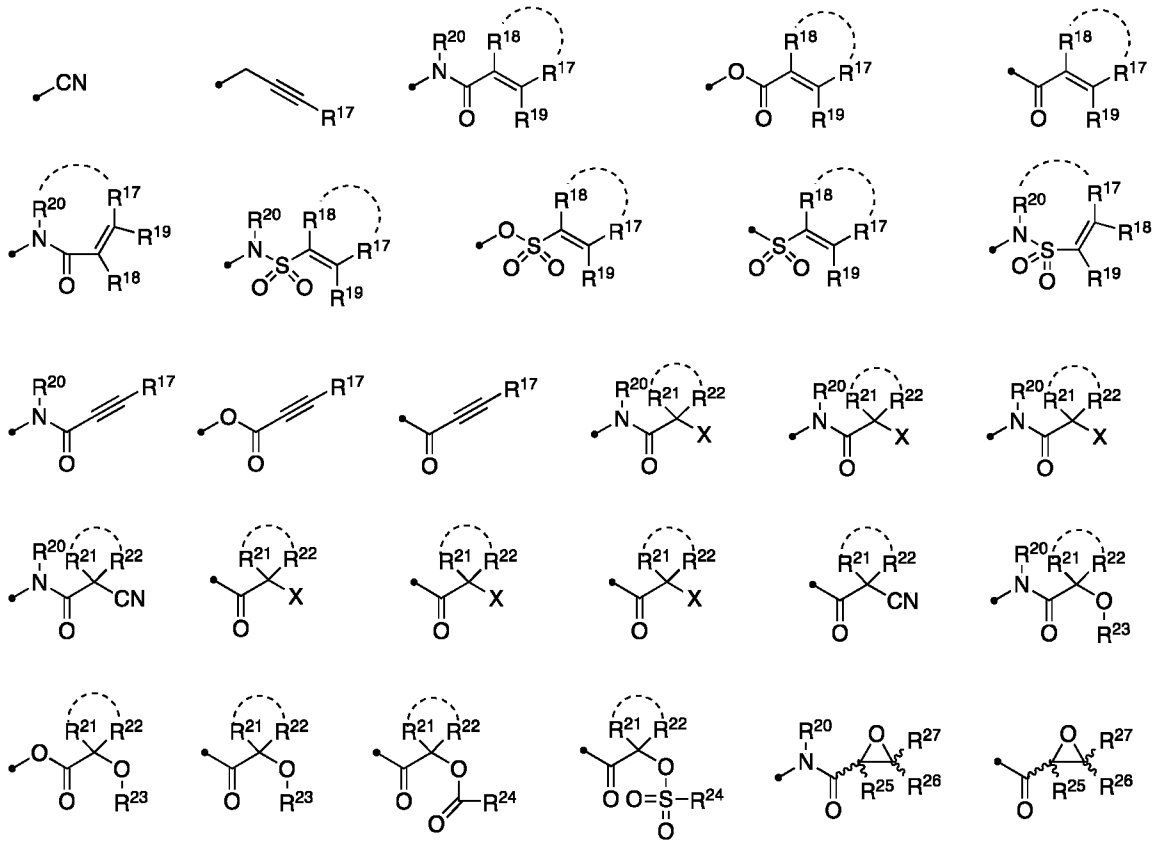
c) 9-, 10- or 11-membered fused partially saturated heterocyclyl,

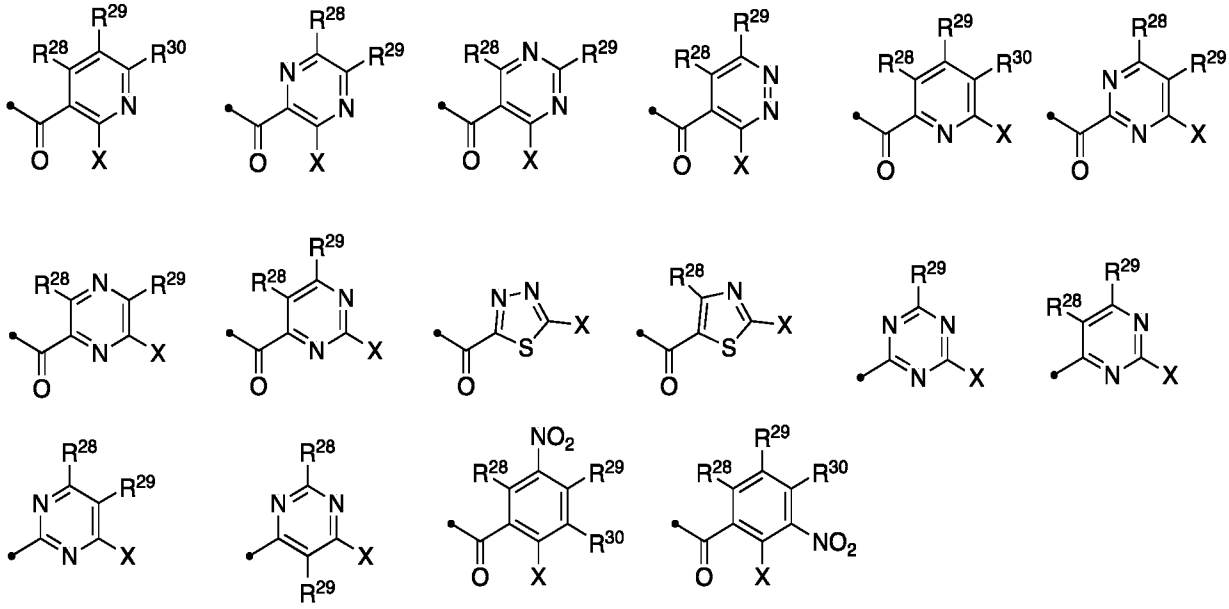
d) 9- or 10-membered fused heteroaryl,

e) naphthyl, and

f) 4-, 5- or 6-membered cycloalkenyl;

E is selected from an electrophilic moiety, selected from





;

R^1 is selected from hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-NHNR^{1A}R^{1B}$, $-C(O)R^{1A}$, $-C(O)$-OR^{1A}, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHNR^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$, $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, rand substituted or unsubstituted heteroaryl;

R^3 is selected from hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHNR^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)$-OR^{3A}, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, 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;

R^4 is selected from hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHNR^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)$-OR^{4A}, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHNR^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, 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; R^3 and R^3 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^6 is selected from hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$,

$-NHNR^{6A}R^{6B}$, $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHNR^{6A}R^{6B}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, 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;

R^7 is selected from hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHNR^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHNR^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, 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;

R^9 is selected from hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHNR^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHNR^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, 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;

R^{10} is selected from hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNR^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNR^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, 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;

R^{11} is selected from hydrogen, halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, -CN, $-SO_{n11}R^{11A}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-NHNR^{11A}R^{11B}$, $-C(O)R^{11A}$, $-C(O)-OR^{11A}$, $-C(O)NR^{11A}R^{11B}$, $-C(O)NHNR^{11A}R^{11B}$, $-OR^{11A}$, $-NR^{11A}SO_2R^{11B}$, $-NR^{11A}C(O)R^{11B}$, $-NR^{11A}C(O)OR^{11B}$, $-NR^{11A}OR^{11B}$, $-N_3$, 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;

R^{12} is selected from hydrogen, halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, -CN, $-SO_{n12}R^{12A}$, $-SO_{v12}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m12}$, $-NR^{12A}R^{12B}$, $-NHNR^{12A}R^{12B}$, $-C(O)R^{12A}$, $-C(O)-OR^{12A}$, $-C(O)NR^{12A}R^{12B}$,

-C(O)NHNR^{12A}R^{12B}, -OR^{12A}, -NR^{12A}SO$_2$R^{12B}, -NR^{12A}C(O)R^{12B}, -NR^{12A}C(O)OR^{12B}, -NR^{12A}OR^{12B}, -N$_3$, 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;

R^{17} is selected from hydrogen, halogen, -CX$^{17}_3$, -CHX$^{17}_2$, -CH$_2$X^{17}, -OCX$^{17}_3$, -OCH$_2$X^{17}, -OCHX$^{17}_2$, -CN, -SO$_{n17}$R^{17A}, -SO$_{v17}$NR^{17A}R^{17B}, -NHC(O)NR^{17A}R^{17B}, -N(O)$_{m17}$, -NR^{17A}R^{17B}, -NHNR^{17A}R^{17B}, -C(O)R^{17A}, -C(O)-OR^{17A}, -C(O)NR^{17A}R^{17B}, -C(O)NHNR^{17A}R^{17B}, -OR^{17A}, -NR^{17A}SO$_2$R^{17B}, -NR^{17A}C(O)R^{17B}, -NR^{17A}C(O)OR^{17B}, -NR^{17A}OR^{17B}, -N$_3$, 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;

R^{18} is selected from hydrogen, halogen, -CX$^{18}_3$, -CHX$^{18}_2$, -CH$_2$X^{18}, -OCX$^{18}_3$, -OCH$_2$X^{18}, -OCHX$^{18}_2$, -CN, -SO$_{n18}$R^{18A}, -SO$_{v18}$NR^{18A}R^{18B}, -NHC(O)NR^{18A}R^{18B}, -N(O)$_{m18}$, -NR^{18A}R^{18B}, -NHNR^{18A}R^{18B}, -C(O)R^{18A}, -C(O)-OR^{18A}, -C(O)NR^{18A}R^{18B}, -C(O)NHNR^{18A}R^{18B}, -OR^{18A}, -NR^{18A}SO$_2$R^{18B}, -NR^{18A}C(O)R^{18B}, -NR^{18A}C(O)OR^{18B}, -NR^{18A}OR^{18B}, -N$_3$, 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; R^{16} and R^{18} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{19} is selected from hydrogen, halogen, -CX$^{19}_3$, -CHX$^{19}_2$, -CH$_2$X^{19}, -OCX$^{19}_3$, -OCH$_2$X^{19}, -OCHX$^{19}_2$, -CN, -SO$_{n19}$R^{19A}, -SO$_{v19}$NR^{19A}R^{19B}, -NHC(O)NR^{19A}R^{19B}, -N(O)$_{m19}$, -NR^{19A}R^{19B}, -NHNR^{19A}R^{19B}, -C(O)R^{19A}, -C(O)-OR^{19A}, -C(O)NR^{19A}R^{19B}, -C(O)NHNR^{19A}R^{19B}, -OR^{19A}, -NR^{19A}SO$_2$R^{19B}, -NR^{19A}C(O)R^{19B}, -NR^{19A}C(O)OR^{19B}, -NR^{19A}OR^{19B}, -N$_3$, 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; R^{16} and R^{19} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{20} is selected from hydrogen, halogen, -CX$^{20}_3$, -CHX$^{20}_2$, -CH$_2$X^{20}, -OCX$^{20}_3$, -OCH$_2$X^{20}, -OCHX$^{20}_2$, -CN, -SO$_{n20}$R^{20A}, -SO$_{v20}$NR^{20A}R^{20B}, -NHC(O)NR^{20A}R^{20B}, -N(O)$_{m20}$, -NR^{20A}R^{20B}, -NHNR^{20A}R^{20B}, -C(O)R^{20A}, -C(O)-OR^{20A}, -C(O)NR^{20A}R^{20B}, -C(O)NHNR^{20A}R^{20B}, -OR^{20A}, -NR^{20A}SO$_2$R^{20B}, -NR^{20A}C(O)R^{20B}, -NR^{20A}C(O)OR^{20B}, -NR^{20A}OR^{20B}, -N$_3$, 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;

R^{21} is selected from hydrogen, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, -CN, $-SO_{n21}R^{21A}$, $-SO_{v21}NR^{21A}R^{21B}$, $-NHC(O)NR^{21A}R^{21B}$, $-N(O)_{m21}$, $-NR^{21A}R^{21B}$, $-NHNR^{21A}R^{21B}$, $-C(O)R^{21A}$, $-C(O)-OR^{21A}$, $-C(O)NR^{21A}R^{21B}$, $-C(O)NHNR^{21A}R^{21B}$, $-OR^{21A}$, $-NR^{21A}SO_2R^{21B}$, $-NR^{21A}C(O)R^{21B}$, $-NR^{21A}C(O)OR^{21B}$, $-NR^{21A}OR^{21B}$, $-N_3$, 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; R^{20} and R^{21} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or heterocycloalkyl;

R^{22} is selected from hydrogen, halogen, $-CX^{22}_3$, $-CHX^{22}_2$, $-CH_2X^{22}$, $-OCX^{22}_3$, $-OCH_2X^{22}$, $-OCHX^{22}_2$, -CN, $-SO_{n22}R^{22A}$, $-SO_{v22}NR^{22A}R^{22B}$, $-NHC(O)NR^{22A}R^{22B}$, $-N(O)_{m22}$, $-NR^{22A}R^{22B}$, $-NHNR^{22A}R^{22B}$, $-C(O)R^{22A}$, $-C(O)-OR^{22A}$, $-C(O)NR^{22A}R^{22B}$, $-C(O)NHNR^{22A}R^{22B}$, $-OR^{22A}$, $-NR^{22A}SO_2R^{22B}$, $-NR^{22A}C(O)R^{22B}$, $-NR^{22A}C(O)OR^{22B}$, $-NR^{22A}OR^{22B}$, $-N_3$, 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;

R^{23} is selected from hydrogen, halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-CH_2X^{23}$, $-OCX^{23}_3$, $-OCH_2X^{23}$, $-OCHX^{23}_2$, -CN, $-SO_{n23}R^{23A}$, $-SO_{v23}NR^{23A}R^{23B}$, $-NHC(O)NR^{23A}R^{23B}$, $-N(O)_{m23}$, $-NR^{23A}R^{23B}$, $-NHNR^{23A}R^{23B}$, $-C(O)R^{23A}$, $-C(O)-OR^{23A}$, $-C(O)NR^{23A}R^{23B}$, $-C(O)NHNR^{23A}R^{23B}$, $-OR^{23A}$, $-NR^{23A}SO_2R^{23B}$, $-NR^{23A}C(O)R^{23B}$, $-NR^{23A}C(O)OR^{23B}$, $-NR^{23A}OR^{23B}$, $-N_3$, 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;

R^{24} is selected from hydrogen, halogen, $-CX^{24}_3$, $-CHX^{24}_2$, $-CH_2X^{24}$, $-OCX^{24}_3$, $-OCH_2X^{24}$, $-OCHX^{24}_2$, -CN, $-SO_{n24}R^{24A}$, $-SO_{v24}NR^{24A}R^{24B}$, $-NHC(O)NR^{24A}R^{24B}$, $-N(O)_{m24}$, $-NR^{24A}R^{24B}$, $-NHNR^{24A}R^{24B}$, $-C(O)R^{24A}$, $-C(O)-OR^{24A}$, $-C(O)NR^{24A}R^{24B}$, $-C(O)NHNR^{24A}R^{24B}$, $-OR^{24A}$, $-NR^{24A}SO_2R^{24B}$, $-NR^{24A}C(O)R^{24B}$, $-NR^{24A}C(O)OR^{24B}$, $-NR^{24A}OR^{24B}$, $-N_3$, 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;

R^{25} is selected from hydrogen, halogen, $-CX^{25}_3$, $-CHX^{25}_2$, $-CH_2X^{25}$, $-OCX^{25}_3$, $-OCH_2X^{25}$, $-OCHX^{25}_2$, -CN, $-SO_{n25}R^{25A}$, $-SO_{v25}NR^{25A}R^{25B}$, $-NHC(O)NR^{25A}R^{25B}$, $-N(O)_{m25}$, $-NR^{25A}R^{25B}$, $-NHNR^{25A}R^{25B}$, $-C(O)R^{25A}$, $-C(O)-OR^{25A}$, $-C(O)NR^{25A}R^{25B}$,

-C(O)NHNR^{25A}R^{25B}, -OR^{25A}, -NR^{25A}SO$_2$R^{25B}, -NR^{25A}C(O)R^{25B}, -NR^{25A}C(O)OR^{25B}, -NR^{25A}OR^{25B}, -N$_3$, 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;

R^{26} is selected from hydrogen, halogen, -CX$^{26}_3$, -CHX$^{26}_2$, -CH$_2$X^{26}, -OCX$^{26}_3$, -OCH$_2$X^{26}, -OCHX$^{26}_2$, -CN, -SO$_{n26}$R^{26A}, -SO$_{v26}$NR^{26A}R^{26B}, -NHC(O)NR^{26A}R^{26B}, -N(O)$_{m26}$, -NR^{26A}R^{26B}, -NHNR^{26A}R^{26B}, -C(O)R^{26A}, -C(O)-OR^{26A}, -C(O)NR^{26A}R^{26B}, -C(O)NHNR^{26A}R^{26B}, -OR^{26A}, -NR^{26A}SO$_2$R^{26B}, -NR^{26A}C(O)R^{26B}, -NR^{26A}C(O)OR^{26B}, -NR^{26A}OR^{26B}, -N$_3$, 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;

R^{27} is selected from hydrogen, halogen, -CX$^{27}_3$, -CHX$^{27}_2$, -CH$_2$X^{27}, -OCX$^{27}_3$, -OCH$_2$X^{27}, -OCHX$^{27}_2$, -CN, -SO$_{n27}$R^{27A}, -SO$_{v27}$NR^{27A}R^{27B}, -NHC(O)NR^{27A}R^{27B}, -N(O)$_{m27}$, -NR^{27A}R^{27B}, -NHNR^{27A}R^{27B}, -C(O)R^{27A}, -C(O)-OR^{27A}, -C(O)NR^{27A}R^{27B}, -C(O)NHNR^{27A}R^{27B}, -OR^{27A}, -NR^{27A}SO$_2$R^{27B}, -NR^{27A}C(O)R^{27B}, -NR^{27A}C(O)OR^{27B}, -NR^{27A}OR^{27B}, -N$_3$, 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;

R^{28} is selected from hydrogen, halogen, -CX$^{28}_3$, -CHX$^{28}_2$, -CH$_2$X^{28}, -OCX$^{28}_3$, -OCH$_2$X^{28}, -OCHX$^{28}_2$, -CN, -SO$_{n28}$R^{28A}, -SO$_{v28}$NR^{28A}R^{28B}, -NHC(O)NR^{28A}R^{28B}, -N(O)$_{m28}$, -NR^{28A}R^{28B}, -NHNR^{28A}R^{28B}, -C(O)R^{28A}, -C(O)-OR^{28A}, -C(O)NR^{28A}R^{28B}, -C(O)NHNR^{28A}R^{28B}, -OR^{28A}, -NR^{28A}SO$_2$R^{28B}, -NR^{28A}C(O)R^{28B}, -NR^{28A}C(O)OR^{28B}, -NR^{28A}OR^{28B}, -N$_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted and unsubstituted heteroaryl;

R^{29} is selected from hydrogen, halogen, -CX$^{29}_3$, -CHX$^{29}_2$, -CH$_2$X^{29}, -OCX$^{29}_3$, -OCH$_2$X^{29}, -OCHX$^{29}_2$, -CN, -SO$_{n29}$R^{29A}, -SO$_{v29}$NR^{29A}R^{29B}, -NHC(O)NR^{29A}R^{29B}, -N(O)$_{m29}$, -NR^{29A}R^{29B}, -NHNR^{29A}R^{29B}, -C(O)R^{29A}, -C(O)-OR^{29A}, -C(O)NR^{29A}R^{29B}, -C(O)NHNR^{29A}R^{29B}, -OR^{29A}, -NR^{29A}SO$_2$R^{29B}, -NR^{29A}C(O)R^{29B}, -NR^{29A}C(O)OR^{29B}, -NR^{29A}OR^{29B}, -N$_3$, 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;

R^{30} is selected from hydrogen, halogen, $-CX^{30}_3$, $-CHX^{30}_2$, $-CH_2X^{30}$, $-OCX^{30}_3$, $-OCH_2X^{30}$, $-OCHX^{30}_2$, -CN, $-SO_{n30}R^{30A}$, $-SO_{v30}NR^{30A}R^{30B}$, $-NHC(O)NR^{30A}R^{30B}$, $-N(O)_{m30}$, $-NR^{30A}R^{30B}$, $-NHNR^{30A}R^{30B}$, $-C(O)R^{30A}$, $-C(O)\text{-}OR^{30A}$, $-C(O)NR^{30A}R^{30B}$, $-C(O)NHNR^{30A}R^{30B}$, $-OR^{30A}$, $-NR^{30A}SO_2R^{30B}$, $-NR^{30A}C(O)R^{30B}$, $-NR^{30A}C(O)OR^{30B}$, $-NR^{30A}OR^{30B}$, $-N_3$, 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;

R^{31} is selected from hydrogen, halogen, $-CX^{31}_3$, $-CHX^{31}_2$, $-CH_2X^{31}$, $-OCX^{31}_3$, $-OCH_2X^{31}$, $-OCHX^{31}_2$, -CN, $-SO_{n31}R^{31A}$, $-SO_{v31}NR^{31A}R^{31B}$, $-NHC(O)NR^{31A}R^{31B}$, $-N(O)_{m31}$, $-NR^{31A}R^{31B}$, $-NHNR^{31A}R^{31B}$, $-C(O)R^{31A}$, $-C(O)\text{-}OR^{31A}$, $-C(O)NR^{31A}R^{31B}$, $-C(O)NHNR^{31A}R^{31B}$, $-OR^{31A}$, $-NR^{31A}SO_2R^{31B}$, $-NR^{31A}C(O)R^{31B}$, $-NR^{31A}C(O)OR^{31B}$, $-NR^{31A}OR^{31B}$, $-N_3$, 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;

R^{32} is selected from hydrogen, halogen, $-CX^{32}_3$, $-CHX^{32}_2$, $-CH_2X^{32}$, $-OCX^{32}_3$, $-OCH_2X^{32}$, $-OCHX^{32}_2$, -CN, $-SO_{n32}R^{32A}$, $-SO_{v32}NR^{32A}R^{32B}$, $-NHC(O)NR^{32A}R^{32B}$, $-N(O)_{m32}$, $-NR^{32A}R^{32B}$, $-NHNR^{32A}R^{32B}$, $-C(O)R^{32A}$, $-C(O)\text{-}OR^{32A}$, $-C(O)NR^{32A}R^{32B}$, $-C(O)NHNR^{32A}R^{32B}$, $-OR^{32A}$, $-NR^{32A}SO_2R^{32B}$, $-NR^{32A}C(O)R^{32B}$, $-NR^{32A}C(O)OR^{32B}$, $-NR^{32A}OR^{32B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted and unsubstituted heteroaryl;

R^{33} is selected from hydrogen, halogen, $-CX^{33}_3$, $-CHX^{33}_2$, $-CH_2X^{33}$, $-OCX^{33}_3$, $-OCH_2X^{33}$, $-OCHX^{33}_2$, -CN, $-SO_{n33}R^{33A}$, $-SO_{v33}NR^{33A}R^{33B}$, $-NHC(O)NR^{33A}R^{33B}$, $-N(O)_{m33}$, $-NR^{33A}R^{33B}$, $-NHNR^{33A}R^{33B}$, $-C(O)R^{33A}$, $-C(O)\text{-}OR^{33A}$, $-C(O)NR^{33A}R^{33B}$, $-C(O)NHNR^{33A}R^{33B}$, $-OR^{33A}$, $-NR^{33A}SO_2R^{33B}$, $-NR^{33A}C(O)R^{33B}$, $-NR^{33A}C(O)OR^{33B}$, $-NR^{33A}OR^{33B}$, $-N_3$, 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;

R^{34} is selected from hydrogen, halogen, $-CX^{34}_3$, $-CHX^{34}_2$, $-CH_2X^{34}$, $-OCX^{34}_3$, $-OCH_2X^{34}$, $-OCHX^{34}_2$, -CN, $-SO_{n34}R^{34A}$, $-SO_{v34}NR^{34A}R^{34B}$, $-NHC(O)NR^{34A}R^{34B}$, $-N(O)_{m34}$, $-NR^{34A}R^{34B}$, $-NHNR^{34A}R^{34B}$, $-C(O)R^{34A}$, $-C(O)\text{-}OR^{34A}$, $-C(O)NR^{34A}R^{34B}$, $-C(O)NHNR^{34A}R^{34B}$, $-OR^{34A}$, $-NR^{34A}SO_2R^{34B}$, $-NR^{34A}C(O)R^{34B}$, $-NR^{34A}C(O)OR^{34B}$, $-NR^{34A}OR^{34B}$, $-N_3$, 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;

R^{35} is selected from hydrogen, halogen, $-CX^{35}_3$, $-CHX^{35}_2$, $-CH_2X^{35}$, $-OCX^{35}_3$, $-OCH_2X^{35}$, $-OCHX^{35}_2$, -CN, $-SO_{n35}R^{35A}$, $-SO_{v35}NR^{35A}R^{35B}$, $-NHC(O)NR^{35A}R^{35B}$, $-N(O)_{m35}$, $-NR^{35A}R^{35B}$, $-NHNR^{35A}R^{35B}$, $-C(O)R^{35A}$, $-C(O)-OR^{35A}$, $-C(O)NR^{35A}R^{35B}$, $-C(O)NHNR^{35A}R^{35B}$, $-OR^{35A}$, $-NR^{35A}SO_2R^{35B}$, $-NR^{35A}C(O)R^{35B}$, $-NR^{35A}C(O)OR^{35B}$, $-NR^{35A}OR^{35B}$, $-N_3$, 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;

Each R^{1A}, R^{1B}, R^{3A}, R^{3B}, R^{4A}, R^{4B}, R^{6A}, R^{6B}, R^{7A}, R^{7B}, R^{9A}, R^{9B}, R^{10A}, R^{10B}, R^{11A}, R^{11B}, R^{17A}, R^{17B}, R^{18A}, R^{18B}, R^{19A}, R^{19B}, R^{20A}, R^{20B}, R^{21A}, R^{21B}, R^{22A}, R^{22B}, R^{23A}, R^{23B}, R^{24A}, R^{24B}, R^{25A}, R^{25B}, R^{26A}, R^{26B}, R^{27A}, R^{27B}, R^{28A}, R^{28B}, R^{29A}, R^{29B}, R^{30A}, R^{30B}, R^{31A}, R^{31B}, R^{32A}, R^{32B}, R^{33A}, R^{33B}, R^{34A}, R^{34B}, R^{35A}, R^{35B}, is independently selected from hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, -C(O)OH, $-C(O)NH_2$, -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, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, 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^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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^{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; R^{13A} and R^{13B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{14A} and R^{14B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl 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; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{20A} and R^{20B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{21A} and R^{21B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{22A} and R^{22B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{23A} and R^{23B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{24A} and R^{24B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{25A} and R^{25B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{26A} and R^{26B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{27A} and R^{27B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{28A} and R^{28B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{29A} and R^{29B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{30A} and R^{30B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

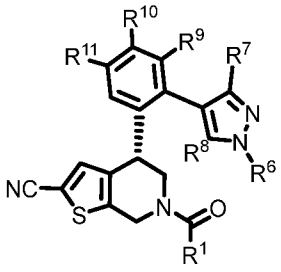
Each m1, m3, m4, m6, m7, m9, m10, m11, m17, m18, m19, m20, m21, m22, m23, m24, m25, m26, m27, m28, m29, m30, m31, m32, m33, m34 and m35 is independently 1 or 2;

Each v1, v3, v4, v6, v7, v9, v10, v11, v17, v18, v19, v20, v21, v22, v23, v24, v25, v26, v27, v28, v29, v30, v31, v32, v33, v34 and v35 is independently 1 or 2;

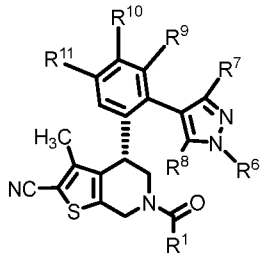
Each n1, n3, n4, n6, n7, n9, n10, n11, n17, n18, n19, n20, n21, n22, n23, n24, n25, n26, n27, n28, n29, n30, n31, n32, n33, n34 and n35 is independently an integer from 0 to 2; and

Each X^1, X^3, X^4, X^6, X^7, X^9, X^{10}, X^{11}, X^{17}, X^{18}, X^{19}, X^{20}, X^{21}, X^{22}, X^{23}, X^{24}, X^{25}, X^{26}, X^{27}, X^{28}, X^{29}, X^{30}, X^{31}, X^{32}, X^{33}, X^{34}, and X^{35} is independently -Cl, -Br, -I or –F.

21. The method of any one of claims 1-18, wherein the compound is of the formula:



23. IV or



V

wherein

R^1 is substituted or unsubstituted C_2-C_6 alkenyl, or substituted or unsubstituted C_2-C_6 alkynyl;

R^6 is selected from H, C_{1-6} alkyl, C_{2-4} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylamino-C_{1-6} alkyl, C_{1-6} alkylaminocarbonyl-C_{1-6} alkyl, aminocarbonyl-C_{1-6} alkyl, C_{1-6} alkoxycarbonyl-C_{1-6} alkyl, carboxy-C_{1-6} alkyl, C_{1-6} alkylcarbonylamino-C_{1-6} alkyl, C_{1-6} cyanoalkyl, C_{1-6} haloalkyl, C_{1-6} alkylsulfonyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, aryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heteroaryl-C_{1-6} alkyl, substituted or unsubstituted 5 or 6 membered heterocyclyl and substituted or unsubstituted 5 or 6 membered heteroaryl;

R^7 is selected from H, carboxy, amino, C_{1-6} alkyl, C_{1-3} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkylaminocarbonyl, and C_{3-6} cycloalkyl;

R^8 is selected from H, carboxy, cyano, C_{1-4} alkyl, C_{1-3} haloalkyl, and C_{1-6} alkylaminocarbonyl;

R^9 is selected from H, halo, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, amino, C_{1-3} alkylcarbonylamino, C_{1-3} alkylsulfonylamino, and C_{1-3} alkylaminocarbonylamino;

R^{10} is selected from H, halo, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, amino, C_{1-3} alkylcarbonylamino, C_{1-3} alkylsulfonylamino, and C_{1-3} alkylaminocarbonylamino; and

R^{11} is selected from H, halo, hydroxy, C_{1-3} alkyl, C_{1-3} haloalkyl, cyano, amino, C_{1-3} alkylcarbonylamino, C_{1-3} alkylsulfonylamino, and C_{1-3} alkylaminocarbonylamino;

or an isomer or stereoisomer of any of the foregoing, or a mixture thereof or a pharmaceutically acceptable salt thereof.

22. The method of any one of claims 1-19, wherein the compound is selected from a compound listed in Table A.

23. The method of claim 13, wherein the anti-CD20 antibody is rituximab.

24. The method of claim 14, wherein the immune checkpoint inhibitor is pembrolizumab.

25. The method of claim 12, wherein the HMA is decitabine.

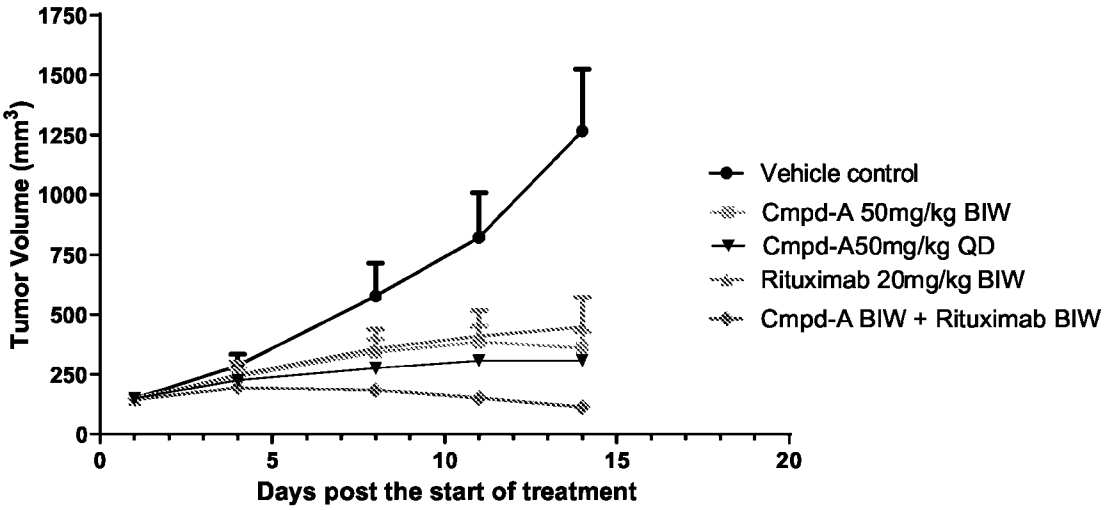


Figure 1

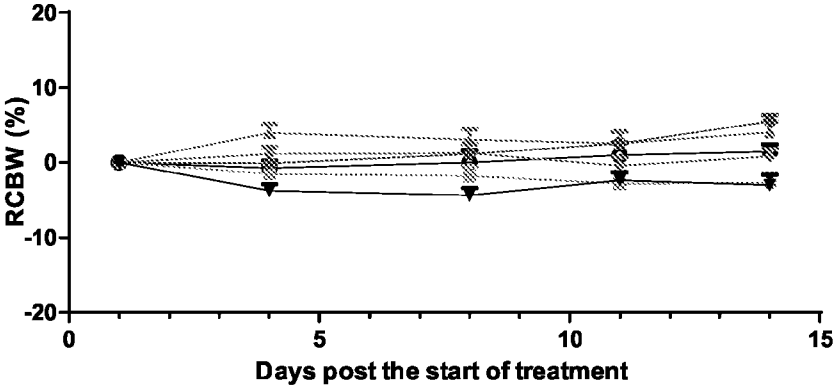


Figure 2

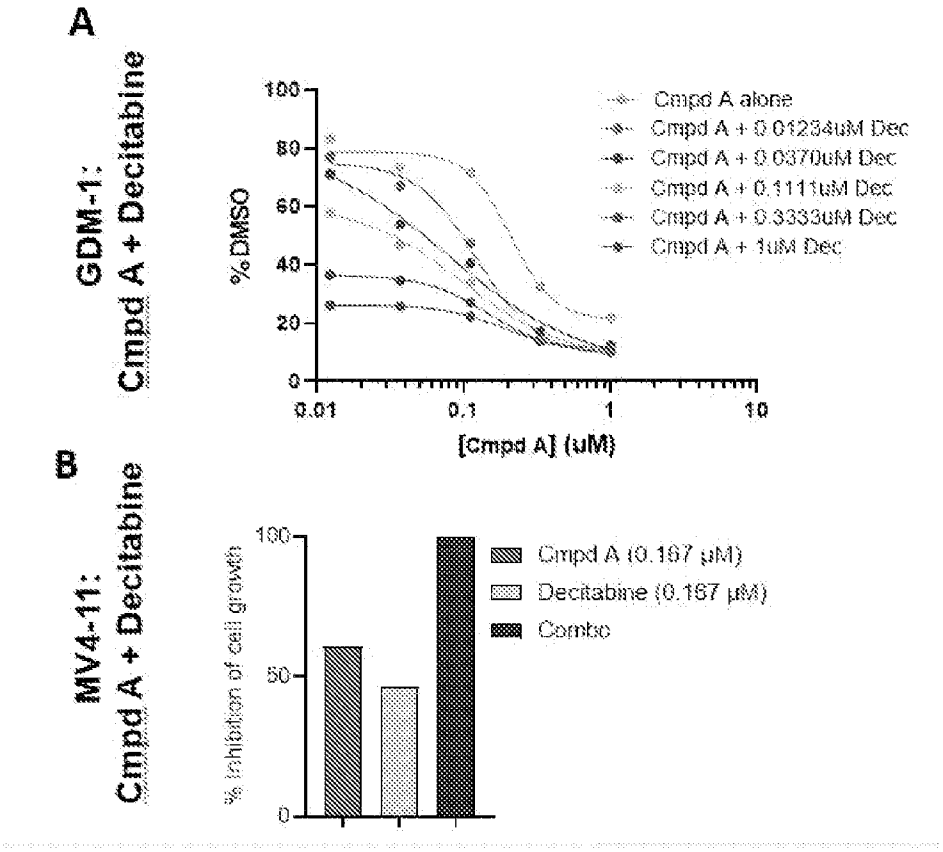


Figure 3

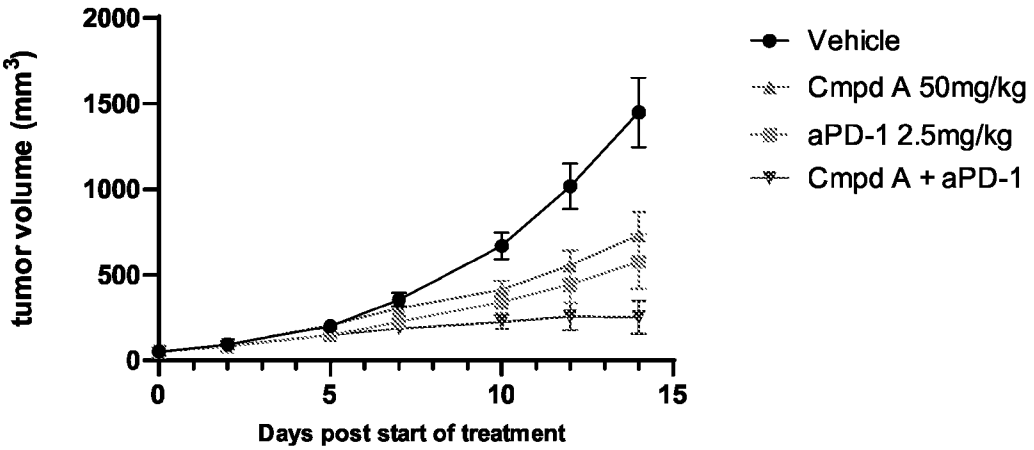


Figure 4

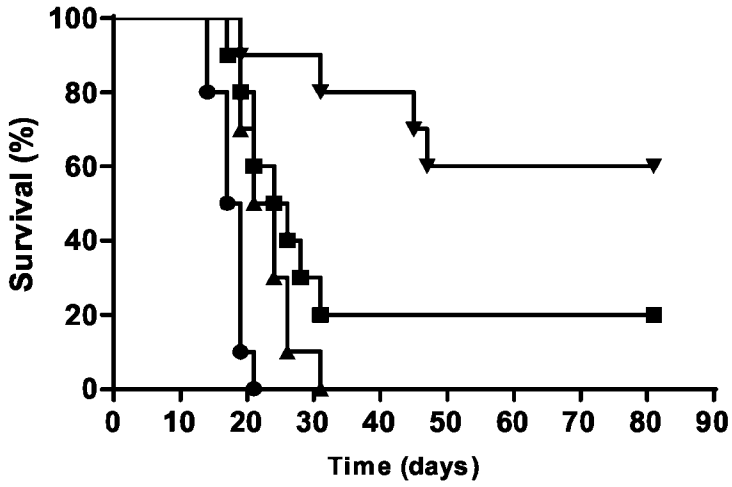


Figure 5

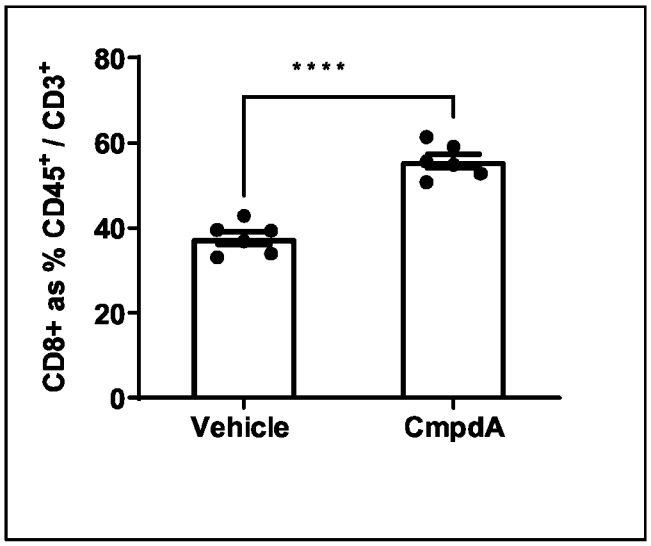


Figure 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/035367

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C07D 495/04 (2023.01)
ADD. - A61K 31/506, 38/00, 39/395, 45/06; A61P 35/00; C07D 471/04 (2023.01)

CPC - INV. - C07D 495/04; A61P 35/00 (2023.08)

ADD. - A61K 31/506 (2023.08)

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 database consulted during the international search (name of database 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	US 2022/0177488 A1 (SUVALENT THERAPEUTICS INC.) 09 June 2022 (09.06.2022) entire document	1-3
A	US 2022/0298171 A1 (CITY OF HOPE et al.) 22 September 2022 (22.09.2022) entire document	1-3
A	WO 2021/150918 A1 (ONCOVALENT THERAPEUTICS INC.) 29 July 2021 (29.07.2021) entire document	1-3
P, X	CANON et al. "Abstract LB318: SB-4826, a first-in-class oral, covalent inhibitor of SUMO E1 that induces IFN signaling and inhibits tumor growth as monotherapy and in combination with immune checkpoint blockade," Cancer Res, 14 April 2023 (14.04.2023), Vol. 83, 8_Supplement, LB318, Pgs. 1. Retrieved from the Internet: <https://aacrjournals.org/cancerres/article/83/8_Supplement/LB318/725425/Abstract-LB318-SB-4826-a-first-in-class-oral> on 29 November 2023 (29.11.2023). entire document	1-3

☐ 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
"D" document cited by the applicant in the international application
"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
30 November 2023	JAN 22 2024
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/035367

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.: 4-25
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:

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.:

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.