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(54) Title: NOVEL MDA-9 ANTAGONIST WITH ANTI-METASTATIC POTENTIAL

(57) Abstract: Disclosed herein are, inter cilia, compounds modulating activity and methods of use thereof for treating MDA-9/Syntenin associated conditions or disorders.

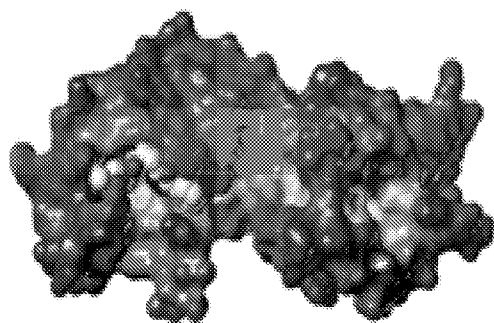


Fig. 1



NOVEL MDA-9 ANTAGONIST WITH ANTI-METASTATIC POTENTIAL

CROSS REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application Serial numbers 63/172,322 filed April 8, 2021 and 63/246,237 filed September 20, 2021. The disclosures of these applications are incorporated herein by reference in their entirety and for all purposes.

BACKGROUND

[0002] Melanoma differentiation associated gene-9 (mda-9)/Syntenin (Jiang *et al.*, *Molecular and Cellular Differentiation* 4(4):317-333, 1996; Lin *et al.*, *Gene* 207(2):105-110, 1998) plays a central pathogenic role in multiple cancers (Das SK, *et al.*, *Pharmacol Res* 155:104695, 2020; Das SK, *et al.*, *Adv Cancer Res* 144:137-191, 2019) including glioblastoma multiforme (GBM) (Kegelman TP, *et al.*, *Neuro Oncol.* 16(1):11, 2014; Talukdar S, *et al.*, *Oncotarget* 7(34):54102-54119, 2016), melanoma (Boukerche *et al.*, *Cancer Res.* 65(23):10901-10911, 2005; Sarkar *et al.*, *Pharmacol Ther* 104(2):101-115, 2004; Helmke BM, *et al.*, *Oncol Rep* 12(2):221-228, 2004; Das SK, *et al.*, *Cancer Res* 73(2):844-854, 2013), lung (Kim WY, *et al.*, *Exp Mol Med* 46:e90, 2014), prostate (Das SK, *et al.*, *Cancer Res* 78(11):2852-2863, 2018; Talukdar S, *et al.*, *Cancers (Basel)* 12(1):53, 2019), urothelial (Dasgupta S *et al.*, *Clin Cancer Res* 19(17):4621-4633, 2013) and breast (Menezes ME, *et al.*, *Oncotarget* 7(49), 2016; Yang Y, *et al.* *Breast Cancer Res* 15(3), 2013; Pradhan *et al.*, *Proc Natl Acad Sci USA* 118(21): in press, 2021). MDA-9/Syntenin regulates the majority of key steps in the metastatic cascade, including intravasation (invasion), motility, cancer cell adhesion, tumor angiogenesis and extravasation (Das, *supra*; Pradhan *et al.*, *Cancer Metastasis Rev* 39(3):769-781, 2020; Sarkar *et al.*, *Cancer Res* 68(9):3087-3093, 2008; Kegelman TP, *et al.*, *Expert Opin Ther Targets* 19(1):97-112, 2015).

[0003] MDA-9/Syntenin is a 298 aa scaffold protein with two PDZ domains, PDZ1 (aa,110-193) and PDZ2 (aa,194-274), that potentially interact with a plethora of proteins including many relevant to cancer phenotypes (Sarkar *et al.*, *supra*; Das *et al.*, *supra*; Pradhan *et al.*, *supra*). Targeting the interaction between MDA-9/Syntenin's PDZ domains through small molecule inhibitors is feasible and recently validated in multiple experimental models (Kegelman TP, *et al.* *Proc Natl Acad Sci U S A* 114(2):370-375, 2017; Das *et al.*, *Mol Cancer Ther.* 18: (11):1997-

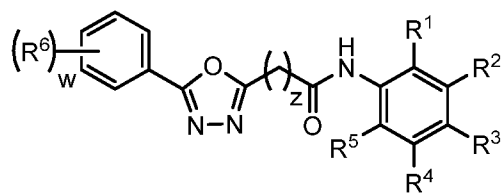
2007, 2019; Bhoopathi P, *et al.*, *Oncogene* 38(41):6781-6793, 2019). One lead molecule, PDZ1i (Kegelman, *supra*; Das, *supra*; Bhoopathi, *supra*; Das *et al.*, *ACS Chem Neurosci.* 10(3):1121-1123, 2019) (IVMT-Rx-1) selectively binds to the PDZ1 domain and the interface between PDZ1 and PDZ2, without binding to the PDZ2 domain of MDA-9/Syntenin or PDZ domains of other sequence similar proteins (Kegelman TP, *et al. Proc Natl Acad Sci U S A* 114(2):370-375, 2017).

[0004] Given the critical roles of MDA-9/Syntenin in cancer and other disorders, there is an unmet need for therapeutic agents capable of modulating this target. Based on both bioinformatics and direct *in vitro* studies and *in vivo* preclinical animal models, MDA-9/Syntenin represents a promising target for developing anti-migration/anti-invasion agents that inhibit cancer invasion/metastasis. This invention identifies IVMT-Rx-4 (Compound 6), an intermediate in PDZ1i synthesis that binds to the PDZ1 domain of MDA-9/Syntenin and displays promising *in vitro* and *in vivo* anti-invasion and anti-metastatic activities. Accordingly, IVMT-Rx-4 represents a potential novel PDZ1 binding therapeutic agent.

BRIEF SUMMARY

[0005] Provided herein, *inter alia*, are small molecule inhibitors of MDA-9/Syntenin gene/protein, pharmaceutical compositions comprising these compounds, and the use of these compounds for the treatment of MDA-9/Syntenin modulated disease or disorder.

[0006] In one aspect, provided herein is a small molecule inhibitor of MDA-9/Syntenin of structural formula (I):



(I), or a pharmaceutically acceptable salt thereof,

wherein: z is an integer from 0 to 8; w is an integer from 0 to 5; R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, $-CN$, $-N_3$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHN R^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHN R^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, $-OCH_2X^{1.1}$, 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^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-N_3$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHN R^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHN R^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, $-OCH_2X^{2.1}$, 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 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-N_3$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NH_2$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NH_2$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, $-OCH_2X^{3.1}$, 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^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, $-CN$, $-N_3$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, $-OCH_2X^{4.1}$, 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^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, $-CN$, $-N_3$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHN R^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHN R^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, $-OCH_2X^{5.1}$, 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^6 is independently halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-CN$, $-N_3$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHN R^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHN R^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$,

$-\text{NR}^{6\text{B}}\text{C}(\text{O})\text{OR}^{6\text{D}}$, $-\text{NR}^{6\text{B}}\text{OR}^{6\text{D}}$, $-\text{OCX}^{6.1}_3$, $-\text{OCHX}^{6.1}_2$, $-\text{OCH}_2\text{X}^{6.1}$, 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; two adjacent R^6 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; $\text{R}^{1\text{A}}$, $\text{R}^{1\text{B}}$, $\text{R}^{1\text{C}}$, $\text{R}^{1\text{D}}$, $\text{R}^{2\text{A}}$, $\text{R}^{2\text{B}}$, $\text{R}^{2\text{C}}$, $\text{R}^{2\text{D}}$, $\text{R}^{3\text{A}}$, $\text{R}^{3\text{B}}$, $\text{R}^{3\text{C}}$, $\text{R}^{3\text{D}}$, $\text{R}^{4\text{A}}$, $\text{R}^{4\text{B}}$, $\text{R}^{4\text{C}}$, $\text{R}^{4\text{D}}$, $\text{R}^{5\text{A}}$, $\text{R}^{5\text{B}}$, $\text{R}^{5\text{C}}$, $\text{R}^{5\text{D}}$, $\text{R}^{6\text{A}}$, $\text{R}^{6\text{B}}$, $\text{R}^{6\text{C}}$, and $\text{R}^{6\text{D}}$ are independently hydrogen, halogen, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{COOH}$, $-\text{CONH}_2$, 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; $\text{R}^{1\text{B}}$ and $\text{R}^{1\text{C}}$, $\text{R}^{2\text{B}}$ and $\text{R}^{2\text{C}}$, $\text{R}^{3\text{B}}$ and $\text{R}^{3\text{C}}$, $\text{R}^{4\text{B}}$ and $\text{R}^{4\text{C}}$, $\text{R}^{5\text{B}}$ and $\text{R}^{5\text{C}}$, and $\text{R}^{6\text{B}}$ and $\text{R}^{6\text{C}}$, substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; $\text{X}^{1.1}$, $\text{X}^{2.1}$, $\text{X}^{3.1}$, $\text{X}^{4.1}$, $\text{X}^{5.1}$, and $\text{X}^{6.1}$ are independently $-\text{Cl}$, $-\text{Br}$, $-\text{I}$ or $-\text{F}$; n_1 , n_2 , n_3 , n_4 , n_5 , and n_6 are independently an integer from 0 to 4; and m_1 , m_2 , m_3 , m_4 , m_5 , m_6 , v_1 , v_2 , v_3 , v_4 , v_5 , and v_6 are independently 1 or 2.

[0007] In another aspect, provided herein is a pharmaceutical composition including a pharmaceutically acceptable excipient and a compound of formula (I).

[0008] In yet another aspect, provided herein is a method of inhibiting MDA-9/Syntenin protein activity, said method comprising contacting the MDA-9/Syntenin protein with the compound of formula (I).

[0009] In yet another aspect, provided herein is a method of treating cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of the compound of formula (I).

[0010] In yet another aspect, provided herein is a method of preventing metastasis of cancer cells in a subject in need thereof, said method comprising administering to said subject an effective amount of the compound of formula (I).

DETAILED DESCRIPTION OF THE DRAWINGS

[0011] FIG. 1 depicts docked structure of the compound of formula (I) (IVMT-Rx-4) on the surface of MDA-9/Syntenin.

[0012] FIGS. 2A-2C depict the inhibitory effect of the compound of formula (I) on breast cancer lung metastasis. FIG. 2A. 4T1-*Luc* cells were assayed using 24 hr trans-well invasion assays with or without treatment with indicated doses of IVMT-Rx-4. Invading cells were stained, counted, and graphically represented. **FIGS. 2B and 2C.** 4T1-*Luc* (2.5×10^4) cells introduced I.V. followed by I.P. IVMT-Rx-4 injections (30 mg/kg 1X every other day, 3X/Week; total 6 injections). Representative *in vivo* BLI images (**FIG. 2B**) as well as H/E sections in lower magnification are presented (**FIG. 2C**). *= pValue <0.05.

[0013] FIGS. 3A-3D depict the effect of combinatorial therapies utilizing the compound of formula (I) on hepatocellular carcinoma. FIG 3A. Analysis of MDA-9/syntenin expression in HCC TMA by IHC. **FIG. 3B.** Percentage of patients in each stage of HCC showing MDA-9/Syntenin expression. **FIG. 3C.** *mda-9/syntenin* mRNA expression analysis in the indicated cells. **FIG. 3D.** MDA-9/Syntenin protein expression analysis in the indicated cells.

[0014] FIG. 4. *mda-9/syntenin* promotes invasion. Basal Matrigel invasion abilities of the indicated cells (Inset). HepG3 cells were infected with Ad.vec or Ad.*mda-9* while Huh7 and QGY-7703 cells were infected with Ad.Consh (control shRNA) or Ad.*mda-9sh* (*mda-9* shRNA) (100 pfu/cell) for 48 hr and then invasion was quantified using Matrigel invasion assay. The data represent mean $\pm$ SEM. *: p<0.05.

[0015] FIGS. 5A-5B. The compound of formula (I) blocks HCC invasion. Basal Matrigel invasion abilities of the representative HCC cells. QGY7703 cells were assayed using 24 hr trans-well invasion assays with or without treatment with IVMT-Rx-4 at 25 and 50 μ M concentration. Invading cells were stained & photographed (**FIG. 5A**), counted, and graphically represented (**FIG. 5B**).

* Statistically significant.

[0016] FIGS. 6A-6B. The compound of formula (I) enhances anti-tumor activity of sorafenib. Subcutaneous xenografts were established in the flanks of athymic nude mice using QGY-7703 cells. The animals (n = 5) were treated with IVMT-Rx-4 or sorafenib alone or in

combination. **FIG. 6A.** Photograph of the tumors at the end of study. **FIG. 6B.** Measurement of tumor weight. The data represent mean $\pm$ S.D. Different letters indicate statistical significance among the groups.

[0017] FIGS. 7A-7B. The compound of formula (I) inhibits HNSCC invasion. Basal Matrigel invasion abilities of the representative HNSCC cells. UM-SCC-1 cells or HN6 cells were assayed using 24 hr trans-well invasion assays with or without treatment with IVMT-Rx-4 at 25 and 50 μ M concentration. Invading cells were stained & photographed (**FIG. 7A**), counted, and graphically represented (**FIG. 7B**). *** $P < 0.001$, **** $P < 0.0001$ by Student's *t*-test. Values are mean $\pm$ SD for triplicate samples from a representative experiment.

[0018] FIGS. 8A-8B. The compound of formula (I) inhibits HNSCC metastasis. HNSCC orthotopic xenograft model through injecting UM-SCC-1 cells into the tongue of nude mice. The animals ($n = 5$) were treated with IVMT-Rx-4 or control vehicles. (**FIG. 8A**) Representative images of tongue tumors from control and treatment groups. Scale bar, 1 mm. (**FIG. 8B**) Measurement of tumor volume. * $P < 0.05$ by Student's *t*-test. (**FIG. 8C**) H&E and immunostaining of metastatic cells in cervical lymph nodes (LN) using anti-pan-cytokeratin. Scale bar, 200 μ m. (**FIG. 8D**) The number of lymph nodes with metastatic tumor cells (LNM) was analyzed by Fisher's exact test. *** $P < 0.001$.

[0019] FIGS. 9A-9B. The compound of formula (I) inhibits pancreatic ductal adenocarcinoma (PDAC) invasion. Established PDAC cells were assayed after 24 hr. using trans-well invasion assays in the presence or absence of IVMT-Rx-4 (25 μ M). **FIG. 9A:** photograph. **FIG. 9B:** graphical presentation. * $P < 0.05$ vs. control.

[0020] FIGS. 10A-10B. The compound of formula (I) enhances apoptosis inducing activity of Chemotherapeutic(s). Pancreatic cancer cells were treated with IVMT-Rx-4 (25 μ M) for 24 hours, and then treated with either 5-FU or Gemcitabine for an additional 48 hours. Cells were then collected, and Western blotting analysis was done for PARP, a molecular index for apoptosis induction (**FIG. 10A**). * $P < 0.05$ vs. control. **FIG. 10B:** Pancreatic cancer cells combined with stromal cells were plated in low attachment 96-well plates and allowed to grow for 2 weeks. Once the organoids were formed, organoids were treated with IVMT-Rx4 (25- μ M) for 24 hours. These cells were again treated with either with 5 μ M 5-FU or with 5 μ M

Gemcitabine for an additional 72 hours. MTS assay was performed, and results are presented in graphically.

[0021] FIGS. 11A-11B. The compound of formula (I) enhances chemotherapeutic (5-FU and Gemcitabine)-mediated proliferation suppression in PDAC organoids. Pancreatic cancer cells combined with stromal cells were plated in low attachment 6-well plates and allowed them to grow for 2 weeks. Once the organoids were formed, organoids were treated with PDZ1i or IVMT-Rx-4 (25 μ M) for 24 hours. These cells were again treated with either with 5 μ M 5-FU or with 5 μ M Gemcitabine for an additional 72 hours. The cells were then photographed, and representative images are shown (**FIG. 11A**). Annexin V assay was performed, and results are represented in a graphical manner (**FIG. 11B**). *P < 0.05 is considered as statistically significant. (PDZ1i data is missing in right panel).

[0022] FIG. 12. The compound of formula (I) inhibits MDA-9/EphA2 interaction in PDAC. Human and murine pancreatic cancer cells were cultured for 24 hours (with 60-70% confluency) and were treated overnight with 25 μ M of IVMT-Rx-4. Cells were then collected and cell lysates were made. Equal amount of cell lysates was immunoprecipitated with MDA-9 antibody. IP samples were subjected to western blot analysis for EphA2 to check the binding of MDA-9/EphA2.

[0023] FIG. 13. The compound of formula (I) downregulates MDA-9 signaling in PDAC, both human (AsPC-1) and murine (KPC) cell lines. Pancreatic cancer cells were cultured for 24 hours (~60-70% confluency) and were treated overnight with 25 μ M of IVMT-Rx-4. Cells were then collected and cell lysates were made. Equal amount of cell lysates was subjected to Western blotting analysis for different MDA-9 downstream molecules.

[0024] FIGS. 14A-14B. The compound of formula (I) synergistically enhances the anti-proliferative activity of ABT199 (Venetoclax) in Acute Myeloid Leukemia (AML) cells. The indicated AML cells were incubated with IVMT-Rx-4 alone or in combination with ABT199 (50 nM) for 48 hrs. Cell proliferation was measured with the ATP lite assay and results plotted graphically. PDZ1i alone or in combination ABT199 was used for comparison (FIG. 14A). The indicated cells were treated with IVMT-Rx-4 alone or in combination with ABT199 for 48 hrs and apoptotic cell death was determined. Fold-changes in comparison with the DMSO-treated

group is presented (FIG. 14B). *P<0.05 vs. control. MV4-11R2 and MOLM13R2 are resistant variants of MV4-11 and MOLM13, respectively.

[0025] FIGS. 15A-15C. The compound of formula (I) suppresses melanoma metastasis and promotes immune activation. C57BL/6 mice were inoculated I.V. with B16 cells (1×10^5) to generate experimental lung metastases. One day after I.V. injection, mice received either 30 mg/kg or less (as indicated) b.w. of IVMT-Rx-4, I.P. 3X a week for the first two weeks (total 6 injections). After 14 days, mice were sacrificed and lungs were collected and representative lungs with tumor metastases are shown (FIG. 15A), nodules were counted, and the average number/lung is presented (FIG. 15B). Lungs were then analyzed for accumulation of CD8⁺IFN- γ ⁺ cells by FACS (FIG. 15C). *P < 0.05 is considered as statistically significant.

[0026] FIGS. 16A-16B. The compound of formula (I) suppresses prostate cancer bone metastasis, enhancing survival. PC-3ML-*Luc* cells were injected through the intracardiac route in athymic nude mice. Vehicle or IVMT-Rx-4 was administered by intraperitoneal injection every alternate day (3 injections per week, total 9 injections). BLI imaging was performed at day 36 to monitor bone metastases. Representative BLI images from each experimental group are presented (FIG. 16A). At this time point, 3 out of 5 mice died due to cancer-associated complications. A Kaplan–Meier survival curve was prepared using GraphPad software and is presented (FIG. 16B).

[0027] FIGS. 17A-17B. The compound of formula (I) with a SOC therapy (Docetaxel) enhances therapeutic outcomes in animals with prostate cancer bone metastasis. FIG. 17A: PC3-ML cells were treated with 25 μ M IVMT-Rx-4, alone or in combination with 0.5 nM or 1 nM docetaxel for 24 hr. MTT assays were then used to measure cell proliferation. FIG. 17B: PC3-ML-*Luc* (1×10^5 cells/mouse) cells were injected by the intracardiac route (I.C.) and randomly divided into four experimental groups. Mice received either DMSO (as vehicle control) or drugs (30 mg/Kg body weight and 5 mg/kg body weight for IVMT-Rx-4 and docetaxel, respectively) either alone or in combination through I.P. injection on every alternate day. In the combination group, the dosages were kept identical as in the “single dose” group. Bone metastases detected by BLI imaging. *P < 0.05 is considered as statistically significant.

[0028] FIGS. 18A-18E. MDA-9 is overexpressed in PDAC and regulates cancer progression/ metastasis phenotypes in PDAC. FIG. 18A: Analysis of MDA-9 expression in human PDAC TMA. FIG. 18B: MDA-9 expression in resected PDAC tissues and normal pancreas (N61). MDA-9 expression was significantly higher in PDAC tissues as compared to normal pancreatic tissue in both A & B. FIG. 18C, left panel, MDA-9 protein expression was significantly higher in PDAC cell lines as compared to LT2 cells. FIG. 18C, right panel, MDA-9 protein expression in human PDAC PDX cell lines. FIG. 18D: PDAC cells were either infected with Ad.*shcon* or Ad.*shmda-9* virus for 48 hr and cell invasion was determined after 18 hr of plating in invasion chambers. * P<0.05 vs *shcon* treated cells. FIG. 18E: mda-9 KD attenuates *in vivo* tumor growth/metastasis. Luciferase expressing PANC1 cells were stably transfected with a lentivirus expressing either *shcon* or *shmda-9*. Stably transfected cells were injected intraperitoneally into nude mice. BLI imaging was done at 5 wks after tumor cell implantation. KD of MDA-9 inhibited pancreatic tumor growth (size) and peritoneal metastases.

[0029] FIFS. 19A-19B. Effect of MDA-9 inhibitor, the compound of formula (I), on PDAC invasion. FIG. 19A: Established PDAC cells were assayed after 24 hr using trans-well invasion assays in the presence or absence of IVMT-Rx-4 (50 μ M). Upper panel, photograph, lower panel, graphical representation. *P<0.05 vs. control. FIG. 19B: PDAC PDX cells were either infected with Ad.*shmda-9* virus or treated with IVMT-Rx-4 (50 μ M). Cell invasion was determined after 24 hr of plating in invasion chambers. Upper panel, photograph, lower panel, graphical representation. *P<0.05 vs. control.

[0030] FIGS. 20A-20C. The compound of formula (I) in combination with gemcitabine induces enhanced cell death. PDAC PDX cells combined with stromal cells were plated in low attachment 6-well plates and allowed to grow for 2 weeks. Once the organoids formed, they were treated with IVMT-Rx-4 (25 μ M) for 24 hours. These cells were then treated with 5 μ M Gemcitabine for an additional 48/72 hours. FIG. 20A: GC46 organoids were collected, and Western blotting analysis was performed for ENT1 (equilibrative nucleoside transporter 1) and Pin1 (proline isomerase). FIG. 20B: Photographs of organoids. FIG. 20C: Annexin V/PI staining was done, and Flow cytometry analysis was performed. Results are represented in a graphical manner.

DETAILED DESCRIPTION

I. Definitions

[0031] 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.

[0032] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

[0033] 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. The alkyl may include a designated number of carbons (*e.g.*, $\text{C}_1\text{-C}_{10}$ means one to ten carbons). In embodiments, the alkyl is fully saturated. In embodiments, the alkyl is monounsaturated. In embodiments, the alkyl is polyunsaturated. Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *t*-butyl, isobutyl, *sec*-butyl, methyl, homologs and isomers of, for example, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker ($-\text{O}-$). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an alkynyl moiety. An alkenyl includes one or more double bonds. An alkynyl includes one or more triple bonds.

[0034] 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, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term “alkenylene,” by itself or as part of another substituent, means, unless

otherwise stated, a divalent radical derived from an alkene. In embodiments, the alkylene is fully saturated. In embodiments, the alkylene is monounsaturated. In embodiments, the alkylene is polyunsaturated. An alkenylene includes one or more double bonds. An alkynylene includes one or more triple bonds.

[0035] 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, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., O, N, S, Si, or P) 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: $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2$, $-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2-\text{CH}_3$, and $-\text{CN}$. Up to two or three heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P). The term “heteroalkenyl,” by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one double bond. A heteroalkenyl may optionally include more than one double bond and/or one or more triple bonds in addition to the one or more double bonds. The term “heteroalkynyl,” by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one triple bond. A heteroalkynyl may optionally include more than one triple bond and/or one or more double bonds in addition to the one or more triple bonds. In embodiments, the heteroalkyl is fully saturated. In embodiments, the heteroalkyl is monounsaturated. In embodiments, the heteroalkyl is polyunsaturated.

[0036] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2\text{-CH}_2\text{-S-CH}_2\text{-CH}_2\text{-}$ and $-\text{CH}_2\text{-S-CH}_2\text{-CH}_2\text{-NH-CH}_2\text{-}$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'$ represents both $-\text{C}(\text{O})_2\text{R}'$ and $-\text{R}'\text{C}(\text{O})_2$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as $-\text{C}(\text{O})\text{R}'$, $-\text{C}(\text{O})\text{NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$, and/or $-\text{SO}_2\text{R}'$. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like, it will be understood that the terms heteroalkyl and $-\text{NR}'\text{R}''$ are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like. The term “heteroalkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from a heteroalkene. The term “heteroalkynylene” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from a heteroalkyne. In embodiments, the heteroalkylene is fully saturated. In embodiments, the heteroalkylene is monounsaturated. In embodiments, the heteroalkylene is polyunsaturated. A heteroalkenylene includes one or more double bonds. A heteroalkynylene includes one or more triple bonds.

[0037] The terms “cycloalkyl” and “heterocycloalkyl,” by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl,” respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A “cycloalkylene” and a “heterocycloalkylene,” alone or

as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. In embodiments, the cycloalkyl is fully saturated. In embodiments, the cycloalkyl is monounsaturated. In embodiments, the cycloalkyl is polyunsaturated. In embodiments, the heterocycloalkyl is fully saturated. In embodiments, the heterocycloalkyl is monounsaturated. In embodiments, the heterocycloalkyl is polyunsaturated.

[0038] In embodiments, the term “cycloalkyl” means a monocyclic, bicyclic, or a multicyclic cycloalkyl ring system. In embodiments, monocyclic ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups can be saturated or unsaturated, but not aromatic. In embodiments, cycloalkyl groups are fully saturated. A bicyclic or multicyclic cycloalkyl ring system refers to multiple rings fused together wherein at least one of the fused rings is a cycloalkyl ring and wherein the multiple rings are attached to the parent molecular moiety through any carbon atom contained within a cycloalkyl ring of the multiple rings.

[0039] In embodiments, a cycloalkyl is a cycloalkenyl. The term “cycloalkenyl” is used in accordance with its plain ordinary meaning. In embodiments, a cycloalkenyl is a monocyclic, bicyclic, or a multicyclic cycloalkenyl ring system. A bicyclic or multicyclic cycloalkenyl ring system refers to multiple rings fused together wherein at least one of the fused rings is a cycloalkenyl ring and wherein the multiple rings are attached to the parent molecular moiety through any carbon atom contained within a cycloalkenyl ring of the multiple rings.

[0040] In embodiments, the term “heterocycloalkyl” means a monocyclic, bicyclic, or multicyclic heterocycloalkyl ring system. In embodiments, heterocycloalkyl groups are fully saturated. A bicyclic or multicyclic heterocycloalkyl ring system refers to multiple rings fused together wherein at least one of the fused rings is a heterocycloalkyl ring and wherein the multiple rings are attached to the parent molecular moiety through any atom contained within a heterocycloalkyl ring of the multiple rings.

[0041] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term

“halo(C₁-C₄)alkyl” includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0042] 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.

[0043] 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 and wherein the multiple rings are attached to the parent molecular moiety through any carbon atom contained within an aryl ring of the multiple rings. 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 and wherein the multiple rings are attached to the parent molecular moiety through any atom contained within a heteroaromatic ring of the multiple rings). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxaliny, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-

oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An “arylene” and a “heteroarylene,” alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

[0044] A fused ring heterocycloalkyl-aryl is an aryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-heteroaryl is a heteroaryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-cycloalkyl is a heterocycloalkyl fused to a cycloalkyl. A fused ring heterocycloalkyl-heterocycloalkyl is a heterocycloalkyl fused to another heterocycloalkyl. Fused ring heterocycloalkyl-aryl, fused ring heterocycloalkyl-heteroaryl, fused ring heterocycloalkyl-cycloalkyl, or fused ring heterocycloalkyl-heterocycloalkyl may each independently be unsubstituted or substituted with one or more of the substituents described herein.

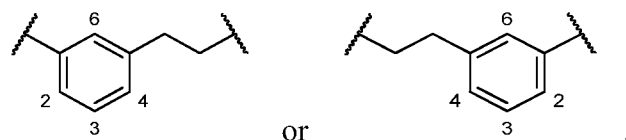
[0045] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocyclic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0046] The symbol “~” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0047] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0048] The term “alkylsulfonyl,” as used herein, means a moiety having the formula $-S(O_2)-R'$, where R' is a substituted or unsubstituted alkyl group as defined above. R' may have a specified number of carbons (e.g., “ C_1 - C_4 alkylsulfonyl”).

[0049] The term “alkylarylene” as an arylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



[0050] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2CH_3$, $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, substituted or unsubstituted C_1 - C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0051] Each of the above terms (e.g., “alkyl,” “heteroalkyl,” “cycloalkyl,” “heterocycloalkyl,” “aryl,” and “heteroaryl”) includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0052] 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, -NO₂, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R'', R''', and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' group when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term “alkyl” is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0053] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR''R''', -NR'C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R''', -ONR'R'', -NR'C(O)NR''NR'''R''', -CN, -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''', and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described 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.

[0054] 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.

[0055] 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.

[0056] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula $-T-C(O)-(CRR')_q-U-$, wherein T and U are independently $-NR-$, $-O-$, $-CRR'-$, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently $-CRR'-$, $-O-$, $-NR-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2NR'-$, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C''R''R''')_d-$, where s and d are independently integers of from 0 to 3, and X' is $-O-$, $-NR'-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R, R', 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.

[0057] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0058] A “substituent group,” as used herein, means a group selected from the following moieties:

(A) oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-N_3$, $-SF_5$, unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or

unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

(B) alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), substituted with at least one substituent selected from:

(i) oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, -SF₅, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

(ii) alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), substituted with at least one substituent selected from:

(a) oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, -SF₅, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

(b) alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), substituted with at least one substituent selected from: oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, -SF₅, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered

heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0059] A “size-limited substituent” or “size-limited substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0060] A “lower substituent” or “lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0061] 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.

[0062] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₂₀ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₈ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0063] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₈ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₇ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0064] 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).

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] In a recited claim or chemical formula description herein, each R substituent or L linker that is described as being “substituted” without reference as to the identity of any chemical moiety that composes the “substituted” group (also referred to herein as an “open substitution” on an R substituent or L linker or an “openly substituted” R substituent or L linker), the recited R

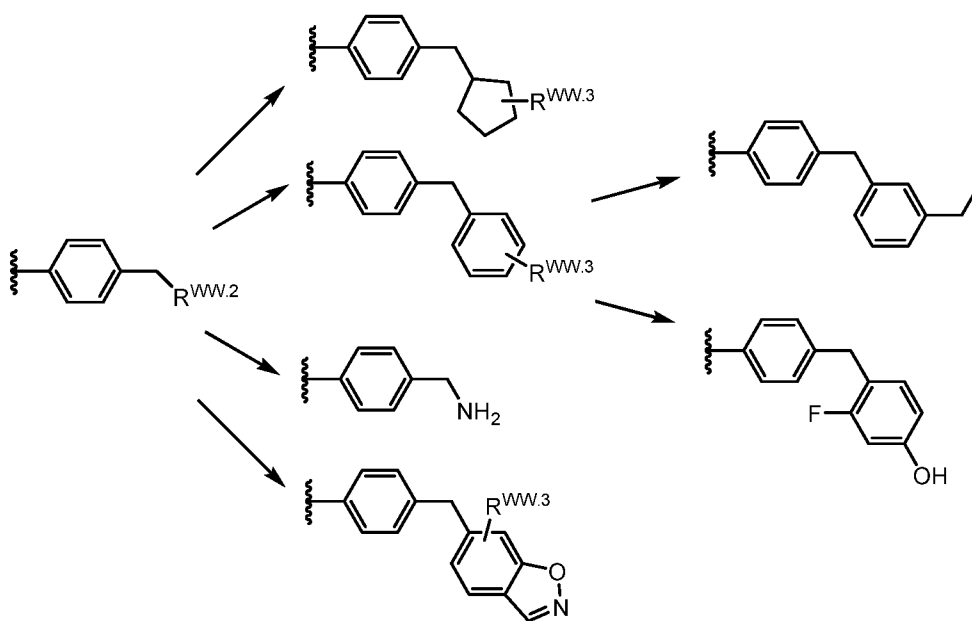
substituent or L linker may, in embodiments, be substituted with one or more first substituent groups as defined below.

[0070] The first substituent group is denoted with a corresponding first decimal point numbering system such that, for example, R^1 may be substituted with one or more first substituent groups denoted by $R^{1.1}$, R^2 may be substituted with one or more first substituent groups denoted by $R^{2.1}$, R^3 may be substituted with one or more first substituent groups denoted by $R^{3.1}$, R^4 may be substituted with one or more first substituent groups denoted by $R^{4.1}$, R^5 may be substituted with one or more first substituent groups denoted by $R^{5.1}$, and the like up to or exceeding an R^{100} that may be substituted with one or more first substituent groups denoted by $R^{100.1}$. As a further example, R^{1A} may be substituted with one or more first substituent groups denoted by $R^{1A.1}$, R^{2A} may be substituted with one or more first substituent groups denoted by $R^{2A.1}$, R^{3A} may be substituted with one or more first substituent groups denoted by $R^{3A.1}$, R^{4A} may be substituted with one or more first substituent groups denoted by $R^{4A.1}$, R^{5A} may be substituted with one or more first substituent groups denoted by $R^{5A.1}$ and the like up to or exceeding an R^{100A} may be substituted with one or more first substituent groups denoted by $R^{100A.1}$. As a further example, L^1 may be substituted with one or more first substituent groups denoted by $R^{L1.1}$, L^2 may be substituted with one or more first substituent groups denoted by $R^{L2.1}$, L^3 may be substituted with one or more first substituent groups denoted by $R^{L3.1}$, L^4 may be substituted with one or more first substituent groups denoted by $R^{L4.1}$, L^5 may be substituted with one or more first substituent groups denoted by $R^{L5.1}$ and the like up to or exceeding an L^{100} which may be substituted with one or more first substituent groups denoted by $R^{L100.1}$. Thus, each numbered R group or L group (alternatively referred to herein as R^{WW} or L^{WW} wherein “WW” represents the stated superscript number of the subject R group or L group) described herein may be substituted with one or more first substituent groups referred to herein generally as $R^{WW.1}$ or $R^{LWW.1}$, respectively. In turn, each first substituent group (e.g., $R^{1.1}$, $R^{2.1}$, $R^{3.1}$, $R^{4.1}$, $R^{5.1}$... $R^{100.1}$; $R^{1A.1}$, $R^{2A.1}$, $R^{3A.1}$, $R^{4A.1}$, $R^{5A.1}$... $R^{100A.1}$; $R^{L1.1}$, $R^{L2.1}$, $R^{L3.1}$, $R^{L4.1}$, $R^{L5.1}$... $R^{L100.1}$) may be further substituted with one or more second substituent groups (e.g., $R^{1.2}$, $R^{2.2}$, $R^{3.2}$, $R^{4.2}$, $R^{5.2}$... $R^{100.2}$; $R^{1A.2}$, $R^{2A.2}$, $R^{3A.2}$, $R^{4A.2}$, $R^{5A.2}$... $R^{100A.2}$; $R^{L1.2}$, $R^{L2.2}$, $R^{L3.2}$, $R^{L4.2}$, $R^{L5.2}$... $R^{L100.2}$, respectively). Thus, each first substituent group, which may alternatively be represented herein as $R^{WW.1}$ as described above, may be further substituted with one or more second substituent groups, which may alternatively be represented herein as $R^{WW.2}$.

[0071] Finally, each second substituent group (e.g., $R^{1.2}$, $R^{2.2}$, $R^{3.2}$, $R^{4.2}$, $R^{5.2}$... $R^{100.2}$; $R^{1A.2}$, $R^{2A.2}$, $R^{3A.2}$, $R^{4A.2}$, $R^{5A.2}$... $R^{100A.2}$; $R^{L1.2}$, $R^{L2.2}$, $R^{L3.2}$, $R^{L4.2}$, $R^{L5.2}$... $R^{L100.2}$) may be further substituted with one or more third substituent groups (e.g., $R^{1.3}$, $R^{2.3}$, $R^{3.3}$, $R^{4.3}$, $R^{5.3}$... $R^{100.3}$; $R^{1A.3}$, $R^{2A.3}$, $R^{3A.3}$, $R^{4A.3}$, $R^{5A.3}$... $R^{100A.3}$; $R^{L1.3}$, $R^{L2.3}$, $R^{L3.3}$, $R^{L4.3}$, $R^{L5.3}$... $R^{L100.3}$; respectively). Thus, each second substituent group, which may alternatively be represented herein as $R^{WW.2}$ as described above, may be further substituted with one or more third substituent groups, which may alternatively be represented herein as $R^{WW.3}$. Each of the first substituent groups may be optionally different. Each of the second substituent groups may be optionally different. Each of the third substituent groups may be optionally different.

[0072] Thus, as used herein, R^{WW} represents a substituent recited in a claim or chemical formula description herein which is openly substituted. “WW” represents the stated superscript number of the subject R group (1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). Likewise, L^{WW} is a linker recited in a claim or chemical formula description herein which is openly substituted. Again, “WW” represents the stated superscript number of the subject L group (1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). As stated above, in embodiments, each R^{WW} may be unsubstituted or independently substituted with one or more first substituent groups, referred to herein as $R^{WW.1}$; each first substituent group, $R^{WW.1}$, may be unsubstituted or independently substituted with one or more second substituent groups, referred to herein as $R^{WW.2}$; and each second substituent group may be unsubstituted or independently substituted with one or more third substituent groups, referred to herein as $R^{WW.3}$. Similarly, each L^{WW} linker may be unsubstituted or independently substituted with one or more first substituent groups, referred to herein as $R^{LWW.1}$; each first substituent group, $R^{LWW.1}$, may be unsubstituted or independently substituted with one or more second substituent groups, referred to herein as $R^{LWW.2}$; and each second substituent group may be unsubstituted or independently substituted with one or more third substituent groups, referred to herein as $R^{LWW.3}$. Each first substituent group is optionally different. Each second substituent group is optionally different. Each third substituent group is optionally different. For example, if R^{WW} is phenyl, the said phenyl group is optionally substituted by one or more $R^{WW.1}$ groups as defined herein below, e.g., when $R^{WW.1}$ is $R^{WW.2}$ -substituted or unsubstituted alkyl, examples of groups so formed include but are not limited to itself optionally substituted by 1 or more $R^{WW.2}$, which $R^{WW.2}$ is optionally substituted by one or more $R^{WW.3}$. By

way of example when the R^{WW} group is phenyl substituted by $R^{WW.1}$, which is methyl, the methyl group may be further substituted to form groups including but not limited to:



[0073] $R^{WW.1}$ is independently oxo, halogen, $-CX^{WW.1}_3$, $-CHX^{WW.1}_2$, $-CH_2X^{WW.1}$, $-OCX^{WW.1}_3$, $-OCH_2X^{WW.1}$, $-OCHX^{WW.1}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-N_3$, $R^{WW.2}$ -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), $R^{WW.2}$ -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $R^{WW.2}$ -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), $R^{WW.2}$ -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $R^{WW.2}$ -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or $R^{WW.2}$ -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{WW.1}$ is independently oxo, halogen, $-CX^{WW.1}_3$, $-CHX^{WW.1}_2$, $-CH_2X^{WW.1}$, $-OCX^{WW.1}_3$, $-OCH_2X^{WW.1}$, $-OCHX^{WW.1}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHC(NH)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 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., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW.1} is independently -F, -Cl, -Br, or -I.

[0074] R^{WW.2} is independently oxo, halogen, -CX^{WW.2}₃, -CHX^{WW.2}₂, -CH₂X^{WW.2}, -OCX^{WW.2}₃, -OCH₂X^{WW.2}, -OCHX^{WW.2}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, R^{WW.3}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{WW.3}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{WW.3}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{WW.3}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{WW.3}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{WW.3}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{WW.2} is independently oxo, halogen, -CX^{WW.2}₃, -CHX^{WW.2}₂, -CH₂X^{WW.2}, -OCX^{WW.2}₃, -OCH₂X^{WW.2}, -OCHX^{WW.2}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 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., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW.2} is independently -F, -Cl, -Br, or -I.

[0075] R^{WW.3} is independently oxo, halogen, -CX^{WW.3}₃, -CHX^{WW.3}₂, -CH₂X^{WW.3}, -OCX^{WW.3}₃, -OCH₂X^{WW.3}, -OCHX^{WW.3}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-

C₂), unsubstituted heteroalkyl (e.g., 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., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW.3} is independently -F, -Cl, -Br, or -I.

[0076] Where two different R^{WW} substituents are joined together to form an openly substituted ring (e.g., substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl or substituted heteroaryl), in embodiments the openly substituted ring may be independently substituted with one or more first substituent groups, referred to herein as R^{WW.1}; each first substituent group, R^{WW.1}, may be unsubstituted or independently substituted with one or more second substituent groups, referred to herein as R^{WW.2}; and each second substituent group, R^{WW.2}, may be unsubstituted or independently substituted with one or more third substituent groups, referred to herein as R^{WW.3}; and each third substituent group, R^{WW.3}, is unsubstituted. Each first substituent group is optionally different. Each second substituent group is optionally different. Each third substituent group is optionally different. In the context of two different R^{WW} substituents joined together to form an openly substituted ring, the “WW” symbol in the R^{WW.1}, R^{WW.2} and R^{WW.3} refers to the designated number of one of the two different R^{WW} substituents. For example, in embodiments where R^{100A} and R^{100B} are optionally joined together to form an openly substituted ring, R^{WW.1} is R^{100A.1}, R^{WW.2} is R^{100A.2}, and R^{WW.3} is R^{100A.3}. Alternatively, in embodiments where R^{100A} and R^{100B} are optionally joined together to form an openly substituted ring, R^{WW.1} is R^{100B.1}, R^{WW.2} is R^{100B.2}, and R^{WW.3} is R^{100B.3}. R^{WW.1}, R^{WW.2} and R^{WW.3} in this paragraph are as defined in the preceding paragraphs.

[0077] R^{LWW.1} is independently oxo, halogen, -CX^{LWW.1.3}, -CHX^{LWW.1.2}, -CH₂X^{LWW.1}, -OCX^{LWW.1.3}, -OCH₂X^{LWW.1}, -OCHX^{LWW.1.2}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, R^{LWW.2}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{LWW.2}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{LWW.2}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-

C₆), R^{LWW.2}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{LWW.2}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{LWW.2}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{LWW.1} is independently oxo, halogen, -CX^{LWW.1}₃, -CHX^{LWW.1}₂, -CH₂X^{LWW.1}, -OCX^{LWW.1}₃, -OCH₂X^{LWW.1}, -OCHX^{LWW.1}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 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., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{LWW.1} is independently -F, -Cl, -Br, or -I.

[0078] R^{LWW.2} is independently oxo, halogen, -CX^{LWW.2}₃, -CHX^{LWW.2}₂, -CH₂X^{LWW.2}, -OCX^{LWW.2}₃, -OCH₂X^{LWW.2}, -OCHX^{LWW.2}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, R^{LWW.3}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{LWW.3}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{LWW.3}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{LWW.3}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{LWW.3}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{LWW.3}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{LWW.2} is independently oxo, halogen, -CX^{LWW.2}₃, -CHX^{LWW.2}₂, -CH₂X^{LWW.2}, -OCX^{LWW.2}₃, -OCH₂X^{LWW.2}, -OCHX^{LWW.2}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 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., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{LWW.2} is independently -F, -Cl, -Br, or -I.

[0079] R^{LWW.3} is independently oxo, halogen, -CX^{LWW.3}₃, -CHX^{LWW.3}₂, -CH₂X^{LWW.3}, -OCX^{LWW.3}₃, -OCH₂X^{LWW.3}, -OCHX^{LWW.3}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 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., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 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., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{LWW.3} is independently -F, -Cl, -Br, or -I.

[0080] In the event that any R group recited in a claim or chemical formula description set forth herein (R^{WW} substituent) is not specifically defined in this disclosure, then that R group (R^{WW} group) is hereby defined as independently oxo, halogen, -CX^{WW}₃, -CHX^{WW}₂, -CH₂X^{WW}, -OCX^{WW}₃, -OCH₂X^{WW}, -OCHX^{WW}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHC(NH)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -N₃, R^{WW.1}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{WW.1}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{WW.1}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{WW.1}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{WW.1}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{WW.1}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW} is independently -F, -Cl, -Br, or -I. Again, "WW" represents the stated superscript number

of the subject R group (e.g., 1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ are as defined above.

[0081] In the event that any L linker group recited in a claim or chemical formula description set forth herein (i.e., an L^{WW} substituent) is not explicitly defined, then that L group (L^{WW} group) is herein defined as independently a bond, -O-, -NH-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -NHC(NH)NH-, -C(O)O-, -OC(O)-, -S-, -SO₂-, -SO₂NH-, $R^{LWW.1}$ -substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), $R^{LWW.1}$ -substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $R^{LWW.1}$ -substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), $R^{LWW.1}$ -substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $R^{LWW.1}$ -substituted or unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or $R^{LWW.1}$ -substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). Again, “WW” represents the stated superscript number of the subject L group (1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). $R^{LWW.1}$, as well as $R^{LWW.2}$ and $R^{LWW.3}$ are as defined above.

[0082] Certain compounds of the present disclosure possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric 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 disclosure. The compounds of the present disclosure do not include those that are known in art to be too unstable to synthesize and/or isolate. The present disclosure 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.

[0083] 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. As used herein, the term “regioisomers” refers to

compounds having the basic carbon skeleton unchanged but their functional groups or substituents change their position on a parent structure.

[0084] 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.

[0085] It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure.

[0086] 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 disclosure.

[0087] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon are within the scope of this disclosure.

[0088] The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure.

[0089] 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.

[0090] “Analog,” or “analogue” is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called “reference” compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0091] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C₁-C₂₀ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C₁-C₂₀ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0092] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as “R-substituted.” Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R¹³ substituents are present, each R¹³ substituent may be distinguished as R^{13.A}, R^{13.B}, R^{13.C}, R^{13.D}, etc., wherein each of R^{13.A}, R^{13.B}, R^{13.C}, R^{13.D}, etc. is defined within the scope of the definition of R¹³ and optionally differently.

[0093] Descriptions of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring

heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0094] A person of ordinary skill in the art will understand when a variable (e.g., moiety or linker) of a compound or of a compound genus (e.g., a genus described herein) is described by a name or formula of a standalone compound with all valencies filled, the unfilled valence(s) of the variable will be dictated by the context in which the variable is used. For example, when a variable of a compound as described herein is connected (e.g., bonded) to the remainder of the compound through a single bond, that variable is understood to represent a monovalent form (i.e., capable of forming a single bond due to an unfilled valence) of a standalone compound (e.g., if the variable is named “methane” in an embodiment but the variable is known to be attached by a single bond to the remainder of the compound, a person of ordinary skill in the art would understand that the variable is actually a monovalent form of methane, i.e., methyl or CH_3). Likewise, for a linker variable (e.g., L^1 , L^2 , or L^3 as described herein), a person of ordinary skill in the art will understand that the variable is the divalent form of a standalone compound (e.g., if the variable is assigned to “PEG” or “polyethylene glycol” in an embodiment but the variable is connected by two separate bonds to the remainder of the compound, a person of ordinary skill in the art would understand that the variable is a divalent (i.e., capable of forming two bonds through two unfilled valences) form of PEG instead of the standalone compound PEG).

[0095] As used herein, the term “salt” refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts.

[0096] The terms “bind” and “bound” as used herein is used in accordance with its plain and ordinary meaning and refers to the association between atoms or molecules. The association can be direct or indirect. For example, bound atoms or molecules may be direct, e.g., by covalent bond or linker (e.g. a first linker or second linker), or indirect, e.g., by non-covalent bond (e.g. electrostatic interactions (e.g. ionic bond, hydrogen bond, halogen bond), van der Waals

interactions (e.g. dipole-dipole, dipole-induced dipole, London dispersion), ring stacking (pi effects), hydrophobic interactions and the like).

[0097] The term “capable of binding” as used herein refers to a moiety (e.g., a compound as described herein) that is able to measurably bind to a target (e.g., a NF- κ B, a Toll-like receptor protein). In embodiments, where a moiety is capable of binding a target, the moiety is capable of binding with a Kd of less than about 10 μ M, 5 μ M, 1 μ M, 500 nM, 250 nM, 100 nM, 75 nM, 50 nM, 25 nM, 15 nM, 10 nM, 5 nM, 1 nM, or about 0.1 nM.

[0098] The terms “disease” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a cancer. In some further instances, “cancer” refers to human cancers and carcinomas, sarcomas, glioblastomas, neuroblastomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers.

[0099] As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g., humans), including leukemias, lymphomas, glioblastomas, neuroblastomas carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, nervous system, head and neck, skin, uterine, testicular, glioma, esophagus, mouth, and liver cancer, including hepatocellular, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (e.g., Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including AML, ALL, and CML), or multiple myeloma. Exemplary cancers that may be treated with a compound or method provided herein include brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, Medulloblastoma, melanoma, cervical cancer, gastric cancer, ovarian cancer, lung cancer, cancer of the head, cancer of the mouth and tongue, Hodgkin's Disease, and Non-Hodgkin's Lymphomas. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, ovary, pancreas, rectum, stomach, mouth and uterus. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast

invasive carcinoma, lung adenocarcinoma, oral squamous cell carcinoma, lung squamous cell carcinoma, non-small cell lung carcinoma, mesothelioma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, metastatic brain tumors (from other sites in the body), malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0100] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[0101] As used herein, the term “lymphoma” refers to a group of cancers affecting hematopoietic and lymphoid tissues. It begins in lymphocytes, the blood cells that are found primarily in lymph nodes, spleen, thymus, and bone marrow. Two main types of lymphoma are non-Hodgkin lymphoma and Hodgkin’s disease. Hodgkin’s disease represents approximately 15% of all diagnosed lymphomas. This is a cancer associated with Reed-Sternberg malignant B lymphocytes. Non-Hodgkin’s lymphomas (NHL) can be classified based on the rate at which cancer grows and the type of cells involved. There are aggressive (high grade) and indolent (low grade) types of NHL. Based on the type of cells involved, there are B-cell and T-cell NHLs. Exemplary B-cell lymphomas that may be treated with a compound or method provided herein include, but are not limited to, small lymphocytic lymphoma, Mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma, extranodal (MALT) lymphoma, nodal (monocytoid B-cell) lymphoma, splenic lymphoma, diffuse large cell B-lymphoma, Burkitt’s lymphoma, lymphoblastic lymphoma, immunoblastic large cell lymphoma, or precursor B-lymphoblastic lymphoma. Exemplary T-cell lymphomas that may be treated with a compound or method provided herein include, but are not limited to, cunatous T-cell lymphoma, peripheral T-cell lymphoma, anaplastic large cell lymphoma, mycosis fungoides, and precursor T-lymphoblastic lymphoma.

[0102] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[0103] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungual melanoma, or superficial spreading melanoma.

[0104] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhus carcinoma, carcinoma scroti, signet-

ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberosus carcinoma, verrucous carcinoma, or carcinoma villosum.

[0105] The term “breast cancer” refers to a cancer that develops in the breast cells and progresses in stages. The term “metastatic breast cancer” (advanced or stage IV) refers to breast cancer that has spread beyond the breast to other parts of the body, such as bones, lungs, liver, or brain.

[0106] The term “hepatocellular carcinoma” refers to a cancer that develops in hepatocytes.

[0107] The term “head and neck squamous cell carcinoma (HNSCC)” refers to a heterogeneous group of tumors that arise from the squamous epithelium of the oral cavity (oral squamous cell carcinoma), oropharynx, larynx and hypopharynx and is associated with high-risk human papilloma viruses (HPV).

[0108] The term “basal Matrigel” refers to soluble basement membrane extract, termed BME/Matrigel, and prepared from an epithelial tumor. It is similar in content to authentic basement membrane, and forms a hydrogel at 24–37 °C. The term “basal Matrigel invasion” refers to a tumor cell ability to invade Matrigel.

[0109] As used herein, the terms “metastasis,” “metastatic,” and “metastatic cancer” can be used interchangeably and refer to the spread of a proliferative disease or disorder, e.g., cancer, from one organ or another non-adjacent organ or body part. “Metastatic cancer” is also called “Stage IV cancer.” Cancer occurs at an originating site, e.g., breast, which site is referred to as a primary tumor, e.g., primary breast cancer. Some cancer cells in the primary tumor or originating site acquire the ability to penetrate and infiltrate surrounding normal tissue in the local area and/or the ability to penetrate the walls of the lymphatic system or vascular system circulating through the system to other sites and tissues in the body. A second clinically detectable tumor formed from cancer cells of a primary tumor is referred to as a metastatic or secondary tumor. When cancer cells metastasize, the metastatic tumor and its cells are presumed to be similar to those of the original tumor. Thus, if lung cancer metastasizes to the breast, the

secondary tumor at the site of the breast consists of abnormal lung cells and not abnormal breast cells. The secondary tumor in the breast is referred to a metastatic lung cancer. Thus, the phrase metastatic cancer refers to a disease in which a subject has or had a primary tumor and has one or more secondary tumors. The phrases non-metastatic cancer or subjects with cancer that is not metastatic refers to diseases in which subjects have a primary tumor but not one or more secondary tumors. For example, metastatic lung cancer refers to a disease in a subject with or with a history of a primary lung tumor and with one or more secondary tumors at a second location or multiple locations, e.g., in the breast.

[0110] The terms “cutaneous metastasis” or “skin metastasis” refer to secondary malignant cell growths in the skin, wherein the malignant cells originate from a primary cancer site (e.g., breast). In cutaneous metastasis, cancerous cells from a primary cancer site may migrate to the skin where they divide and cause lesions. Cutaneous metastasis may result from the migration of cancer cells from breast cancer tumors to the skin.

[0111] The term “visceral metastasis” refer to secondary malignant cell growths in the internal organs (e.g., heart, lungs, liver, pancreas, intestines) or body cavities (e.g., pleura, peritoneum), wherein the malignant cells originate from a primary cancer site (e.g., head and neck, liver, breast). In visceral metastasis, cancerous cells from a primary cancer site may migrate to the internal organs where they divide and cause lesions. Visceral metastasis may result from the migration of cancer cells from liver cancer tumors or head and neck tumors to internal organs.

[0112] The terms “treating”, or “treatment” refers to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing.

[0113] “Treating” or “treatment” as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject’s condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease’s transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, “treatment” as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease’s spread; relieve the disease’s symptoms (e.g., ocular pain, seeing halos around lights, red eye, very high intraocular pressure), fully or partially remove the disease’s underlying cause, shorten a disease’s duration, or do a combination of these things.

[0114] “Treating” and “treatment” as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of an active agent. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of active agent, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient. In embodiments, the treating or treatment is no prophylactic treatment.

[0115] The term “prevent” refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment.

[0116] “Patient” or “subject in need thereof” refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals,

bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0117] An “effective amount” is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an “effective amount” is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a “therapeutically effective amount.” A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A “prophylactically effective amount” of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An “activity decreasing amount,” as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A “function disrupting amount,” as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.,* Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0118] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0119] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0120] The term “therapeutically effective amount,” as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as “-fold” increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

[0121] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present disclosure, should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0122] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or

transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. In embodiments, the administering does not include administration of any active agent other than the recited active agent.

[0123] As used herein, the term "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds provided herein can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present disclosure can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0124] As used herein, the term "control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

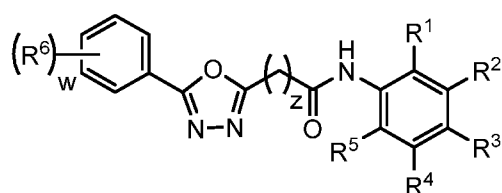
[0125] Cancer model organism, as used herein, is an organism exhibiting a phenotype indicative of cancer, or the activity of cancer causing elements, within the organism. The term cancer is defined above. A wide variety of organisms may serve as cancer model organisms, and include for example, cancer cells and mammalian organisms such as rodents (e.g., mouse or rat) and primates (such as humans). Cancer cell lines are widely understood by those skilled in the art as cells exhibiting phenotypes or genotypes similar to in vivo cancers. Cancer cell lines as used herein includes cell lines from animals (e.g., mice) and from humans.

[0126] As used herein, the terms “selective” or “selectivity” or the like of a compound refers to the compound’s ability to discriminate between molecular targets.

[0127] As used herein, the terms “specific”, “specifically”, “specificity”, or the like of a compound refers to the compound’s ability to cause a particular action, such as inhibition, to a particular molecular target with minimal or no action to other proteins in the cell.

II. Compounds

[0128] In an aspect, provided herein is a compound having the formula (I):



[0129] The symbol z is an integer from 0 to 8. The symbol w is an integer from 0 to 5. R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, $-CN$, $-N_3$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHN R^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHN R^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, $-OCH_2X^{1.1}$, 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^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-N_3$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHN R^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHN R^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, $-OCH_2X^{2.1}$, 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 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-N_3$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NH_2$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NH_2$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, $-OCH_2X^{3.1}$, 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^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, $-CN$, $-N_3$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, $-OCH_2X^{4.1}$, 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^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, $-CN$, $-N_3$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHN R^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHN R^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, $-OCH_2X^{5.1}$, 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^6 is independently halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-CN$, $-N_3$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHN R^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHN R^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, $-OCH_2X^{6.1}$, 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; two adjacent R^6 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted

heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{1B} and R^{1C} , R^{2B} and R^{2C} , R^{3B} and R^{3C} , R^{4B} and R^{4C} , R^{5B} and R^{5C} , and R^{6B} and R^{6C} , substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$, $X^{5.1}$, and $X^{6.1}$ are independently $-\text{Cl}$, $-\text{Br}$, $-\text{I}$ or $-\text{F}$. The symbols $n1$, $n2$, $n3$, $n4$, $n5$, and $n6$ are independently an integer from 0 to 4. The symbols $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $v1$, $v2$, $v3$, $v4$, $v5$, and $v6$ are independently 1 or 2.

[0130] In embodiments, R^1 is hydrogen, halogen, $-\text{CX}^{1.1}_3$, $-\text{CHX}^{1.1}_2$, $-\text{CH}_2\text{X}^{1.1}$, $-\text{OCX}^{1.1}_3$, $-\text{OCHX}^{1.1}_2$, $-\text{OCH}_2\text{X}^{1.1}$, $-\text{CN}$, $-\text{N}_3$, $-\text{SO}_{n1}\text{R}^{1A}$, $-\text{SO}_{v1}\text{NR}^{1B}\text{R}^{1C}$, $-\text{NHN}\text{R}^{1B}\text{R}^{1C}$, $-\text{ONR}^{1B}\text{R}^{1C}$, $-\text{NHC}(\text{O})\text{NHN}\text{R}^{1B}\text{R}^{1C}$, $-\text{NHC}(\text{O})\text{NR}^{1B}\text{R}^{1C}$, $-\text{N}(\text{O})_{m1}$, $-\text{NR}^{1B}\text{R}^{1C}$, $-\text{C}(\text{O})\text{R}^{1D}$, $-\text{C}(\text{O})\text{OR}^{1D}$, $-\text{C}(\text{O})\text{NR}^{1B}\text{R}^{1C}$, $-\text{OR}^{1A}$, $-\text{NR}^{1B}\text{SO}_2\text{R}^{1A}$, $-\text{NR}^{1B}\text{C}(\text{O})\text{R}^{1D}$, $-\text{NR}^{1B}\text{C}(\text{O})\text{OR}^{1D}$, $-\text{NR}^{1B}\text{OR}^{1D}$, 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.

[0131] In embodiments, R^1 is hydrogen, halogen (e.g., $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$), $-\text{CX}^{1.1}_3$, $-\text{CHX}^{1.1}_2$, $-\text{CH}_2\text{X}^{1.1}$, $-\text{OCX}^{1.1}_3$, $-\text{OCHX}^{1.1}_2$, $-\text{OCH}_2\text{X}^{1.1}$, $-\text{CN}$, $-\text{S}(\text{O})_2\text{R}^{1A}$, $-\text{SR}^{1A}$, $-\text{S}(\text{O})\text{R}^{1A}$, $-\text{SO}_2\text{NR}^{1B}\text{R}^{1C}$, $-\text{NHC}(\text{O})\text{NR}^{1B}\text{R}^{1C}$, $-\text{N}(\text{O})_2$, $-\text{NR}^{1B}\text{R}^{1C}$, $-\text{NHN}\text{R}^{1B}\text{R}^{1C}$, $-\text{C}(\text{O})\text{R}^{1D}$, $-\text{C}(\text{O})\text{-OR}^{1D}$, $-\text{C}(\text{O})\text{NR}^{1B}\text{R}^{1C}$, $-\text{C}(\text{O})\text{NHN}\text{R}^{1B}\text{R}^{1C}$, $-\text{OR}^{1A}$, $-\text{NR}^{1B}\text{SO}_2\text{R}^{1A}$, $-\text{NR}^{1B}\text{C}(\text{O})\text{R}^{1D}$, $-\text{NR}^{1B}\text{C}(\text{O})\text{OR}^{1D}$, $-\text{NR}^{1B}\text{OR}^{1D}$, $-\text{N}_3$, (e.g., $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{N}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NHCH}_3$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{NHSO}_2\text{H}$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NCH}_3\text{C}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NCH}_3\text{C}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{NCH}_3\text{OH}$, or $-\text{NCH}_3\text{OCH}_3$), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, or $\text{C}_1\text{-C}_4$), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group)

or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{1.1} is independently -F, -Cl, -Br, or -I.

[0132] In embodiments, R¹ is hydrogen, -F, -Cl, -Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -N₃, -CN, -SH, -SCH₃, -SO₂H, -SO₂CH₃, -SO₂NH₂, -SO₂NHCH₃, -NHC(O)NH₂, -NHC(O)NHCH₃, -NO₂, -NH₂, -NHCH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H, -NCH₃C(O)H, -NHC(O)OH, -NCH₃C(O)OH, -NHOH, -NCH₃OH, -NCH₃OCH₃, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0133] In embodiments, R¹ is hydrogen, -F, -Cl, -Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -N₃, -CN,

-SH, -SCH₃, -SO₂H, -SO₂CH₃, -SO₂NH₂, -SO₂NHCH₃, -NHC(O)NH₂, -NHC(O)NHCH₃, -NO₂, -NH₂, -NHCH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H, -NCH₃C(O)H, -NHC(O)OH, -NCH₃C(O)OH, -NHOH, -NCH₃OH, -NCH₃OCH₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0134] In embodiments, R¹ is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R¹¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R¹¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R¹¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R¹¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R¹¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R¹¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0135] In embodiments, R¹ is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0136] In embodiments, R¹ is R¹¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹ is R¹¹-substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹ is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or

C₁-C₄ alkyl). In embodiments, R¹ is R¹¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹ is R¹¹-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹ is R¹¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹ is R¹¹-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹ is R¹¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹ is R¹¹-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹ is R¹¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹ is R¹¹-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹ is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹ is R¹¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R¹ is R¹¹-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R¹ is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0137] R¹¹ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R¹²-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R¹²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R¹²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R¹²-substituted or unsubstituted

heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R¹²-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R¹²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0138] In embodiments, R¹¹ is independently halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0139] In embodiments, R¹¹ is independently R¹²-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹¹ is independently R¹²-substituted (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹¹ is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹¹ is independently R¹²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹¹ is independently R¹²-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹¹ is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹¹ is independently R¹²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹¹ is independently R¹²-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹¹ is independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹¹ is independently R¹²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹¹ is independently R¹²-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹¹ is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹¹ is independently R¹²-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹¹

is independently R¹²-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹¹ is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹¹ is independently R¹²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R¹¹ is independently R¹²-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R¹¹ is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0140] R¹² is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R¹³-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R¹³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R¹³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R¹³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R¹³-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R¹³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0141] In embodiments, R¹² is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0142] In embodiments, R¹² is independently R¹³-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹² is independently R¹³-substituted (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹² is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹² is independently R¹³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹² is independently R¹³-

substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{12} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{12} is independently R^{13} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{12} is independently R^{13} -substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{12} is independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{12} is independently R^{13} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{12} is independently R^{13} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{12} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{12} is independently R^{13} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{12} is independently R^{13} -substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{12} is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{12} is independently R^{13} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{12} is independently R^{13} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{12} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0143] R^{13} is independently halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-

C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0144] In embodiments, R¹³ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0145] In embodiments, R¹³ is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0146] In embodiments, the definitions for R^{1A}, R^{1B}, R^{1C}, and R^{1D} are the same as the definition of R¹.

[0147] In embodiments, a substituted R^{1A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1A} 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, when R^{1A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1A} is substituted, it is substituted with at least one lower substituent group.

[0148] In embodiments, a substituted R^{1B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1B} 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, when R^{1B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1B} is substituted, it is substituted with at least one lower substituent group.

[0149] In embodiments, a substituted R^{1C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1C} 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, when R^{1C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1C} is substituted, it is substituted with at least one lower substituent group.

[0150] In embodiments, a substituted ring formed when R^{1B} and R^{1C} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{1B} and R^{1C} substituents bonded to the same nitrogen atom are joined 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, when the substituted ring formed when R^{1B} and R^{1C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{1B} and R^{1C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed

when R^{1B} and R^{1C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0151] In embodiments, a substituted R^{1D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1D} 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, when R^{1D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1D} is substituted, it is substituted with at least one lower substituent group.

[0152] In embodiments, R^1 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-NH_2$, unsubstituted alkyl or unsubstituted heteroalkyl. In embodiments, R^1 is hydrogen. In embodiments, R^1 is halogen. In embodiments, R^1 is $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^1 is $-CF_3$. In embodiments, R^1 is $-CCl_3$. In embodiments, R^1 is $-CBr_3$. In embodiments, R^1 is $-Cl_3$. In embodiments, R^1 is $-COOH$. In embodiments, R^1 is $-NH_2$. In embodiments, R^1 is unsubstituted C_1 - C_3 alkyl. In embodiments, R^1 is methyl. In embodiments, R^1 is unsubstituted C_2 - C_4 heteroalkyl.

[0153] In embodiments, R^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-N_3$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNr^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNr^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, $-OCH_2X^{2.1}$, 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.

[0154] In embodiments, R^2 is hydrogen, halogen (e.g., $-F$, $-Cl$, $-Br$, $-I$), $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, $-OCH_2X^{2.1}$, $-CN$, $-S(O)_2R^{2A}$, $-SR^{2A}$, $-S(O)R^{2A}$, $-SO_2NR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_2$, $-NR^{2B}R^{2C}$, $-NHNr^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)-OR^{2D}$, $-C(O)NR^{2B}R^{2C}$,

$-\text{C}(\text{O})\text{NHN}^{\text{2B}}\text{R}^{\text{2C}}$, $-\text{OR}^{\text{2A}}$, $-\text{NR}^{\text{2B}}\text{SO}_2\text{R}^{\text{2A}}$, $-\text{NR}^{\text{2B}}\text{C}(\text{O})\text{R}^{\text{2D}}$, $-\text{NR}^{\text{2B}}\text{C}(\text{O})\text{OR}^{\text{2D}}$, $-\text{NR}^{\text{2B}}\text{OR}^{\text{2D}}$, $-\text{N}_3$,
 (e.g., $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$,
 $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$,
 $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{N}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$,
 $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NHCH}_3$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{OH}$,
 $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{NHSO}_2\text{H}$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{H}$,
 $-\text{NCH}_3\text{C}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NCH}_3\text{C}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{NCH}_3\text{OH}$, or $-\text{NCH}_3\text{OCH}_3$), substituted
 (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent
 group) or unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, or $\text{C}_1\text{-C}_4$), substituted (e.g., substituted with a
 substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
 heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g.,
 substituted with a substituent group, a size-limited substituent group, or lower substituent group)
 or unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, or $\text{C}_5\text{-C}_6$), substituted (e.g., substituted with a
 substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
 heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g.,
 substituted with a substituent group, a size-limited substituent group, or lower substituent group)
 or unsubstituted aryl (e.g., $\text{C}_6\text{-C}_{10}$, C_6 , or phenyl), or substituted (e.g., substituted with a
 substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
 heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $\text{X}^{1.1}$ is independently
 $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$.

[0155] In embodiments, R^2 is hydrogen, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$,
 $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$,
 $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{N}_3$, $-\text{CN}$,
 $-\text{SH}$, $-\text{SCH}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NHCH}_3$,
 $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$,
 $-\text{OH}$, $-\text{OCH}_3$, $-\text{NHSO}_2\text{H}$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NCH}_3\text{C}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$,
 $-\text{NCH}_3\text{C}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{NCH}_3\text{OH}$, $-\text{NCH}_3\text{OCH}_3$, substituted (e.g., substituted with a
 substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
 alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, or $\text{C}_1\text{-C}_4$), substituted (e.g., substituted with a substituent group, a size-
 limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0156] In embodiments, R² is hydrogen, -F, -Cl, -Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -N₃, -CN, -SH, -SCH₃, -SO₂H, -SO₂CH₃, -SO₂NH₂, -SO₂NHCH₃, -NHC(O)NH₂, -NHC(O)NHCH₃, -NO₂, -NH₂, -NHCH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H, -NCH₃C(O)H, -NHC(O)OH, -NCH₃C(O)OH, -NHOH, -NCH₃OH, -NCH₃OCH₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0157] In embodiments, R² is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R²¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R²¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R²¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R²¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6

membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{21} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{21} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0158] In embodiments, R^2 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0159] In embodiments, R^2 is R^{21} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^2 is R^{21} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^2 is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^2 is R^{21} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^2 is R^{21} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^2 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^2 is R^{21} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^2 is R^{21} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^2 is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^2 is R^{21} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^2 is R^{21} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^2 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^2 is R^{21} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^2 is R^{21} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^2 is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^2 is R^{21} -substituted or

unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^2 is R^{21} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^2 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0160] R^{21} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{22} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{22} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{22} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{22} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{22} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{22} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0161] In embodiments, R^{21} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0162] In embodiments, R^{21} is independently R^{22} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{21} is independently R^{22} -substituted (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{21} is independently unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{21} is independently R^{22} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{21} is independently R^{22} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{21} is independently unsubstituted heteroalkyl (e.g., 2

to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{21} is independently R^{22} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{21} is independently R^{22} -substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{21} is independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{21} is independently R^{22} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{21} is independently R^{22} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{21} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{21} is independently R^{22} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{21} is independently R^{22} -substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{21} is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{21} is independently R^{22} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{21} is independently R^{22} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{21} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0163] R^{22} is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{23} -substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{23} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{23} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀

aryl, or phenyl), or R²³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0164] In embodiments, R²² is independently halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0165] In embodiments, R²² is independently R²³-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R²² is independently R²³-substituted (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R²² is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R²² is independently R²³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R²² is independently R²³-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R²² is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R²² is independently R²³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R²² is independently R²³-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R²² is independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R²² is independently R²³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R²² is independently R²³-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R²² is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R²² is independently R²³-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R²² is independently R²³-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R²² is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R²² is

independently R^{23} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{22} is independently R^{23} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{22} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0166] R^{23} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0167] In embodiments, R^{23} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0168] In embodiments, R^{23} is independently unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0169] In embodiments, the definitions for R^{2A} , R^{2B} , R^{2C} , and R^{2D} are the same as the definition of R^2 .

[0170] In embodiments, a substituted R^{2A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2A} 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, when R^{2A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2A} is substituted, it is substituted with at least one lower substituent group.

[0171] In embodiments, a substituted R^{2B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2B} 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, when R^{2B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2B} is substituted, it is substituted with at least one lower substituent group.

[0172] In embodiments, a substituted R^{2C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2C} 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, when R^{2C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2C} is substituted, it is substituted with at least

one size-limited substituent group. In embodiments, when R^{2C} is substituted, it is substituted with at least one lower substituent group.

[0173] In embodiments, a substituted ring formed when R^{2B} and R^{2C} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{2B} and R^{2C} substituents bonded to the same nitrogen atom are joined 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, when the substituted ring formed when R^{2B} and R^{2C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{2B} and R^{2C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{2B} and R^{2C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0174] In embodiments, a substituted R^{2D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2D} 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, when R^{2D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2D} is substituted, it is substituted with at least one lower substituent group.

[0175] In embodiments, R^2 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-NH_2$, unsubstituted alkyl, or unsubstituted heteroalkyl. In embodiments, R^2 is hydrogen. In embodiments, R^2 is halogen. In embodiments, R^2 is $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^2 is $-CF_3$. In embodiments, R^2 is $-CCl_3$. In embodiments, R^2 is $-CBr_3$. In embodiments, R^2 is $-CI_3$. In

embodiments, R^2 is $-\text{COOH}$. In embodiments, R^2 is $-\text{NH}_2$. In embodiments, R^2 is unsubstituted C_1 - C_3 alkyl. In embodiments, R^2 is methyl. In embodiments, R^2 is unsubstituted C_2 - C_4 heteroalkyl.

[0176] In embodiments, R^3 is hydrogen, halogen, $-\text{CX}^{3.1}_3$, $-\text{CHX}^{3.1}_2$, $-\text{CH}_2\text{X}^{3.1}$, $-\text{CN}$, $-\text{N}_3$, $-\text{SO}_m\text{R}^{3A}$, $-\text{SO}_v\text{NR}^{3B}\text{R}^{3C}$, $-\text{NHN}\text{R}^{3B}\text{R}^{3C}$, $-\text{ON}\text{R}^{3B}\text{R}^{3C}$, $-\text{NHC}(\text{O})\text{NHN}\text{R}^{3B}\text{R}^{3C}$, $-\text{NHC}(\text{O})\text{NR}^{3B}\text{R}^{3C}$, $-\text{N}(\text{O})_m$, $-\text{NH}_2$, $-\text{C}(\text{O})\text{R}^{3D}$, $-\text{C}(\text{O})\text{OR}^{3D}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OR}^{3A}$, $-\text{NR}^{3B}\text{SO}_2\text{R}^{3A}$, $-\text{NR}^{3B}\text{C}(\text{O})\text{OR}^{3D}$, $-\text{NR}^{3B}\text{OR}^{3D}$, $-\text{OCX}^{3.1}_3$, $-\text{OCHX}^{3.1}_2$, $-\text{OCH}_2\text{X}^{3.1}$, 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.

[0177] In embodiments, R^3 is hydrogen, halogen (e.g., $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$), $-\text{CX}^{3.1}_3$, $-\text{CHX}^{3.1}_2$, $-\text{CH}_2\text{X}^{3.1}$, $-\text{OCX}^{3.1}_3$, $-\text{OCHX}^{3.1}_2$, $-\text{OCH}_2\text{X}^{3.1}$, $-\text{CN}$, $-\text{S}(\text{O})_2\text{R}^{3A}$, $-\text{SR}^{3A}$, $-\text{S}(\text{O})\text{R}^{3A}$, $-\text{SO}_2\text{NR}^{3B}\text{R}^{3C}$, $-\text{NHC}(\text{O})\text{NR}^{3B}\text{R}^{3C}$, $-\text{N}(\text{O})_2$, $-\text{NR}^{3B}\text{R}^{3C}$, $-\text{NHN}\text{R}^{3B}\text{R}^{3C}$, $-\text{C}(\text{O})\text{R}^{3D}$, $-\text{C}(\text{O})\text{OR}^{3D}$, $-\text{C}(\text{O})\text{NR}^{3B}\text{R}^{3C}$, $-\text{C}(\text{O})\text{NHN}\text{R}^{3B}\text{R}^{3C}$, $-\text{OR}^{3A}$, $-\text{NR}^{3B}\text{SO}_2\text{R}^{3A}$, $-\text{NR}^{3B}\text{C}(\text{O})\text{R}^{3D}$, $-\text{NR}^{3B}\text{C}(\text{O})\text{OR}^{3D}$, $-\text{NR}^{3B}\text{OR}^{3D}$, $-\text{N}_3$, (e.g., $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{N}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NHCH}_3$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{NHSO}_2\text{H}$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NCH}_3\text{C}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NCH}_3\text{C}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{NCH}_3\text{OH}$, or $-\text{NCH}_3\text{OCH}_3$), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6 - C_{10} , C_6 , or phenyl), or substituted (e.g., substituted with a

substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^{1.1}$ is independently -F, -Cl, -Br, or -I.

[0178] In embodiments, R^3 is hydrogen, -F, -Cl, -Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -N₃, -CN, -SH, -SCH₃, -SO₂H, -SO₂CH₃, -SO₂NH₂, -SO₂NHCH₃, -NHC(O)NH₂, -NHC(O)NHCH₃, -NO₂, -NH₂, -NHCH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H, -NCH₃C(O)H, -NHC(O)OH, -NCH₃C(O)OH, -NHOH, -NCH₃OH, -NCH₃OCH₃, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0179] In embodiments, R^3 is hydrogen, -F, -Cl, -Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -N₃, -CN, -SH, -SCH₃, -SO₂H, -SO₂CH₃, -SO₂NH₂, -SO₂NHCH₃, -NHC(O)NH₂, -NHC(O)NHCH₃, -NO₂, -NH₂, -NHCH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H, -NCH₃C(O)H, -NHC(O)OH, -NCH₃C(O)OH, -NHOH, -NCH₃OH, -NCH₃OCH₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered),

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

[0180] In embodiments, R³ is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R³¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R³¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R³¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R³¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R³¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R³¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0181] In embodiments, R³ is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0182] In embodiments, R³ is R³¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R³ is R³¹-substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R³ is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R³ is R³¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R³ is R³¹-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R³ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered

heteroalkyl). In embodiments, R^3 is R^{31} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^3 is R^{31} -substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^3 is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^3 is R^{31} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^3 is R^{31} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^3 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^3 is R^{31} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^3 is R^{31} -substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^3 is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^3 is R^{31} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^3 is R^{31} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^3 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0183] R^{31} is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{32} -substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{32} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{32} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{32} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{32} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{32} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0184] In embodiments, R^{31} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0185] In embodiments, R^{31} is independently R^{32} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{31} is independently R^{32} -substituted (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{31} is independently unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{31} is independently R^{32} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{31} is independently R^{32} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{31} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{31} is independently R^{32} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{31} is independently R^{32} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{31} is independently unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{31} is independently R^{32} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{31} is independently R^{32} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{31} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{31} is independently R^{32} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{31} is independently R^{32} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{31} is independently unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{31} is independently R^{32} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{31} is independently R^{32} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5

to 6 membered heteroaryl). In embodiments, R^{31} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0186] R^{32} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{33} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{33} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{33} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{33} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{33} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{33} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0187] In embodiments, R^{32} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0188] In embodiments, R^{32} is independently R^{33} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{32} is independently R^{33} -substituted (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{32} is unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{32} is independently R^{33} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{32} is independently R^{33} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{32} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{32} is independently R^{33} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{32} is independently R^{33} -

substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R³² is independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R³² is independently R³³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R³² is independently R³³-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R³² is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R³² is independently R³³-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R³² is independently R³³-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R³² is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R³² is independently R³³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R³² is independently R³³-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R³² is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0189] R³³ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0190] In embodiments, R³³ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,

-NHC(O)NHNH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0191] In embodiments, R³³ is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0192] In embodiments, the definitions for R^{3A}, R^{3B}, R^{3C}, and R^{3D} are the same as the definition of R³.

[0193] In embodiments, a substituted R^{3A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3A} 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, when R^{3A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{3A} is substituted, it is substituted with at least one lower substituent group.

[0194] In embodiments, a substituted R^{3B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3B} 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, when R^{3B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{3B} is substituted, it is substituted with at least one lower substituent group.

[0195] In embodiments, a substituted R^{3C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3C} 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, when R^{3C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{3C} is substituted, it is substituted with at least one lower substituent group.

[0196] In embodiments, a substituted ring formed when R^{3B} and R^{3C} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{3B} and R^{3C} substituents bonded to the same nitrogen atom are joined 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, when the substituted ring formed when R^{3B} and R^{3C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{3B} and R^{3C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{3B} and R^{3C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0197] In embodiments, a substituted R^{3D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3D} 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, when R^{3D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{3D} is substituted, it is substituted with at least one lower substituent group.

[0198] In embodiments, R^3 is hydrogen, halogen, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted alkyl or unsubstituted heteroalkyl. In embodiments, R^3 is hydrogen. In embodiments, R^3 is halogen. In embodiments, R^3 is $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$. In embodiments, R^3 is $-\text{CF}_3$. In embodiments, R^3 is $-\text{CCl}_3$. In embodiments, R^3 is $-\text{CBr}_3$. In embodiments, R^3 is $-\text{Cl}_3$. In embodiments, R^3 is $-\text{COOH}$. In embodiments, R^3 is $-\text{NH}_2$. In embodiments, R^3 is unsubstituted C_1 - C_3 alkyl. In embodiments, R^3 is methyl. In embodiments, R^3 is unsubstituted C_2 - C_4 heteroalkyl.

[0199] In embodiments, R^4 is hydrogen, halogen, $-\text{CX}^{4.1}_3$, $-\text{CHX}^{4.1}_2$, $-\text{CH}_2\text{X}^{4.1}$, $-\text{CN}$, $-\text{N}_3$, $-\text{SO}_{\text{n}}\text{R}^{4\text{A}}$, $-\text{SO}_{\text{v}}\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{NHN}\text{R}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{ON}\text{R}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{NHC}(\text{O})\text{NHN}\text{R}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{NHC}(\text{O})\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{N}(\text{O})_{\text{m}4}$, $-\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{C}(\text{O})\text{R}^{4\text{D}}$, $-\text{C}(\text{O})\text{OR}^{4\text{D}}$, $-\text{C}(\text{O})\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{OR}^{4\text{A}}$, $-\text{NR}^{4\text{B}}\text{SO}_2\text{R}^{4\text{A}}$, $-\text{NR}^{4\text{B}}\text{C}(\text{O})\text{R}^{4\text{D}}$, $-\text{NR}^{4\text{B}}\text{C}(\text{O})\text{OR}^{4\text{D}}$, $-\text{NR}^{4\text{B}}\text{OR}^{4\text{D}}$, $-\text{OCX}^{4.1}_3$, $-\text{OCHX}^{4.1}_2$, $-\text{OCH}_2\text{X}^{4.1}$, 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.

[0200] In embodiments, R^4 is hydrogen, halogen (e.g., $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$), $-\text{CX}^{4.1}_3$, $-\text{CHX}^{4.1}_2$, $-\text{CH}_2\text{X}^{4.1}$, $-\text{OCX}^{4.1}_3$, $-\text{OCHX}^{4.1}_2$, $-\text{OCH}_2\text{X}^{4.1}$, $-\text{CN}$, $-\text{S}(\text{O})_2\text{R}^{4\text{A}}$, $-\text{SR}^{4\text{A}}$, $-\text{S}(\text{O})\text{R}^{4\text{A}}$, $-\text{SO}_2\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{NHC}(\text{O})\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{N}(\text{O})_2$, $-\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{NHN}\text{R}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{C}(\text{O})\text{R}^{4\text{D}}$, $-\text{C}(\text{O})\text{-OR}^{4\text{D}}$, $-\text{C}(\text{O})\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{C}(\text{O})\text{NHN}\text{R}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{OR}^{4\text{A}}$, $-\text{NR}^{4\text{B}}\text{SO}_2\text{R}^{4\text{A}}$, $-\text{NR}^{4\text{B}}\text{C}(\text{O})\text{R}^{4\text{D}}$, $-\text{NR}^{4\text{B}}\text{C}(\text{O})\text{OR}^{4\text{D}}$, $-\text{NR}^{4\text{B}}\text{OR}^{4\text{D}}$, $-\text{N}_3$, (e.g., $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{N}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NHCH}_3$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{OH}$,

-C(O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H, -NCH₃C(O)H, -NHC(O)OH, -NCH₃C(O)OH, -NHOH, -NCH₃OH, or -NCH₃OCH₃), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{1.1} is independently -F, -Cl, -Br, or -I.

[0201] In embodiments, R⁴ is hydrogen, -F, -Cl, -Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -N₃, -CN, -SH, -SCH₃, -SO₂H, -SO₂CH₃, -SO₂NH₂, -SO₂NHCH₃, -NHC(O)NH₂, -NHC(O)NHCH₃, -NO₂, -NH₂, -NHCH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H, -NCH₃C(O)H, -NHC(O)OH, -NCH₃C(O)OH, -NHOH, -NCH₃OH, -NCH₃OCH₃, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g., substituted with

a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0202] In embodiments, R⁴ is hydrogen, -F, -Cl, -Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -N₃, -CN, -SH, -SCH₃, -SO₂H, -SO₂CH₃, -SO₂NH₂, -SO₂NHCH₃, -NHC(O)NH₂, -NHC(O)NHCH₃, -NO₂, -NH₂, -NHCH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H, -NCH₃C(O)H, -NHC(O)OH, -NCH₃C(O)OH, -NHOH, -NCH₃OH, -NCH₃OCH₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0203] In embodiments, R⁴ is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R⁴¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R⁴¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R⁴¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R⁴¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R⁴¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R⁴¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0204] In embodiments, R^4 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0205] In embodiments, R^4 is R^{41} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^4 is R^{41} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^4 is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^4 is R^{41} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^4 is R^{41} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^4 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^4 is R^{41} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^4 is R^{41} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^4 is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^4 is R^{41} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^4 is R^{41} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^4 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^4 is R^{41} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^4 is R^{41} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^4 is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^4 is R^{41} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^4 is R^{41} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^4 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0206] R^{41} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{42} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{42} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{42} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{42} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{42} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{42} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0207] In embodiments, R^{41} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0208] In embodiments, R^{41} is independently R^{42} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{41} is independently R^{42} -substituted (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{41} is independently unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{41} is independently R^{42} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{41} is independently R^{42} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{41} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{41} is independently R^{42} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{41} is independently R^{42} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{41} is independently unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6

cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁴¹ is independently R⁴²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁴¹ is independently R⁴²-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁴¹ is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁴¹ is independently R⁴²-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁴¹ is independently R⁴²-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁴¹ is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁴¹ is independently R⁴²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁴¹ is independently R⁴²-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁴¹ is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0209] R⁴² is independently halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R⁴³-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R⁴³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R⁴³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R⁴³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R⁴³-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R⁴³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0210] In embodiments, R⁴² is independently halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃,

-OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0211] In embodiments, R⁴² is independently R⁴³-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁴² is independently R⁴³-substituted (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁴² is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁴² is independently R⁴³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁴² is independently R⁴³-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁴² is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁴² is independently R⁴³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁴² is independently R⁴³-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁴² is independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁴² is independently R⁴³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁴² is independently R⁴³-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁴² is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁴² is independently R⁴³-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁴² is independently R⁴³-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁴² is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁴² is independently R⁴³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁴² is independently R⁴³-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁴² is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0212] R^{43} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0213] In embodiments, R^{43} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0214] In embodiments, R^{43} is independently unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0215] In embodiments, the definitions for R^{4A} , R^{4B} , R^{4C} , and R^{4D} are the same as the definition of R^4 .

[0216] In embodiments, a substituted R^{4A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or

lower substituent group; wherein if the substituted R^{4A} 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, when R^{4A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{4A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{4A} is substituted, it is substituted with at least one lower substituent group.

[0217] In embodiments, a substituted R^{4B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{4B} 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, when R^{4B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{4B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{4B} is substituted, it is substituted with at least one lower substituent group.

[0218] In embodiments, a substituted R^{4C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{4C} 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, when R^{4C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{4C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{4C} is substituted, it is substituted with at least one lower substituent group.

[0219] In embodiments, a substituted ring formed when R^{4B} and R^{4C} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower

substituent group; wherein if the substituted ring formed when R^{4B} and R^{4C} substituents bonded to the same nitrogen atom are joined 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, when the substituted ring formed when R^{4B} and R^{4C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{4B} and R^{4C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{4B} and R^{4C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0220] In embodiments, a substituted R^{4D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{4D} 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, when R^{4D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{4D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{4D} is substituted, it is substituted with at least one lower substituent group.

[0221] In embodiments, R^4 is hydrogen, halogen, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted alkyl or unsubstituted heteroalkyl. In embodiments, R^4 is hydrogen. In embodiments, R^4 is halogen. In embodiments, R^4 is $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$. In embodiments, R^4 is $-\text{CF}_3$. In embodiments, R^4 is $-\text{CCl}_3$. In embodiments, R^4 is $-\text{CBr}_3$. In embodiments, R^4 is $-\text{Cl}_3$. In embodiments, R^4 is $-\text{COOH}$. In embodiments, R^4 is $-\text{NH}_2$. In embodiments, R^4 is unsubstituted C_1 - C_3 alkyl. In embodiments, R^4 is methyl. In embodiments, R^4 is unsubstituted C_2 - C_4 heteroalkyl.

[0222] In embodiments, R^5 is hydrogen, halogen, $-\text{CX}^{5.1}_3$, $-\text{CHX}^{5.1}_2$, $-\text{CH}_2\text{X}^{5.1}$, $-\text{CN}$, $-\text{N}_3$, $-\text{SO}_{n5}\text{R}^{5A}$, $-\text{SO}_{v5}\text{NR}^{5B}\text{R}^{5C}$, $-\text{NHN}\text{R}^{5B}\text{R}^{5C}$, $-\text{ONR}^{5B}\text{R}^{5C}$, $-\text{NHC}(\text{O})\text{NHN}\text{R}^{5B}\text{R}^{5C}$,

$-\text{NHC(O)NR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{N(O)}_{\text{m}5}$, $-\text{NR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{C(O)R}^{5\text{D}}$, $-\text{C(O)OR}^{5\text{D}}$, $-\text{C(O)NR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{OR}^{5\text{A}}$,
 $-\text{NR}^{5\text{B}}\text{SO}_2\text{R}^{5\text{A}}$, $-\text{NR}^{5\text{B}}\text{C(O)R}^{5\text{D}}$, $-\text{NR}^{5\text{B}}\text{C(O)OR}^{5\text{D}}$, $-\text{NR}^{5\text{B}}\text{OR}^{5\text{D}}$, $-\text{OCX}^{5.1}_3$, $-\text{OCHX}^{5.1}_2$,
 $-\text{OCH}_2\text{X}^{5.1}$, 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.

[0223] In embodiments, R^5 is hydrogen, halogen (e.g., -F, -Cl, -Br, -I), $-\text{CX}^{5.1}_3$, $-\text{CHX}^{5.1}_2$,
 $-\text{CH}_2\text{X}^{5.1}$, $-\text{OCX}^{5.1}_3$, $-\text{OCHX}^{5.1}_2$, $-\text{OCH}_2\text{X}^{5.1}$, -CN, $-\text{S(O)}_2\text{R}^{5\text{A}}$, $-\text{SR}^{5\text{A}}$, $-\text{S(O)R}^{5\text{A}}$, $-\text{SO}_2\text{NR}^{5\text{B}}\text{R}^{5\text{C}}$,
 $-\text{NHC(O)NR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{N(O)}_2$, $-\text{NR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{NHNR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{C(O)R}^{5\text{D}}$, $-\text{C(O)-OR}^{5\text{D}}$, $-\text{C(O)NR}^{5\text{B}}\text{R}^{5\text{C}}$,
 $-\text{C(O)NHNR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{OR}^{5\text{A}}$, $-\text{NR}^{5\text{B}}\text{SO}_2\text{R}^{5\text{A}}$, $-\text{NR}^{5\text{B}}\text{C(O)R}^{5\text{D}}$, $-\text{NR}^{5\text{B}}\text{C(O)OR}^{5\text{D}}$, $-\text{NR}^{5\text{B}}\text{OR}^{5\text{D}}$, $-\text{N}_3$,
(e.g., $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$,
 $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$,
 $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{N}_3$, -CN, -SH, -SCH₃, -SO₂H, -SO₂CH₃, -SO₂NH₂, -SO₂NHCH₃,
 $-\text{NHC(O)NH}_2$, $-\text{NHC(O)NHCH}_3$, -NO₂, -NH₂, -NHCH₃, -C(O)H, -C(O)CH₃, -C(O)OH,
 $-\text{C(O)OCH}_3$, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H,
 $-\text{NCH}_3\text{C(O)H}$, $-\text{NHC(O)OH}$, $-\text{NCH}_3\text{C(O)OH}$, -NHOH, -NCH₃OH, or -NCH₃OCH₃), substituted
(e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent
group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted (e.g., substituted with a
substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g.,
substituted with a substituent group, a size-limited substituent group, or lower substituent group)
or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted (e.g., substituted with a
substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g.,
substituted with a substituent group, a size-limited substituent group, or lower substituent group)
or unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or substituted (e.g., substituted with a
substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $\text{X}^{1.1}$ is independently
-F, -Cl, -Br, or -I.

[0224] In embodiments, R^5 is hydrogen, -F, -Cl, -Br, -I, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$,
 $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$,

$-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{N}_3$, $-\text{CN}$,
 $-\text{SH}$, $-\text{SCH}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NHCH}_3$,
 $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$,
 $-\text{OH}$, $-\text{OCH}_3$, $-\text{NHSO}_2\text{H}$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NCH}_3\text{C}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$,
 $-\text{NCH}_3\text{C}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{NCH}_3\text{OH}$, $-\text{NCH}_3\text{OCH}_3$, substituted (e.g., substituted with a
substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), substituted (e.g., substituted with a substituent group, a size-
limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g., substituted with a
substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), substituted (e.g., substituted with a substituent group, a
size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl
(e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g., substituted with
a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
aryl (e.g., C_6 - C_{10} , C_6 , or phenyl), or substituted (e.g., substituted with a substituent group, a size-
limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered).

[0225] In embodiments, R^5 is hydrogen, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$,
 $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCI}_3$,
 $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{N}_3$, $-\text{CN}$,
 $-\text{SH}$, $-\text{SCH}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NHCH}_3$,
 $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$,
 $-\text{OH}$, $-\text{OCH}_3$, $-\text{NHSO}_2\text{H}$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NCH}_3\text{C}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$,
 $-\text{NCH}_3\text{C}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{NCH}_3\text{OH}$, $-\text{NCH}_3\text{OCH}_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or
 C_1 - C_4), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered),
unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to
8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{10} , C_6 , or
phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6
membered).

[0226] In embodiments, R^5 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{51} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{51} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{51} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{51} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{51} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{51} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0227] In embodiments, R^5 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0228] In embodiments, R^5 is R^{51} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^5 is R^{51} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^5 is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^5 is R^{51} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^5 is R^{51} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^5 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^5 is R^{51} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^5 is R^{51} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^5 is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In

embodiments, R^5 is R^{51} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^5 is R^{51} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^5 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^5 is R^{51} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^5 is R^{51} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^5 is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^5 is R^{51} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^5 is R^{51} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^5 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0229] R^{51} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{52} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{52} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{52} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{52} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{52} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{52} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0230] In embodiments, R^{51} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$,

-OCF₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0231] In embodiments, R⁵¹ is independently R⁵²-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁵¹ is independently R⁵²-substituted (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁵¹ is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁵¹ is independently R⁵²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁵¹ is independently R⁵²-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁵¹ is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁵¹ is independently R⁵²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁵¹ is independently R⁵²-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁵¹ is independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁵¹ is independently R⁵²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁵¹ is independently R⁵²-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁵¹ is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁵¹ is independently R⁵²-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁵¹ is independently R⁵²-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁵¹ is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁵¹ is independently R⁵²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁵¹ is independently R⁵²-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁵¹ is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0232] R^{52} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{53} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{53} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{53} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{53} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{53} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{53} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0233] In embodiments, R^{52} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0234] In embodiments, R^{52} is independently R^{53} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{52} is independently R^{53} -substituted (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{52} is independently unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{52} is independently R^{53} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{52} is independently R^{53} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{52} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{52} is independently R^{53} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{52} is independently R^{53} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{52} is independently unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6

cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁵² is independently R⁵³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁵² is independently R⁵³-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁵² is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁵² is independently R⁵³-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁵² is independently R⁵³-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁵² is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁵² is independently R⁵³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁵² is R⁵³-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁵² is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0235] R⁵³ is independently halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0236] In embodiments, R⁵³ is independently halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃,

-OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0237] In embodiments, R⁵³ is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0238] In embodiments, the definitions for R^{5A}, R^{5B}, R^{5C}, and R^{5D} are the same as the definition of R⁵.

[0239] In embodiments, a substituted R^{5A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{5A} 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, when R^{5A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{5A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5A} is substituted, it is substituted with at least one lower substituent group.

[0240] In embodiments, a substituted R^{5B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{5B} 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, when R^{5B} is substituted, it is substituted with at least

one substituent group. In embodiments, when R^{5B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5B} is substituted, it is substituted with at least one lower substituent group.

[0241] In embodiments, a substituted R^{5C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{5C} 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, when R^{5C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{5C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5C} is substituted, it is substituted with at least one lower substituent group.

[0242] In embodiments, a substituted ring formed when R^{5B} and R^{5C} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{5B} and R^{5C} substituents bonded to the same nitrogen atom are joined 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, when the substituted ring formed when R^{5B} and R^{5C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{5B} and R^{5C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{5B} and R^{5C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0243] In embodiments, a substituted R^{5D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or

lower substituent group; wherein if the substituted R^{5D} 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, when R^{5D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{5D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5D} is substituted, it is substituted with at least one lower substituent group.

[0244] In embodiments, R^5 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-NH_2$, unsubstituted alkyl or unsubstituted heteroalkyl. In embodiments, R^5 is hydrogen. In embodiments, R^5 is halogen. In embodiments, R^5 is $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^5 is $-CF_3$. In embodiments, R^5 is $-CCl_3$. In embodiments, R^5 is $-CBr_3$. In embodiments, R^5 is $-CI_3$. In embodiments, R^5 is $-COOH$. In embodiments, R^5 is $-NH_2$. In embodiments, R^5 is unsubstituted C_1 - C_3 alkyl. In embodiments, R^5 is methyl. In embodiments, R^5 is unsubstituted C_2 - C_4 heteroalkyl.

[0245] In embodiments, R^6 is independently halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-CN$, $-N_3$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHN R^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHN R^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, $-OCH_2X^{6.1}$, 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; two adjacent R^6 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0246] In embodiments, R^6 is independently halogen (e.g., $-F$, $-Cl$, $-Br$, $-I$), $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, $-OCH_2X^{6.1}$, $-CN$, $-S(O)_2R^{6A}$, $-SR^{6A}$, $-S(O)R^{6A}$, $-SO_2NR^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_2$, $-NR^{6B}R^{6C}$, $-NHN R^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)-OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-C(O)NHN R^{6B}R^{6D}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-N_3$, (e.g., $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-CI_3$, $-CHI_2$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$,

$-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{N}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$,
 $-\text{SO}_2\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NHCH}_3$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$,
 $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{NHSO}_2\text{H}$, $-\text{NHSO}_2\text{CH}_3$,
 $-\text{NHC}(\text{O})\text{H}$, $-\text{NCH}_3\text{C}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NCH}_3\text{C}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{NCH}_3\text{OH}$, or $-\text{NCH}_3\text{OCH}_3$),
 substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower
 substituent group) or unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, or $\text{C}_1\text{-C}_4$), substituted (e.g.,
 substituted with a substituent group, a size-limited substituent group, or lower substituent group)
 or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered),
 substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower
 substituent group) or unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, or $\text{C}_5\text{-C}_6$), substituted (e.g.,
 substituted with a substituent group, a size-limited substituent group, or lower substituent group)
 or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered),
 substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower
 substituent group) or unsubstituted aryl (e.g., $\text{C}_6\text{-C}_{10}$, C_6 , or phenyl), or substituted (e.g.,
 substituted with a substituent group, a size-limited substituent group, or lower substituent group)
 or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $\text{X}^{1,1}$
 is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$.

[0247] In embodiments, R^6 is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$,
 $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$,
 $-\text{OCI}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$,
 $-\text{N}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{NH}_2$,
 $-\text{NHC}(\text{O})\text{NHCH}_3$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OCH}_3$,
 $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{NHSO}_2\text{H}$, $-\text{NHSO}_2\text{CH}_3$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NCH}_3\text{C}(\text{O})\text{H}$,
 $-\text{NHC}(\text{O})\text{OH}$, $-\text{NCH}_3\text{C}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{NCH}_3\text{OH}$, $-\text{NCH}_3\text{OCH}_3$, substituted (e.g., substituted
 with a substituent group, a size-limited substituent group, or lower substituent group) or
 unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, or $\text{C}_1\text{-C}_4$), substituted (e.g., substituted with a substituent
 group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl
 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted (e.g., substituted with
 a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted
 cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, or $\text{C}_5\text{-C}_6$), substituted (e.g., substituted with a substituent group, a

size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0248] In embodiments, R⁶ is independently -F, -Cl, -Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -N₃, -CN, -SH, -SCH₃, -SO₂H, -SO₂CH₃, -SO₂NH₂, -SO₂NHCH₃, -NHC(O)NH₂, -NHC(O)NHCH₃, -NO₂, -NH₂, -NHCH₃, -C(O)H, -C(O)CH₃, -C(O)OH, -C(O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -OH, -OCH₃, -NHSO₂H, -NHSO₂CH₃, -NHC(O)H, -NCH₃C(O)H, -NHC(O)OH, -NCH₃C(O)OH, -NHOH, -NCH₃OH, -NCH₃OCH₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0249] In embodiments, R⁶ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R⁶¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R⁶¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R⁶¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R⁶¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R⁶¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R⁶¹-substituted or unsubstituted

heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0250] In embodiments, R^6 is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0251] In embodiments, R^6 is independently R^{61} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^6 is independently R^{61} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^6 is independently an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^6 is independently R^{61} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^6 is independently R^{61} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^6 is independently an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^6 is independently R^{61} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^6 is independently R^{61} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^6 is independently an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^6 is independently R^{61} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^6 is independently R^{61} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^6 is independently an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^6 is independently R^{61} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^6 is independently R^{61} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^6 is independently an unsubstituted aryl (e.g., C_6 - C_{10} aryl,

C₁₀ aryl, or phenyl). In embodiments, R⁶ is independently R⁶¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁶ is independently R⁶¹-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁶ is independently an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0252] R⁶¹ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R⁶²-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R⁶²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R⁶²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R⁶²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R⁶²-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R⁶²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0253] In embodiments, R⁶¹ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0254] In embodiments, R⁶¹ is independently R⁶²-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁶¹ is independently R⁶²-substituted (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁶¹ is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁶¹ is independently R⁶²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁶¹ is independently R⁶²-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4

membered heteroalkyl). In embodiments, R^{61} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{61} is independently R^{62} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{61} is independently R^{62} -substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{61} is independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{61} is independently R^{62} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{61} is independently R^{62} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{61} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{61} is independently R^{62} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{61} is independently R^{62} -substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{61} is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{61} is independently R^{62} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{61} is independently R^{62} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{61} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0255] R^{62} is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{63} -substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{63} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{63} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{63} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{63} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀

aryl, or phenyl), or R⁶³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0256] In embodiments, R⁶² is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0257] In embodiments, R⁶² is independently R⁶³-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁶² is independently R⁶³-substituted (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁶² is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁶² is independently R⁶³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁶² is independently R⁶³-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁶² is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁶² is independently R⁶³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁶² is independently R⁶³-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁶² is unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁶² is independently R⁶³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁶² is independently R⁶³-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁶² is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁶² is independently R⁶³-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁶² is independently R⁶³-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁶² is independently unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁶² is independently

R⁶³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁶² is independently R⁶³-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁶² is independently unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0258] R⁶³ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0259] In embodiments, R⁶³ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -N₃, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, or -OCH₂I.

[0260] In embodiments, R⁶³ is independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0261] In embodiments, the definitions for R^{6A} , R^{6B} , R^{6C} , and R^{6D} are the same as the definition of R^6 .

[0262] In embodiments, a substituted R^{6A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6A} 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, when R^{6A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{6A} is substituted, it is substituted with at least one lower substituent group.

[0263] In embodiments, a substituted R^{6B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6B} 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, when R^{6B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{6B} is substituted, it is substituted with at least one lower substituent group.

[0264] In embodiments, a substituted R^{6C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6C} 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, when R^{6C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6C} is substituted, it is substituted with at least

one size-limited substituent group. In embodiments, when R^{6C} is substituted, it is substituted with at least one lower substituent group.

[0265] In embodiments, a substituted ring formed when R^{6B} and R^{6C} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{6B} and R^{6C} substituents bonded to the same nitrogen atom are joined 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, when the substituted ring formed when R^{6B} and R^{6C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{6B} and R^{6C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{6B} and R^{6C} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0266] In embodiments, a substituted R^{6D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6D} 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, when R^{6D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{6D} is substituted, it is substituted with at least one lower substituent group.

[0267] In embodiments, R^6 is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-NH_2$, unsubstituted alkyl or unsubstituted heteroalkyl. In embodiments, R^6 is hydrogen. In embodiments, R^6 is halogen. In embodiments, R^6 is $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^6 is $-CF_3$. In embodiments, R^6 is $-CCl_3$. In embodiments, R^6 is $-CBr_3$. In embodiments, R^6 is $-CI_3$. In

embodiments, R^6 is $-\text{COOH}$. In embodiments, R^6 is $-\text{NH}_2$. In embodiments, R^6 is unsubstituted $\text{C}_1\text{-C}_3$ alkyl. In embodiments, R^6 is methyl. In embodiments, R^6 is unsubstituted $\text{C}_2\text{-C}_4$ heteroalkyl.

In embodiments, z is an integer from 0 to 8. In embodiments, z is 0. In embodiments, z is 1. In embodiments, z is 2. In embodiments, z is 3. In embodiments, z is 4. In embodiments, z is 5. In embodiments, z is 6. In embodiments, z is 7. In embodiments, z is 8.

In embodiments, w is an integer from 0 to 5. In embodiments, w is 0. In embodiments, w is 1. In embodiments, w is 2. In embodiments, w is 3. In embodiments, w is 4. In embodiments, w is 5.

[0268] In embodiments, n_1 is an integer from 0 to 4. In embodiments, n_1 is 0. In embodiments, n_1 is 1. In embodiments, n_1 is 2. In embodiments, n_1 is 3. In embodiments, n_1 is 4.

[0269] In embodiments, n_2 is an integer from 0 to 4. In embodiments, n_2 is 0. In embodiments, n_2 is 1. In embodiments, n_2 is 2. In embodiments, n_2 is 3. In embodiments, n_2 is 4.

[0270] In embodiments, n_3 is an integer from 0 to 4. In embodiments, n_3 is 0. In embodiments, n_3 is 1. In embodiments, n_3 is 2. In embodiments, n_3 is 3. In embodiments, n_3 is 4.

[0271] In embodiments, n_4 is an integer from 0 to 4. In embodiments, n_4 is 0. In embodiments, n_4 is 1. In embodiments, n_4 is 2. In embodiments, n_4 is 3. In embodiments, n_4 is 4.

[0272] In embodiments, n_5 is an integer from 0 to 4. In embodiments, n_5 is 0. In embodiments, n_5 is 1. In embodiments, n_5 is 2. In embodiments, n_5 is 3. In embodiments, n_5 is 4.

[0273] In embodiments, n_6 is an integer from 0 to 4. In embodiments, n_6 is 0. In embodiments, n_6 is 1. In embodiments, n_6 is 2. In embodiments, n_6 is 3. In embodiments, n_6 is 4.

[0274] In embodiments, m_1 is 1 or 2. In embodiments, m_1 is 1. In embodiments, m_1 is 2.

[0275] In embodiments, m_2 is 1 or 2. In embodiments, m_2 is 1. In embodiments, m_2 is 2.

[0276] In embodiments, m_3 is 1 or 2. In embodiments, m_3 is 1. In embodiments, m_3 is 2.

[0277] In embodiments, m_4 is 1 or 2. In embodiments, m_4 is 1. In embodiments, m_4 is 2.

[0278] In embodiments, m_5 is 1 or 2. In embodiments, m_5 is 1. In embodiments, m_5 is 2.

[0279] In embodiments, m6 is 1 or 2. In embodiments, m6 is 1. In embodiments, m6 is 2.

[0280] In embodiments, v1 is 1 or 2. In embodiments, v1 is 1. In embodiments, v1 is 2.

[0281] In embodiments, v2 is 1 or 2. In embodiments, v2 is 1. In embodiments, v2 is 2.

[0282] In embodiments, v3 is 1 or 2. In embodiments, v3 is 1. In embodiments, v3 is 2.

[0283] In embodiments, v4 is 1 or 2. In embodiments, v4 is 1. In embodiments, v4 is 2.

[0284] In embodiments, v5 is 1 or 2. In embodiments, v5 is 1. In embodiments, v5 is 2.

[0285] In embodiments, v6 is 1 or 2. In embodiments, v6 is 1. In embodiments, v6 is 2.

[0286] In embodiments, $X^{1.1}$ is independently halogen. In embodiments, halogen is -F, -Cl, -Br, or -I. In embodiments, $X^{1.1}$ is independently -F. In embodiments, $X^{1.1}$ is independently -Cl. In embodiments, $X^{1.1}$ is independently -Br. In embodiments, $X^{1.1}$ is independently -I.

[0287] In embodiments, $X^{2.1}$ is independently halogen. In embodiments, halogen is -F, -Cl, -Br, or -I. In embodiments, $X^{2.1}$ is independently -F. In embodiments, $X^{2.1}$ is independently -Cl. In embodiments, $X^{2.1}$ is independently -Br. In embodiments, $X^{2.1}$ is independently -I.

[0288] In embodiments, $X^{3.1}$ is independently halogen. In embodiments, halogen is -F, -Cl, -Br, or -I. In embodiments, $X^{3.1}$ is independently -F. In embodiments, $X^{3.1}$ is independently -Cl. In embodiments, $X^{3.1}$ is independently -Br. In embodiments, $X^{3.1}$ is independently -I.

[0289] In embodiments, $X^{4.1}$ is independently halogen. In embodiments, halogen is -F, -Cl, -Br, or -I. In embodiments, $X^{4.1}$ is independently -F. In embodiments, $X^{4.1}$ is independently -Cl. In embodiments, $X^{4.1}$ is independently -Br. In embodiments, $X^{4.1}$ is independently -I.

[0290] In embodiments, $X^{5.1}$ is independently halogen. In embodiments, halogen is -F, -Cl, -Br, or -I. In embodiments, $X^{5.1}$ is independently -F. In embodiments, $X^{5.1}$ is independently -Cl. In embodiments, $X^{5.1}$ is independently -Br. In embodiments, $X^{5.1}$ is independently -I.

[0291] In embodiments, $X^{6.1}$ is independently halogen. In embodiments, halogen is -F, -Cl, -Br, or -I. In embodiments, $X^{6.1}$ is independently -F. In embodiments, $X^{6.1}$ is independently -Cl. In embodiments, $X^{6.1}$ is independently -Br. In embodiments, $X^{6.1}$ is independently -I.

[0292] 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).

[0293] 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.

[0294] 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.

[0295] 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.

[0296] 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.

[0297] In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl,

substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl, substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl, or substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl.

[0298] In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0299] In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently unsubstituted alkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted alkyl alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl).

[0300] In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently

substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently unsubstituted heteroalkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered).

[0301] In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently an unsubstituted cycloalkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are independently substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^6, R^{6A}, R^{6B}, R^{6C},$ and R^{6D} are

independently substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R², R^{2A}, R^{2B}, R^{2C}, R^{2D}, R³, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R⁴, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R⁵, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R⁶, R^{6A}, R^{6B}, R^{6C}, and R^{6D} are independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0302] In embodiments, R¹, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R², R^{2A}, R^{2B}, R^{2C}, R^{2D}, R³, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R⁴, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R⁵, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R⁶, R^{6A}, R^{6B}, R^{6C}, and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl. In embodiments, R¹, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R², R^{2A}, R^{2B}, R^{2C}, R^{2D}, R³, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R⁴, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R⁵, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R⁶, R^{6A}, R^{6B}, R^{6C}, and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl. In embodiments, R¹, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R², R^{2A}, R^{2B}, R^{2C}, R^{2D}, R³, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R⁴, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R⁵, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R⁶, R^{6A}, R^{6B}, R^{6C}, and R^{6D} are independently an unsubstituted heterocycloalkyl. In embodiments, R¹, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R², R^{2A}, R^{2B}, R^{2C}, R^{2D}, R³, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R⁴, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R⁵, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R⁶, R^{6A}, R^{6B}, R^{6C}, and R^{6D} are independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R¹, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R², R^{2A}, R^{2B}, R^{2C}, R^{2D}, R³, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R⁴, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R⁵, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R⁶, R^{6A}, R^{6B}, R^{6C}, and R^{6D} are independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R¹, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R², R^{2A}, R^{2B}, R^{2C}, R^{2D}, R³, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R⁴, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R⁵, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R⁶, R^{6A}, R^{6B}, R^{6C}, and R^{6D} are independently an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered).

[0303] In embodiments, R¹, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R², R^{2A}, R^{2B}, R^{2C}, R^{2D}, R³, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R⁴, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R⁵, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R⁶, R^{6A}, R^{6B}, R^{6C}, and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl. In embodiments, R¹, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R², R^{2A}, R^{2B}, R^{2C}, R^{2D}, R³, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R⁴, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R⁵, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R⁶, R^{6A}, R^{6B}, R^{6C}, and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-

limited substituent group, or lower substituent group) aryl. In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently an unsubstituted aryl. In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0304] In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroaryl. In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl. In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently an unsubstituted heteroaryl. In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^6 , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0305] In embodiments, when R^{1A} is substituted, R^{1A} is substituted with one or more first substituent groups denoted by $R^{1A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.1}$ substituent group is substituted, the $R^{1A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.2}$ substituent group is substituted, the $R^{1A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1A} , $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1A} , $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$, respectively.

[0306] In embodiments, when R^{1B} is substituted, R^{1B} is substituted with one or more first substituent groups denoted by $R^{1B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.1}$ substituent group is substituted, the $R^{1B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.2}$ substituent group is substituted, the $R^{1B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1B} , $R^{1B.1}$, $R^{1B.2}$, and $R^{1B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1B} , $R^{1B.1}$, $R^{1B.2}$, and $R^{1B.3}$, respectively.

[0307] In embodiments, when R^{1C} is substituted, R^{1C} is substituted with one or more first substituent groups denoted by $R^{1C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1C.1}$ substituent group is substituted, the $R^{1C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1C.2}$ substituent group is substituted, the $R^{1C.2}$

substituent group is substituted with one or more third substituent groups denoted by $R^{1C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1C} , $R^{1C.1}$, $R^{1C.2}$, and $R^{1C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1C} , $R^{1C.1}$, $R^{1C.2}$, and $R^{1C.3}$, respectively.

[0308] In embodiments, when R^{1B} and R^{1C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{1B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.1}$ substituent group is substituted, the $R^{1B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.2}$ substituent group is substituted, the $R^{1B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{1B.1}$, $R^{1B.2}$, and $R^{1B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{1B.1}$, $R^{1B.2}$, and $R^{1B.3}$, respectively.

[0309] In embodiments, when R^{1B} and R^{1C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{1C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1C.1}$ substituent group is substituted, the $R^{1C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1C.2}$ substituent group is substituted, the $R^{1C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above

embodiments, $R^{1C.1}$, $R^{1C.2}$, and $R^{1C.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{1C.1}$, $R^{1C.2}$, and $R^{1C.3}$, respectively.

[0310] In embodiments, when R^{1D} is substituted, R^{1D} is substituted with one or more first substituent groups denoted by $R^{1D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1D.1}$ substituent group is substituted, the $R^{1D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1D.2}$ substituent group is substituted, the $R^{1D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1D} , $R^{1D.1}$, $R^{1D.2}$, and $R^{1D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1D} , $R^{1D.1}$, $R^{1D.2}$, and $R^{1D.3}$, respectively.

[0311] In embodiments, when R^{2A} is substituted, R^{2A} is substituted with one or more first substituent groups denoted by $R^{2A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2A.1}$ substituent group is substituted, the $R^{2A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2A.2}$ substituent group is substituted, the $R^{2A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{2A} , $R^{2A.1}$, $R^{2A.2}$, and $R^{2A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{2A} , $R^{2A.1}$, $R^{2A.2}$, and $R^{2A.3}$, respectively.

[0312] In embodiments, when R^{2B} is substituted, R^{2B} is substituted with one or more first substituent groups denoted by $R^{2B.1}$ as explained in the definitions section above in the

description of “first substituent group(s)”. In embodiments, when an $R^{2B.1}$ substituent group is substituted, the $R^{2B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2B.2}$ substituent group is substituted, the $R^{2B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{2B} , $R^{2B.1}$, $R^{2B.2}$, and $R^{2B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{2B} , $R^{2B.1}$, $R^{2B.2}$, and $R^{2B.3}$, respectively.

[0313] In embodiments, when R^{2C} is substituted, R^{2C} is substituted with one or more first substituent groups denoted by $R^{2C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2C.1}$ substituent group is substituted, the $R^{2C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2C.2}$ substituent group is substituted, the $R^{2C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{2C} , $R^{2C.1}$, $R^{2C.2}$, and $R^{2C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{2C} , $R^{2C.1}$, $R^{2C.2}$, and $R^{2C.3}$, respectively.

[0314] In embodiments, when R^{2B} and R^{2C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{2B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2B.1}$ substituent group is substituted, the $R^{2B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2B.2}$ substituent group is substituted, the $R^{2B.2}$ substituent group is

substituted with one or more third substituent groups denoted by $R^{2B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{2B.1}$, $R^{2B.2}$, and $R^{2B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{2B.1}$, $R^{2B.2}$, and $R^{2B.3}$, respectively.

[0315] In embodiments, when R^{2B} and R^{2C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{2C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2C.1}$ substituent group is substituted, the $R^{2C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2C.2}$ substituent group is substituted, the $R^{2C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{2C.1}$, $R^{2C.2}$, and $R^{2C.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{2C.1}$, $R^{2C.2}$, and $R^{2C.3}$, respectively.

[0316] In embodiments, when R^{2D} is substituted, R^{2D} is substituted with one or more first substituent groups denoted by $R^{2D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2D.1}$ substituent group is substituted, the $R^{2D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2D.2}$ substituent group is substituted, the $R^{2D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{2D} , $R^{2D.1}$, $R^{2D.2}$, and $R^{2D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the

description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{2D} , $R^{2D.1}$, $R^{2D.2}$, and $R^{2D.3}$, respectively.

[0317] In embodiments, when R^{3A} is substituted, R^{3A} is substituted with one or more first substituent groups denoted by $R^{3A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3A.1}$ substituent group is substituted, the $R^{3A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3A.2}$ substituent group is substituted, the $R^{3A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{3A} , $R^{3A.1}$, $R^{3A.2}$, and $R^{3A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{3A} , $R^{3A.1}$, $R^{3A.2}$, and $R^{3A.3}$, respectively.

[0318] In embodiments, when R^{3B} is substituted, R^{3B} is substituted with one or more first substituent groups denoted by $R^{3B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3B.1}$ substituent group is substituted, the $R^{3B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3B.2}$ substituent group is substituted, the $R^{3B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{3B} , $R^{3B.1}$, $R^{3B.2}$, and $R^{3B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{3B} , $R^{3B.1}$, $R^{3B.2}$, and $R^{3B.3}$, respectively.

[0319] In embodiments, when R^{3C} is substituted, R^{3C} is substituted with one or more first substituent groups denoted by $R^{3C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3C.1}$ substituent group is substituted, the $R^{3C.1}$ substituent group is substituted with one or more second substituent groups

denoted by $R^{3C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3C.2}$ substituent group is substituted, the $R^{3C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{3C} , $R^{3C.1}$, $R^{3C.2}$, and $R^{3C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{3C} , $R^{3C.1}$, $R^{3C.2}$, and $R^{3C.3}$, respectively.

[0320] In embodiments, when R^{3B} and R^{3C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{3B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3B.1}$ substituent group is substituted, the $R^{3B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3B.2}$ substituent group is substituted, the $R^{3B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{3B.1}$, $R^{3B.2}$, and $R^{3B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{3B.1}$, $R^{3B.2}$, and $R^{3B.3}$, respectively.

[0321] In embodiments, when R^{3B} and R^{3C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{3C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3C.1}$ substituent group is substituted, the $R^{3C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3C.2}$ substituent group is substituted, the $R^{3C.2}$ substituent group is

substituted with one or more third substituent groups denoted by $R^{3C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{3C.1}$, $R^{3C.2}$, and $R^{3C.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{3C.1}$, $R^{3C.2}$, and $R^{3C.3}$, respectively.

[0322] In embodiments, when R^{3D} is substituted, R^{3D} is substituted with one or more first substituent groups denoted by $R^{3D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3D.1}$ substituent group is substituted, the $R^{3D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3D.2}$ substituent group is substituted, the $R^{3D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{3D} , $R^{3D.1}$, $R^{3D.2}$, and $R^{3D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{3D} , $R^{3D.1}$, $R^{3D.2}$, and $R^{3D.3}$, respectively.

[0323] In embodiments, when R^{4A} is substituted, R^{4A} is substituted with one or more first substituent groups denoted by $R^{4A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4A.1}$ substituent group is substituted, the $R^{4A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4A.2}$ substituent group is substituted, the $R^{4A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{4A} , $R^{4A.1}$, $R^{4A.2}$, and $R^{4A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{4A} , $R^{4A.1}$, $R^{4A.2}$, and $R^{4A.3}$, respectively.

[0324] In embodiments, when R^{4B} is substituted, R^{4B} is substituted with one or more first substituent groups denoted by $R^{4B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4B.1}$ substituent group is substituted, the $R^{4B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4B.2}$ substituent group is substituted, the $R^{4B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{4B} , $R^{4B.1}$, $R^{4B.2}$, and $R^{4B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{4B} , $R^{4B.1}$, $R^{4B.2}$, and $R^{4B.3}$, respectively.

[0325] In embodiments, when R^{4C} is substituted, R^{4C} is substituted with one or more first substituent groups denoted by $R^{4C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4C.1}$ substituent group is substituted, the $R^{4C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4C.2}$ substituent group is substituted, the $R^{4C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{4C} , $R^{4C.1}$, $R^{4C.2}$, and $R^{4C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{4C} , $R^{4C.1}$, $R^{4C.2}$, and $R^{4C.3}$, respectively.

[0326] In embodiments, when R^{4B} and R^{4C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{4B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4B.1}$ substituent group is substituted, the $R^{4B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4B.2}$ as

explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4B.2}$ substituent group is substituted, the $R^{4B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{4B.1}$, $R^{4B.2}$, and $R^{4B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{4B.1}$, $R^{4B.2}$, and $R^{4B.3}$, respectively.

[0327] In embodiments, when R^{4B} and R^{4C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{4C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4C.1}$ substituent group is substituted, the $R^{4C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4C.2}$ substituent group is substituted, the $R^{4C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{4C.1}$, $R^{4C.2}$, and $R^{4C.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{4C.1}$, $R^{4C.2}$, and $R^{4C.3}$, respectively.

[0328] In embodiments, when R^{4D} is substituted, R^{4D} is substituted with one or more first substituent groups denoted by $R^{4D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4D.1}$ substituent group is substituted, the $R^{4D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4D.2}$ substituent group is substituted, the $R^{4D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the

above embodiments, R^{4D} , $R^{4D.1}$, $R^{4D.2}$, and $R^{4D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{4D} , $R^{4D.1}$, $R^{4D.2}$, and $R^{4D.3}$, respectively.

[0329] In embodiments, when R^{5A} is substituted, R^{5A} is substituted with one or more first substituent groups denoted by $R^{5A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5A.1}$ substituent group is substituted, the $R^{5A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5A.2}$ substituent group is substituted, the $R^{5A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{5A} , $R^{5A.1}$, $R^{5A.2}$, and $R^{5A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{5A} , $R^{5A.1}$, $R^{5A.2}$, and $R^{5A.3}$, respectively.

[0330] In embodiments, when R^{5B} is substituted, R^{5B} is substituted with one or more first substituent groups denoted by $R^{5B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5B.1}$ substituent group is substituted, the $R^{5B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5B.2}$ substituent group is substituted, the $R^{5B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{5B} , $R^{5B.1}$, $R^{5B.2}$, and $R^{5B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{5B} , $R^{5B.1}$, $R^{5B.2}$, and $R^{5B.3}$, respectively.

[0331] In embodiments, when R^{5C} is substituted, R^{5C} is substituted with one or more first substituent groups denoted by $R^{5C.1}$ as explained in the definitions section above in the

description of “first substituent group(s)”. In embodiments, when an $R^{5C.1}$ substituent group is substituted, the $R^{5C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5C.2}$ substituent group is substituted, the $R^{5C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{5C} , $R^{5C.1}$, $R^{5C.2}$, and $R^{5C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{5C} , $R^{5C.1}$, $R^{5C.2}$, and $R^{5C.3}$, respectively.

[0332] In embodiments, when R^{5B} and R^{5C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{5B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5B.1}$ substituent group is substituted, the $R^{5B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5B.2}$ substituent group is substituted, the $R^{5B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{5B.1}$, $R^{5B.2}$, and $R^{5B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{5B.1}$, $R^{5B.2}$, and $R^{5B.3}$, respectively.

[0333] In embodiments, when R^{5B} and R^{5C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{5C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5C.1}$ substituent group is substituted, the $R^{5C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5C.2}$ as

explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5C.2}$ substituent group is substituted, the $R^{5C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{5C.1}$, $R^{5C.2}$, and $R^{5C.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{5C.1}$, $R^{5C.2}$, and $R^{5C.3}$, respectively.

[0334] In embodiments, when R^{5D} is substituted, R^{5D} is substituted with one or more first substituent groups denoted by $R^{5D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5D.1}$ substituent group is substituted, the $R^{5D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5D.2}$ substituent group is substituted, the $R^{5D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{5D} , $R^{5D.1}$, $R^{5D.2}$, and $R^{5D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{5D} , $R^{5D.1}$, $R^{5D.2}$, and $R^{5D.3}$, respectively.

[0335] In embodiments, when R^{6A} is substituted, R^{6A} is substituted with one or more first substituent groups denoted by $R^{6A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6A.1}$ substituent group is substituted, the $R^{6A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6A.2}$ substituent group is substituted, the $R^{6A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{6A} , $R^{6A.1}$, $R^{6A.2}$, and $R^{6A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the

description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{6A} , $R^{6A.1}$, $R^{6A.2}$, and $R^{6A.3}$, respectively.

[0336] In embodiments, when R^{6B} is substituted, R^{6B} is substituted with one or more first substituent groups denoted by $R^{6B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6B.1}$ substituent group is substituted, the $R^{6B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6B.2}$ substituent group is substituted, the $R^{6B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{6B} , $R^{6B.1}$, $R^{6B.2}$, and $R^{6B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{6B} , $R^{6B.1}$, $R^{6B.2}$, and $R^{6B.3}$, respectively.

[0337] In embodiments, when R^{6C} is substituted, R^{6C} is substituted with one or more first substituent groups denoted by $R^{6C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6C.1}$ substituent group is substituted, the $R^{6C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6C.2}$ substituent group is substituted, the $R^{6C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{6C} , $R^{6C.1}$, $R^{6C.2}$, and $R^{6C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{6C} , $R^{6C.1}$, $R^{6C.2}$, and $R^{6C.3}$, respectively.

[0338] In embodiments, when R^{6B} and R^{6C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{6B.1}$ as explained in the definitions section above in the description of “first

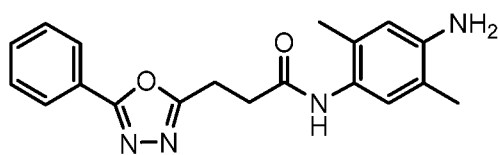
substituent group(s)". In embodiments, when an $R^{6B.1}$ substituent group is substituted, the $R^{6B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6B.2}$ as explained in the definitions section above in the description of "first substituent group(s)". In embodiments, when an $R^{6B.2}$ substituent group is substituted, the $R^{6B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6B.3}$ as explained in the definitions section above in the description of "first substituent group(s)". In the above embodiments, $R^{6B.1}$, $R^{6B.2}$, and $R^{6B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of "first substituent group(s)", wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{6B.1}$, $R^{6B.2}$, and $R^{6B.3}$, respectively.

[0339] In embodiments, when R^{6B} and R^{6C} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{6C.1}$ as explained in the definitions section above in the description of "first substituent group(s)". In embodiments, when an $R^{6C.1}$ substituent group is substituted, the $R^{6C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6C.2}$ as explained in the definitions section above in the description of "first substituent group(s)". In embodiments, when an $R^{6C.2}$ substituent group is substituted, the $R^{6C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6C.3}$ as explained in the definitions section above in the description of "first substituent group(s)". In the above embodiments, $R^{6C.1}$, $R^{6C.2}$, and $R^{6C.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of "first substituent group(s)", wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{6C.1}$, $R^{6C.2}$, and $R^{6C.3}$, respectively.

[0340] In embodiments, when R^{6D} is substituted, R^{6D} is substituted with one or more first substituent groups denoted by $R^{6D.1}$ as explained in the definitions section above in the description of "first substituent group(s)". In embodiments, when an $R^{6D.1}$ substituent group is substituted, the $R^{6D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6D.2}$ as explained in the definitions section above in the description of "first substituent group(s)". In embodiments, when an $R^{6D.2}$ substituent group is substituted, the $R^{6D.2}$

substituent group is substituted with one or more third substituent groups denoted by $R^{6D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{6D} , $R^{6D.1}$, $R^{6D.2}$, and $R^{6D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{6D} , $R^{6D.1}$, $R^{6D.2}$, and $R^{6D.3}$, respectively.

[0341] In embodiments, the compound is:



[0342] In embodiments, the compound is useful as a comparator compound. In embodiments, the comparator compound can be used to assess the activity of a test compound as set forth in an assay described herein (e.g., in the examples section, figures, or tables).

[0343] In embodiments, the compound is a compound as described herein, including in embodiments. In embodiments the compound is a compound described herein (e.g., in the examples section, figures, tables, or claims).

III. Pharmaceutical compositions

[0344] In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, e.g., structural Formula (I) and a pharmaceutically acceptable excipient.

[0345] The compounds as described herein of the present disclosure may be in the form of compositions suitable for administration to a subject. In general, such compositions are “pharmaceutical compositions” comprising a compound (e.g., compounds described herein) and one or more pharmaceutically acceptable or physiologically acceptable excipients (e.g., acceptable diluents or carriers). In certain embodiments, the compounds are present in a therapeutically effective amount. The pharmaceutical compositions may be used in the methods of the present disclosure; thus, for example, the pharmaceutical compositions can be

administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic and prophylactic methods and uses described herein.

[0346] The pharmaceutical compositions of the present disclosure can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein.

[0347] The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of MDA-9/Syntenin, or a compound described herein) may be in a form suitable for parenteral use, for example, in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor® EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

[0348] Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound (e.g., MDA-9/Syntenin inhibitor) disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

[0349] The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of MDA-9/Syntenin, or a compound described herein) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture thereof. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[0350] The tablets, capsules and the like suitable for oral administration may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by techniques known in the art to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinylacetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide/glycolide copolymers, polylactide/glycolide copolymers, or ethylenevinylacetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethylcellulose or gelatin-microcapsules or poly(methylmethacrylate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nano-capsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations will be apparent to those skilled in the art.

[0351] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active

ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0352] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., polyoxy-ethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptadecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

[0353] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

[0354] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, and optionally one or more suspending agents and/or preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

[0355] The pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

[0356] The pharmaceutical compositions typically comprise a therapeutically effective amount of a compound described herein contemplated by the present disclosure and one or more pharmaceutically and physiologically acceptable formulation agents. Suitable pharmaceutically acceptable or physiologically acceptable diluents, carriers or excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate-buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer; N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES); 2-(N-Morpholino)ethanesulfonic acid (MES); 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES); 3-(N-Morpholino)propanesulfonic acid (MOPS); and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

[0357] After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

[0358] Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time-

delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a Wnt/catenin signaling pathway inhibitor, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

[0359] Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release a compound disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

[0360] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor[®] EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium; for this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids, such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

[0361] The present disclosure contemplates the administration of the compounds described herein in the form of suppositories for rectal administration. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

[0362] The compounds described herein contemplated by the present disclosure may be in the form of any other suitable pharmaceutical composition (e.g., sprays for nasal or inhalation use) currently known or developed in the future.

IV. Methods of use

[0363] In an aspect, there is provided a method of inhibiting MDA-9/Syntenin protein activity, said method comprising contacting the MDA-9/Syntenin protein with the compound described herein, including embodiments (e.g., structural Formula (I), or a pharmaceutically acceptable salt thereof).

[0364] In an aspect, there is provided a method of treating an MDA-9/Syntenin modulated disease or disorder, including administering to a patient in need thereof a therapeutically effective amount of a compound or pharmaceutical composition as described herein, including embodiments (e.g., structural Formula (I) or a pharmaceutically acceptable salt thereof).

[0365] In an aspect, there is provided a method of treating cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of the compound described herein, including embodiments (e.g., structural Formula (I), or a pharmaceutically acceptable salt thereof). In embodiments, the cancer is associated with increased MDA-9/Syntenin gene expression.

[0366] In accordance with the present disclosure, a compound (e.g., a compound described herein) or pharmaceutical salt thereof can be used to treat or prevent a proliferative condition or disorder, including a cancer, for example, brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, medulloblastoma, melanoma, cervical cancer, gastric cancer, ovarian cancer, lung cancer, cancer of the head, oral cancer, Hodgkin's Disease, and Non-Hodgkin's Lymphomas. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, mouth, liver, kidney, lung, ovary, pancreas, rectum, stomach, and uterus. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, hepatocellular carcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, oral squamous cell carcinoma, breast invasive carcinoma, lung

adenocarcinoma, lung squamous cell carcinoma, non-small cell lung carcinoma, mesothelioma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, metastatic tumors in the brain from other organ sites, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer. The present disclosure also provides methods of treating or preventing other cancer-related diseases, disorders or conditions, including, for example, immunogenic tumors, non-immunogenic tumors, dormant tumors, virus-induced cancers (e.g., epithelial cell cancers, endothelial cell cancers, squamous cell carcinomas and papillomavirus), adenocarcinomas, lymphomas, carcinomas, melanomas, leukemias, myelomas, sarcomas, teratocarcinomas, chemically-induced cancers, metastasis, and angiogenesis. The disclosure contemplates reducing tolerance to a tumor cell or cancer cell antigen, e.g., by modulating activity of a regulatory T-cell and/or a CD8+ T-cell (see, e.g., Ramirez-Montagut, et al. (2003) *Oncogene* 22:3180-87; and Sawaya, et al. (2003) *New Engl. J. Med.* 349:1501-09). In some embodiments, the tumor or cancer is breast cancer, ovarian cancer, colon adenocarcinoma, lung adenocarcinoma, lung small cell carcinoma, pancreatic adenocarcinoma, pancreatic neuroendocrine tumors, glioblastoma, prostate cancer, hepatocellular carcinoma, myeloma, leukemia, and lymphoma. The use of the term(s) cancer-related diseases, disorders and conditions is meant to refer broadly to conditions that are associated, directly or indirectly, with cancer, and includes, e.g., angiogenesis and precancerous conditions such as dysplasia. In embodiments, the cancer is breast cancer, ovarian cancer, colon adenocarcinoma, lung adenocarcinoma, lung small cell carcinoma, pancreatic adenocarcinoma, pancreatic neuroendocrine tumors, glioblastoma, prostate cancer, hepatocellular carcinoma, myeloma, leukemia, and lymphoma.

[0367] In embodiments, a cancer can be metastatic or at risk of becoming metastatic, or may occur in a diffuse tissue, including cancers of the blood or bone marrow (e.g., leukemia). In some further embodiments, the compounds of the disclosure can be used to overcome T-cell tolerance.

[0368] In embodiments, the cancer is breast cancer, hepatocellular carcinoma (HCC), head and neck squamous cell carcinoma (HNSCC), oral squamous cell carcinoma (OSCC), melanoma, brain cancer, glioblastoma, head and neck cancer, urothelial cancer, uveal melanoma, gastric cancer, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, or neuroblastoma.

[0369] In some embodiments, the present disclosure provides methods for treating a proliferative condition, cancer, tumor, or precancerous condition with a compound described herein and at least one additional therapeutic or diagnostic agent, examples of which are set forth elsewhere herein.

[0370] In embodiments, an additional therapeutic agent is an anti-cancer agent. In embodiments, the anti-cancer agent is a mitotic inhibitor or a histone deacetylase (HDAC) inhibitor. In embodiments, the anti-cancer agent is a mitotic inhibitor. In embodiments, the anti-cancer agent is a histone deacetylase (HDAC) inhibitor.

[0371] In embodiments drawn to methods of treating cancer, the administration of a therapeutically effective amount of a compound described herein results in a cancer survival rate greater than the cancer survival rate observed by not administering a therapeutically effective amount of the compound. In further embodiments drawn to methods of treating cancer, the administration of a therapeutically effective amount of a compound described herein results in a reduction of tumor size or a slowing of tumor growth greater than reduction of tumor size or tumor growth observed following lack of administration of a therapeutically effective amount of the compound.

[0372] In an aspect, there is provided a method of preventing metastasis of cancer cells in a subject in need thereof, said method comprising administering to said subject an effective amount of the compound or pharmaceutical composition as described herein, including embodiments (e.g., structural Formula (I) or a pharmaceutically acceptable salt thereof). In embodiments, the cancer cells are associated with increased MDA-9/Syntenin gene expression.

[0373] In embodiments, the cancer cells are breast cancer, hepatocellular carcinoma (HCC) cancer, head and neck squamous cell carcinoma (HNSCC) cancer, oral squamous cell carcinoma (OSCC), melanoma, brain cancer, glioblastoma, head and neck cancer, urothelial cancer, uveal

melanoma, gastric cancer, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, or neuroblastoma cells.

[0374] In embodiments, the present disclosure provides methods for preventing metastasis of cancer cells in a subject with a compound described herein and at least one additional therapeutic or diagnostic agent, examples of which are set forth elsewhere herein.

[0375] In embodiments, an additional therapeutic agent is an anti-cancer agent. In embodiments, the anti-cancer agent is a multi-kinase inhibitor.

[0376] In embodiments, a multi-kinase inhibitor is selected from, but not limited to, fasudil, sirolimus (rapamune), imatinib, gefitinib, erlotinib, sorafenib, sunitinib, dasatinib, lapatinib, nilotinib, temsirolimus, everofimus, pazopanib, ruxolitinib, vandetanib, vemurafenib, crizotinib, icotinib, axitinib, tofacitinib, bosutinib, cabozantinib, ponatinib, regorafenib, afatinib, dabrafenib, trametinib, ibrutinib, nintedanib, idelalisib, ceritinib, apatinib, rivoceranib, ripasudil, alectinib, cobimetinib, lenvatinib, palbociclib, radotinib, osimertinib, olmutinib, teratinib, ribociclib, copanlisib, abemaciclib, acalabrutinib, midostaurin, brigatinib, baricitinib, netardusil, tivozanib, simotinib, fostamatinib, encorafenib, binimetinib, catequentinib, duvelisib, dacomitinib, lortatinib, lacotrectinib, gilteritinib, pyrotinib, fruquintinib, erdafitinib, alpelisib, umbralisib, leniolisib, pexidartinib, entrectinib, upadacitinib, fedratinib, zanubrutinib, flumatinib, peficitinib, delgocitinib, avapritinib, selumetinib, tucatinib, pemigatinib, capmatinib (tabrecta), selpercatinib, ripretinib, tirabrutinib, almonertinib, pralsetinib, filgotinib, tirbanbulin, orelabrutinib, tepotinib, and trilacidib.

[0377] In embodiments, a method of treating cancer comprises administering to a subject in need thereof a therapeutically effective amount of IVMT-Rx-4 and a multi-kinase inhibitor. In embodiments, the multi-kinase inhibitor is sorafenib. In embodiments, the multi-kinase inhibitor is regorafenib. In embodiments, a method of treating cancer comprises administering to a subject in need thereof a therapeutically effective amount of IVMT-Rx-4 and sorafenib. In embodiments, a method of treating cancer comprises administering to a subject in need thereof a therapeutically effective amount of IVMT-Rx-4 and regorafenib.

[0378] The present disclosure contemplates the administration of the compounds described herein, and compositions (e.g., pharmaceutical salts, pharmaceutical composition) thereof, in any

appropriate manner. Suitable routes of administration include oral, parenteral (e.g., intramuscular, intravenous, subcutaneous (e.g., injection or implant), intraperitoneal, intracisternal, intraarticular, intraperitoneal, intracerebral (intraparenchymal) and intracerebroventricular), nasal, vaginal, sublingual, intraocular, rectal, topical (e.g., transdermal), buccal and inhalation. Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compounds disclosed herein over a defined period of time. In embodiments, the administration is parenteral administration.

[0379] The compounds of the present disclosure may be administered to a subject in an amount that is dependent upon, for example, the goal of administration (e.g., the degree of resolution desired); the age, weight, sex, and health and physical condition of the subject to which the formulation is being administered; the route of administration; and the nature of the disease, disorder, condition or symptom thereof. The dosing regimen may also take into consideration the existence, nature, and extent of any adverse effects associated with the agent(s) being administered. Effective dosage amounts and dosage regimens can readily be determined from, for example, safety and dose-escalation trials, *in vivo* studies (e.g., animal models), and other methods known to the skilled artisan.

[0380] In general, dosing parameters dictate that the dosage amount be less than an amount that could be irreversibly toxic to the subject (the maximum tolerated dose (MTD)) and not less than an amount required to produce a measurable effect on the subject. Such amounts are determined by, for example, the pharmacokinetic and pharmacodynamic parameters associated with ADME, taking into consideration the route of administration and other factors.

[0381] An effective dose (ED) is the dose or amount of an agent that produces a therapeutic response or desired effect in some fraction of the subjects taking it. The “median effective dose” or ED₅₀ of an agent is the dose or amount of an agent that produces a therapeutic response or desired effect in 50% of the population to which it is administered. Although the ED₅₀ is commonly used as a measure of reasonable expectance of an agent’s effect, it is not necessarily the dose that a clinician might deem appropriate taking into consideration all relevant factors. Thus, in some situations the effective amount is more than the calculated ED₅₀, in other situations the effective amount is less than the calculated ED₅₀, and in still other situations the effective amount is the same as the calculated ED₅₀.

[0382] In addition, an effective dose of the compounds of the present disclosure may be an amount that, when administered in one or more doses to a subject, produces a desired result relative to a healthy subject. For example, for a subject experiencing a particular disorder, an effective dose may be one that improves a diagnostic parameter, measure, marker and the like of that disorder by at least about 5%, at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or more than 90%, where 100% is defined as the diagnostic parameter, measure, marker and the like exhibited by a normal subject.

[0383] In embodiments, the compounds contemplated by the present disclosure may be administered (e.g., intravenously) at dosage levels of about 0.01 mg/kg to about 50 mg/kg, or about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one, two, three, four or more times a day, to obtain the desired therapeutic effect. For administration of a parenteral (intravenous) agent, the compositions can be provided in the form of solutions, suspensions, and/or emulsions, for example water or water/propylene glycol solutions. In embodiments, pharmaceutical compositions are injectable, sterile solutions, which can be oily or aqueous solutions, suspensions, or emulsions. In embodiments, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-block polymers, and the like.

[0384] In embodiments, the dosage of the desired compound is contained in a “unit dosage form”, e.g., ampoules. The phrase “unit dosage form” refers to physically discrete units, each unit including a predetermined amount of a compound (e.g., a compound described herein), sufficient to produce the desired effect. It will be appreciated that the parameters of a unit dosage form will depend on the particular agent and the effect to be achieved.

V. KITS

[0385] In another aspect, provided herein is a kit including a compound described herein or pharmaceutical compositions thereof. The kits are generally in the form of a physical structure housing various components, as described below, and may be utilized, for example, in practicing the methods described above.

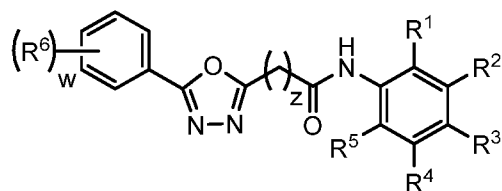
[0386] A kit may include one or more of the compounds disclosed herein (e.g., provided in a sterile container), which may be in the form of a pharmaceutical composition suitable for administration to a subject. In embodiments, the compound has the structure of Formula (I), or a pharmaceutically acceptable salt thereof. The compounds described herein can be provided in a form that is ready for use (e.g., a tablet or capsule) or in a form requiring, for example, reconstitution or dilution (e.g., a powder) prior to administration. When the compound is in a form that needs to be reconstituted or diluted by a user, the kit may also include diluents (e.g., sterile water), buffers, pharmaceutically acceptable excipients, and the like, packaged with, or separately from, the compound. Each component of the kit may be enclosed within an individual container, and all of the various containers may be within a single package. A kit of the present disclosure may be designed for conditions necessary to properly maintain the components housed therein (e.g., refrigeration or freezing).

[0387] A kit may contain a label or packaging insert including identifying information for the components therein and instructions for their use (e.g., dosing parameters, clinical pharmacology of the active ingredient(s), including mechanism of action, pharmacokinetics and pharmacodynamics, adverse effects, contraindications, etc.). Labels or inserts can include manufacturer information such as lot numbers and expiration dates. The label or packaging insert may be, e.g., integrated into the physical structure housing the components, contained separately within the physical structure, or affixed to a component of the kit (e.g., an ampule, tube or vial).

[0388] Labels or inserts can additionally include, or be incorporated into, a computer readable medium, such as a disk (e.g., hard disk, card, memory disk), optical disk such as CD- or DVD-ROM/RAM, DVD, MP3, magnetic tape, or an electrical storage media such as RAM and ROM or hybrids of these such as magnetic/optical storage media, FLASH media or memory-type cards. In some embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g., via the internet, are provided.

NUMBERED EMBODIMENTS

[0389] Embodiment 1. A compound having a structure of formula (I):



(I), or a pharmaceutically acceptable salt thereof,

wherein:

z is an integer from 0 to 8;

w is an integer from 0 to 5;

R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, $-CN$, $-N_3$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHN R^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHN R^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, $-OCH_2X^{1.1}$, 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^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-N_3$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHN R^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHN R^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, $-OCH_2X^{2.1}$, 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 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-N_3$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NH_2$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NH_2$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, $-OCH_2X^{3.1}$, 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^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, $-CN$, $-N_3$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, $-OCH_2X^{4.1}$, 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^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, $-CN$, $-N_3$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHN R^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHN R^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, $-OCH_2X^{5.1}$, 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^6 is independently halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-CN$, $-N_3$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHN R^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHN R^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, $-OCH_2X^{6.1}$, 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; two adjacent R^6 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, 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^{1B} and R^{1C} , R^{2B} and R^{2C} , R^{3B} and R^{3C} , R^{4B} and R^{4C} , R^{5B} and R^{5C} , and R^{6B} and R^{6C} , substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

$X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$, $X^{5.1}$, and $X^{6.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$;

n_1 , n_2 , n_3 , n_4 , n_5 , and n_6 are independently an integer from 0 to 4; and

m_1 , m_2 , m_3 , m_4 , m_5 , m_6 , v_1 , v_2 , v_3 , v_4 , v_5 , and v_6 are independently 1 or 2.

[0390] Embodiment 2. The compound of embodiment 1, wherein R^1 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-NH_2$, unsubstituted alkyl or unsubstituted heteroalkyl.

[0391] Embodiment 3. The compound of embodiment 1 or 2, wherein R^1 is hydrogen, $-COOH$, $-NH_2$, unsubstituted C_1 - C_3 alkyl or unsubstituted C_2 - C_4 heteroalkyl.

[0392] Embodiment 4. The compound of any one of embodiments 1 to 3, wherein R^1 is unsubstituted C_1 - C_3 alkyl.

[0393] Embodiment 5. The compound of any one of embodiments 1 to 4, wherein R^1 is methyl.

[0394] Embodiment 6. The compound of any one of embodiments 1 to 5, wherein R^2 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-NH_2$, unsubstituted alkyl or unsubstituted heteroalkyl.

[0395] Embodiment 7. The compound of any one of embodiments 1 to 6, wherein R^2 is hydrogen, $-COOH$, $-NH_2$, unsubstituted C_1 - C_3 alkyl or unsubstituted C_2 - C_4 heteroalkyl.

[0396] Embodiment 8. The compound of any one of embodiments 1 to 7, wherein R^2 is hydrogen.

[0397] Embodiment 9. The compound of any one of embodiments 1 to 8, wherein R^3 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-NH_2$, unsubstituted alkyl or unsubstituted heteroalkyl.

[0398] Embodiment 10. The compound of any one of embodiments 1 to 9, wherein R^3 is hydrogen, $-COOH$, $-NH_2$, unsubstituted C_1 - C_3 alkyl or unsubstituted C_2 - C_4 heteroalkyl.

[0399] Embodiment 11. The compound of any one of embodiments 1 to 10, wherein R^3 is $-NH_2$.

[0400] Embodiment 12. The compound of any one of embodiments 1 to 11, wherein R^4 is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-NH_2$, unsubstituted alkyl or unsubstituted heteroalkyl.

[0401] Embodiment 13. The compound of any one of embodiments 1 to 12, wherein R^4 is hydrogen, $-COOH$, $-NH_2$, unsubstituted C_1 - C_3 alkyl or unsubstituted C_2 - C_4 heteroalkyl.

[0402] Embodiment 14. The compound of any one of embodiments 1 to 13, wherein R⁴ is unsubstituted C₁-C₃ alkyl.

[0403] Embodiment 15. The compound of any one of embodiments 1 to 14, wherein R⁴ is methyl.

[0404] Embodiment 16. The compound of any one of embodiments 1 to 15, wherein R⁵ is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -NH₂, unsubstituted alkyl or unsubstituted heteroalkyl.

[0405] Embodiment 17. The compound of any one of embodiments 1 to 16, wherein R⁵ is hydrogen, -COOH, -NH₂, unsubstituted C₁-C₃ alkyl or unsubstituted C₂-C₄ heteroalkyl.

[0406] Embodiment 18. The compound of any one of embodiments 1 to 17, wherein R⁵ is hydrogen.

[0407] Embodiment 19. The compound of any one of embodiments 1 to 18, wherein R⁶ is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -NH₂, unsubstituted alkyl or unsubstituted heteroalkyl.

[0408] Embodiment 20. The compound of any one of embodiments 1 to 19, wherein R⁶ is hydrogen, -COOH, -NH₂, unsubstituted C₁-C₃ alkyl or unsubstituted C₂-C₄ heteroalkyl.

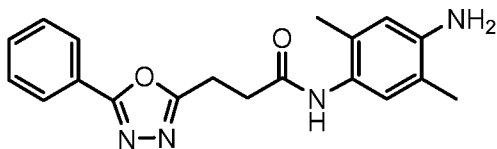
[0409] Embodiment 21. The compound of any one of embodiments 1 to 20, wherein z is an integer from 1 to 4.

[0410] Embodiment 22. The compound of embodiment 21, wherein z is 2.

[0411] Embodiment 23. The compound of any one of embodiments 1 to 22, wherein w is an integer from 0 to 2.

[0412] Embodiment 24. The compound of embodiment 23, wherein w is 0.

[0413] Embodiment 25. The compound of any one of embodiments 1 to 24, wherein the compound is:



[0414] Embodiment 26. A pharmaceutical composition comprising a compound of any one of embodiments 1 to 25 and a pharmaceutically acceptable excipient.

[0415] Embodiment 27. A method of inhibiting MDA-9/Syntenin protein activity, said method comprising contacting the MDA-9/Syntenin protein with the compound of any one of embodiments 1 to 25.

[0416] Embodiment 28. A method of treating cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of the compound of any one of embodiments 1 to 25.

[0417] Embodiment 29. The method of embodiment 28, wherein said cancer is associated with increased MDA-9/Syntenin gene expression.

[0418] Embodiment 30. The method of embodiment 28 or 29, wherein said cancer is breast cancer, hepatocellular carcinoma (HCC), head and neck squamous cell carcinoma (HNSCC), melanoma, brain cancer, glioblastoma, head and neck cancer, urothelial cancer, uveal melanoma, gastric cancer, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, or neuroblastoma.

[0419] Embodiment 31. The method of any one of embodiments 28-30, further comprising administering to said subject an anti-cancer agent, wherein the anti-cancer agent is a multi-kinase inhibitor.

[0420] Embodiment 32. The method of any one of embodiments 28-31, wherein the multi-kinase inhibitor is sorafenib.

[0421] Embodiment 33. The method of embodiment 32, wherein the cancer is hepatocellular carcinoma.

[0422] Embodiment 34. A method of preventing metastasis of cancer cells in a subject in need thereof, said method comprising administering to said subject an effective amount of the compound of any one of embodiments 1 to 25.

[0423] Embodiment 35. The method of embodiment 34, wherein said cancer cells are associated with increased MDA-9/Syntenin gene expression.

[0424] Embodiment 36. The method of embodiment 34 or 35, wherein said cancer cells are breast cancer, hepatocellular carcinoma (HCC) cancer, head and neck squamous cell carcinoma (HNSCC) cancer, melanoma, brain cancer, glioblastoma, head and neck cancer, urothelial cancer, uveal melanoma, gastric cancer, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, or neuroblastoma cells.

[0425] Embodiment 37. The method of any one of embodiments 34-36, further comprising administering to said subject an anti-cancer agent, wherein the anti-cancer agent is a multi-kinase inhibitor.

[0426] Embodiment 38. The method of embodiment 37, wherein the multi-kinase inhibitor is sorafenib.

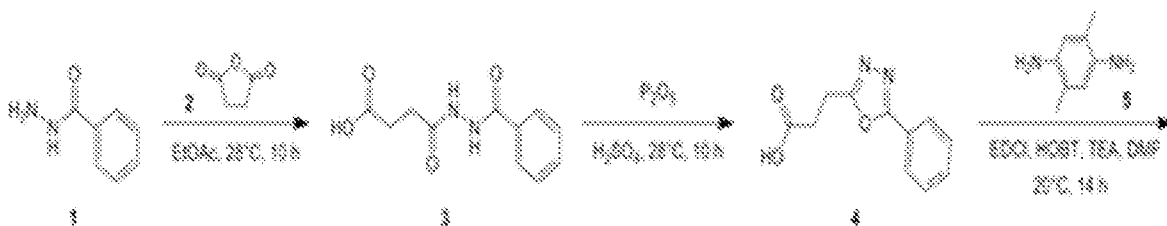
[0427] Embodiment 39. The method of any one of embodiments 28-30, further comprising administering to said subject an anti-cancer agent, wherein the anti-cancer agent is gemcitabine.

[0428] Embodiment 40. The method of any one of embodiments 34-36, further comprising administering to said subject an anti-cancer agent, wherein the anti-cancer agent is gemcitabine.

EXAMPLES

Example 1. Synthesis scheme for IVMT-Rx-4

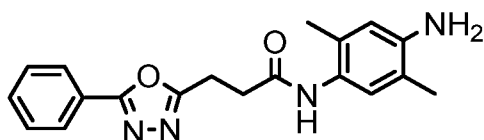
[0429]



Step 1: 92.2% yield

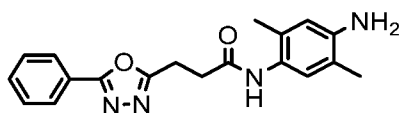
Step 2: 66.8% yield

Step 3: 63.4% yield



IVMT-Rx-4 (compound of formula (I))

[0430] The compound of formula (I) has the following chemical structure:



Example 2. Comparative ADME analysis of IVMT-Rx-4 vs PDZ1i

[0431] The data are presented in Tables 1 and 2.

[0432] Table 1.

Tier 1 ADME Assays <i>IVMT-Rx-4</i> vs. <i>PDZ1i</i>		
Assay	<i>IVMT-Rx-4</i>	<i>PDZ1i</i>
Thermodynamic solubility in PBS, pH 7.4	~160**	10
Log D by shake flask (pH 7.4)	1.49**	0.5
Plasma protein binding by equilibrium dialysis or ultrafiltration (human only)	5.62% free**	0.1% free
Caco-2 Bidirectional	A-B: 21.5×10^6 cm/s B-A: 19.9×10^6 cm/s Efflux 0.92**	A-B: 0.04×10^6 cm/s B-A: 11.5×10^6 cm/s Efflux 300
Stability in liver microsomes (human, monkey, dog, rat, mouse) with both NADPH and UDPGA added	Minimal degradation: >3.5 hr t _{1/2} in all species	Minimal degradation: >4 hr t _{1/2} in all species
Drug-substrate based CYP Inhibition (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4_M, 3A4_T)	2E1 (~8 μ M); 3A4 (~10 μ M), minimal (>10 μ M) with others	2C8 (~2 μ M) > 2E1 (~8 μ M), minimal (>10 μ M) with others
Time Dependent Inhibition (TDI), CYP4A only	No TDI	No TDI
PXR assay	No induction	No induction
hERG assay by manual patch-clamp system (n=3)	>30 μ M	>30 μ M
Mini-Ames Assay (2-strain option: TA98 & TA100)	Weakly positive for 2 strains	Negative

Table 2.

Comparison of “PDZ1i” and “IVMT-Rx-4” Mouse PK

	PDZ1i				IVMT-Rx-4			
	Q	PO	IP	SC	Q	PO	IP	SC
Dose (mpk)	3	10	10	10	3	10	10	10
CL (mL/min/kg)	~0.182	—	—	—	98.5±8.62	—	—	—
V _d (L/kg)	~0.177	—	—	—	1.75±0.272	—	—	—
C _{max} (µg/mL)	—	1.18±0.181	65.7±5.99	64.5±3.56	—	1.02±0.0546	2.05±0.351	1.01±0.210
T _{max} (hr)	—	2 (1-8)	1 (1-1)	1 (1-1)	—	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.5 (0.5-0.5)
AUC _{0-24hr} (µg hr/kg)	~208	19.0±5.31	588±75.6	647±41.5	0.510±0.0469	0.974	1.19	1.35
t _{1/2} (hr)	~13.1	~15.7	~10.5	~12.7	0.452±0.173	1.37	1.02	0.696
F (%)	—	2.74 ± 0.766	81.2 ± 16.9	93.2 ± 5.99	—	57.2	69.3	79.2

Formulation: PEG400/DMSO/10% HP-β-CD(10/5/85) for all groups

Very low systemic clearance for PDZ1i; high (with blood flow) for IVMT-Rx-4

Very low volume of distribution for PDZ1i; somewhat higher (still low) for IVMT-Rx-4

Long half-life for PDZ1i (10-15 hr); very short (~0.5 hr after IV) for IVMT-Rx-4

Very low bioavailability from PO (<3%) for PDZ1i – consistent low permeability in Caco-2 cells; higher (57.2%) for IVMT-Rx-4

Good bioavailability from IP (~80%) and SC (~90%) for PDZ1i; also good for IVMT-Rx-4 (70-80%) but exposures of IVMT-Rx-4 are much lower

[0433] A synthesis product of IVMT-Rx-1 (PDZ1i) compound of formula (I) unexpectedly demonstrated better solubility than IVMT-Rx-1 (PDZ1i) and has ADME traits superior to IVMT-Rx-1, *e.g.*, no efflux. Its synthesis is simpler than IVMT-Rx-1 (PDZ1i). The other synthesis component of PDZ1i, referred to as compound 7 in the synthesis scheme of IVMT-Rx-1, is insoluble and devoid of testable anti-invasion or anti-metastatic functions.

Example 3. The compound of formula (I) effectively inhibits breast cancer lung metastasis

[0434] The anti-invasive properties of the compound of formula (I) in breast cancer have been scrutinized using a combination of *in vitro* assays and animal modeling. Using mouse 4T1 cells, triple negative murine breast cancer cell line (Das *et al. Proc Natl Acad Sci USA*, in press, 2021),

the compound of formula (I) reduced invasion (**FIG. 2A**). *In vivo* in syngeneic BALB/c mice, the compound of formula (I) significantly reduced tumor burden in the lungs using a 4T1-*Luc* experimental metastasis model (**FIGS. 2B and 2C**).

Example 4. Combinatorial Therapies Utilizing the Compound of Formula (I) for Effective Treatment of hepatocellular carcinoma.

[0435] In clinic the compound of formula (I) will be used in combination with existing therapies. The anti-tumor efficacy of the compound of formula (I) was tested with a second therapeutic modality in context of hepatocellular carcinoma (HCC). The mortality rate of HCC parallels that of incidence since HCC is notoriously resistant to standard radio therapy and chemotherapy (Llovet JM *et al.*, *Lancet* 362(9399):1907-1917, 2003; Chidambaranathan-Reghupaty S *et al. Adv Cancer Res.* 149:1-61, 2021). MDA-9/Syntenin overexpression occurs in a significant percentage of human HCC patients (**FIGS. 3A-3D and 4**). Forced expression of MDA-9/ Syntenin in poorly invasive human HCC cells increases while knockdown of MDA-9/Syntenin in highly invasive human HCC cells decreases Matrigel invasion (**FIG.4**), confirming a key role of MDA-9/syntenin in promoting advanced progression of HCC. The compound of formula (I) (at 25 μ M) concentration significantly (~70%) inhibited Matrigel invasion of QGY-7703 cells (**FIGS. 5A and 5B**). To explore the anti-tumor activity of the compound of formula (I) in combination with sorafenib, subcutaneous xenografts were established on the flanks of athymic nude mice using QGY-7703 cells. After establishment of the tumors (~100 mm³), the animals were treated with I.P. injections of the compound of formula (I) (30 mg/kg) or sorafenib (25 mg/kg, a dose that is less than what is achieved clinically) or both three times a week for two weeks. The animals were sacrificed one week after the last injection. The compound of formula (I) alone did not induce any changes or a significant reduction in tumor growth. As anticipated, sorafenib reduced tumor growth by ~50% (**FIGS. 6A and 6B**). The combinatorial treatment resulted in profound inhibition in tumor growth (>90%) (**FIGS. 6A and 6B**) strengthening the rationale to translate this into the clinic. Additionally, this data indicates that the compound of formula (I) can lower the dose of sorafenib to obtain enhanced efficacy of this drug against HCC.

Example 5. The compound of formula (I) effectively inhibits invasive growth and metastasis of head and neck squamous cell carcinoma (HNSCC).

[0436] Using *in vitro* assays and a HNSCC orthotopic xenograft model, we have validated that the compound of formula (I) has the ability to strongly suppress tumorigenesis and metastasis of HNSCC. As shown in **FIGS. 7A and 7B**, the compound of formula (I) significantly inhibited Matrigel invasion of two HNSCC cells, UM-SCC-1 and HN6. To explore the anti-tumor activity, a HNSCC orthotopic xenograft model was established. UM-SCC-1 cells (10^6) were directly injected into the tongues of nude mice. Seven days after inoculation, the tumor bearing mice were randomly divided into two groups. The treatment group was intraperitoneally injected with the compound of formula (I) (30mg/kg) 3 times per week and control group was injected with vehicle for 21 days. The mice were sacrificed at the endpoint and the tumor bearing tongues were dissected. The lymph nodes were harvested and assessed in the orthotopic xenograft model. The compound of formula (I) significantly suppressed HNSCC growth *in vivo* (**Fig. 8A & 8B**). In addition, HNSCC lymph node metastases were significantly suppressed by the compound of formula (I) treatment (**Fig. 8C & 8D**).

Example 6. The compound of formula (I) synergistically enhances the anti-proliferative activity of ABT199 (Venetoclax) in Acute Myeloid Leukemia (AML) cells.

[0437] The AML cells were incubated with the compound of formula (I) alone or in combination with ABT199 (50 nM) for 48 hrs. Cell proliferation was measured with the ATP lite assay and results plotted graphically. PDZ1i alone or in combination ABT199 was used for comparison (**FIG. 14A**). The AML cells were treated with the compound of formula (I) alone or in combination with ABT199 for 48 hrs and apoptotic cell death was determined. Fold-changes in comparison with the DMSO-treated group are shown in **FIG. 14B**. * $P < 0.05$ vs. control. MV4-11R2 and MOLM13R2 are resistant variants of MV4-11 and MOLM13, respectively. The results indicate significant synergy when the compound of formula (I) and ABT199 are used in combination.

Example 7. The compound of formula (I) suppresses melanoma metastasis and promotes immune activation.

[0438] C57BL/6 mice were inoculated I.V. with B16 cells (1×10^5) to generate experimental lung metastases. One day after I.V. injection, mice received either 30 mg/kg or less (as indicated)

b.w. of the compound of formula (I), I.P. 3X a week for the first two weeks (total 6 injections). After 14 days, mice were sacrificed and lungs were collected and nodules were counted. Lungs were then analyzed for accumulation of CD8⁺IFN- γ ⁺ cells by FACS. *P < 0.05. The results (**FIGS. 15A-15C**) show significant dose-dependent anti-metastatic activity of the compound of formula (I) and its immune-activation ability.

Example 8. The compound of formula (I) suppresses prostate cancer bone metastasis, enhancing survival.

[0439] PC-3ML-*Luc* cells were injected through the intracardiac route in athymic nude mice. Vehicle or the compound of formula (I) was administered by intraperitoneal injection every alternate day (3 injections per week, total 9 injections). BLI imaging was performed at day 36 to monitor bone metastases. Representative BLI images from each experimental group are presented in **FIG. 16A**. At this time point, 3 out of 5 mice died due to cancer-associated complications in the control group. A Kaplan–Meier survival curve was prepared using GraphPad software and is shown in **FIG. 16B**. The results indicate that the compound of formula (I) enhances survival in animals with prostate cancer bone metastasis.

Example 9. The compound of formula (I) with a SOC therapy (Docetaxel) enhances therapeutic outcomes in animals with prostate cancer bone metastasis.

[0440] Mice received either DMSO (as vehicle control) or drugs (30 mg/Kg body weight and 5 mg/kg body weight of the compound of formula (I) and docetaxel, respectively) either alone or in combination through I.P. injection on every alternate day. In the combination group, the dosages were kept identical as in the “single dose” group. Bone metastases were detected by BLI imaging. *P < 0.05. The results (**FIGS. 17A and 17B**) demonstrate that the combination therapy of the compound of formula (I) and Docetaxel enhances therapeutic outcomes in animals with prostate cancer bone metastasis.

Example 10. The compound of formula (I) inhibits pancreatic ductal adenocarcinoma (PDAC) invasion.

[0441] Established PDAC cells were assayed after 24 hr. using trans-well invasion assays in the presence or absence of IVMT-Rx-4 (25 μ M). The results are shown in **FIGS. 9A and 9B** and demonstrate an anti-cancer activity of the compound of formula (I). *P<0.05 vs. control.

Example 11. The compound of formula (I) enhances apoptosis inducing activity of Chemotherapeutic(s) and 5-FU and Gemcitabine-mediated proliferation suppression in PDAC organoids.

[0442] Pancreatic cancer cells were treated with the compound of formula (I) (25 μ M) for 24 hours, and then treated with either 5-FU or Gemcitabine for an additional 48 hours. Cells were then collected, and Western blotting analysis was done for PARP, a molecular index for apoptosis induction (**FIG. 10A**). The *P<0.05 vs. control. Pancreatic cancer cells combined with stromal cells were plated in low attachment 96-well plates and allowed to grow for 2 weeks. Once the organoids were formed, organoids were treated with the compound of formula (I) (25- μ M) for 24 hours. These cells were again treated with either with 5 μ M 5-FU or with 5 μ M Gemcitabine for an additional 72 hours. MTS assay was performed, and results are presented in **FIG. 10B**. The effects of the compound of formula (I) on 5-FU and Gemcitabine-mediated proliferation suppression in PDAC organoids are shown in **FIG. 11A** (photo) and **FIG. 11B** (graph).

Example 12. The compound of formula (I) inhibits MDA-9/EphA2 interaction and downregulates MDA-9 signaling in PDAC cell lines.

[0443] Human (AsPC-1) and murine (KPC) pancreatic cancer cells were cultured for 24 hours (with 60-70% confluency) and were treated overnight with 25 μ M of the compound of formula (I). Cells were then collected and cell lysates were made. Equal amount of cell lysates was immunoprecipitated with MDA-9 antibody or subjected to Western blotting analysis for different MDA-9 downstream molecules. IP samples were subjected to western blot analysis for EphA2 to check the binding of MDA-9/EphA2. The results are shown in **FIG. 12** and **FIG. 13**.

Example 13. The compound of formula (I) synergizes with gemcitabine to induce PDAC cell death.

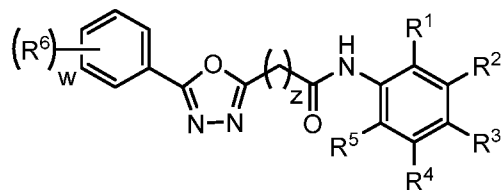
[0444] Significant synergy was observed between the compound of formula (I) and gemcitabine in inducing apoptosis in PDAC PDOs. Treatment with the compound of formula (I) or gemcitabine alone did not significantly change organoid morphology, however, the combination significantly dispersed the organoid structure inducing cell death. The results are shown in **FIG. 20C**.

[0445] The compound of formula (I) is a new potetial PDZ1 domain antagonist with better solubility and lower efflux than IVMT-Rx-1 (PDZ1i). In addition, the synthesis of the compound of formula (I) is simplier than of IVMT-Rx-1. All these characteristics are favorable traits for drug development.

[0446] It is understood that the examples described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A compound having a structure of formula (I):



(I), or a pharmaceutically acceptable salt

thereof, wherein:

z is an integer from 0 to 8;

w is an integer from 0 to 5;

R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, $-CN$, $-N_3$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHN R^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHN R^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, $-OCH_2X^{1.1}$, 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^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-N_3$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHN R^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHN R^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, $-OCH_2X^{2.1}$, 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 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-N_3$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NH_2$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NH_2$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, $-OCH_2X^{3.1}$, 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^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, $-CN$, $-N_3$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, $-OCH_2X^{4.1}$, 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^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, $-CN$, $-N_3$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHN R^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHN R^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, $-OCH_2X^{5.1}$, 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^6 is independently halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-CN$, $-N_3$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHN R^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHN R^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, $-OCH_2X^{6.1}$, 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; two adjacent R^6 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, 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^{1B} and R^{1C} , R^{2B} and R^{2C} , R^{3B} and R^{3C} , R^{4B} and R^{4C} , R^{5B} and R^{5C} , and R^{6B} and R^{6C} , substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

$X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$, $X^{5.1}$, and $X^{6.1}$ are independently $-\text{Cl}$, $-\text{Br}$, $-\text{I}$ or $-\text{F}$;

n_1 , n_2 , n_3 , n_4 , n_5 , and n_6 are independently an integer from 0 to 4; and

m_1 , m_2 , m_3 , m_4 , m_5 , m_6 , v_1 , v_2 , v_3 , v_4 , v_5 , and v_6 are independently 1 or 2.

2. The compound of claim 1, wherein R^1 is hydrogen, halogen, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted alkyl or unsubstituted heteroalkyl.

3. The compound of claim 1, wherein R^1 is hydrogen, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted $\text{C}_1\text{-C}_3$ alkyl or unsubstituted $\text{C}_2\text{-C}_4$ heteroalkyl.

4. The compound of claim 1, wherein R^1 is unsubstituted $\text{C}_1\text{-C}_3$ alkyl.

5. The compound of claim 1, wherein R^1 is methyl.

6. The compound of claim 1, wherein R^2 is hydrogen, halogen, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted alkyl or unsubstituted heteroalkyl.

7. The compound of claim 1, wherein R^2 is hydrogen, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted $\text{C}_1\text{-C}_3$ alkyl or unsubstituted $\text{C}_2\text{-C}_4$ heteroalkyl.

8. The compound of claim 1, wherein R^2 is hydrogen.

9. The compound of claim 1, wherein R^3 is hydrogen, halogen, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted alkyl or unsubstituted heteroalkyl.

10. The compound of claim 1, wherein R^3 is hydrogen, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted $\text{C}_1\text{-C}_3$ alkyl or unsubstituted $\text{C}_2\text{-C}_4$ heteroalkyl.

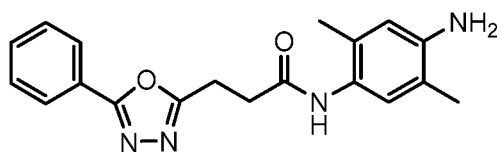
11. The compound of claim 1, wherein R^3 is $-\text{NH}_2$.

12. The compound of claim 1, wherein R^4 is hydrogen, halogen, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted alkyl or unsubstituted heteroalkyl.

13. The compound of claim 1, wherein R^4 is hydrogen, $-\text{COOH}$, $-\text{NH}_2$, unsubstituted $\text{C}_1\text{-C}_3$ alkyl or unsubstituted $\text{C}_2\text{-C}_4$ heteroalkyl.

14. The compound of claim 1, wherein R^4 is unsubstituted $\text{C}_1\text{-C}_3$ alkyl.

15. The compound of claim 1, wherein R⁴ is methyl.
16. The compound of claim 1, wherein R⁵ is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -NH₂, unsubstituted alkyl or unsubstituted heteroalkyl.
17. The compound of claim 1, wherein R⁵ is hydrogen, -COOH, -NH₂, unsubstituted C₁-C₃ alkyl or unsubstituted C₂-C₄ heteroalkyl.
18. The compound of claim 1, wherein R⁵ is hydrogen.
19. The compound of claim 1, wherein R⁶ is independently halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -NH₂, unsubstituted alkyl or unsubstituted heteroalkyl.
20. The compound of claim 1, wherein R⁶ is independently -COOH, -NH₂, unsubstituted C₁-C₃ alkyl or unsubstituted C₂-C₄ heteroalkyl.
21. The compound of claim 1, wherein z is an integer from 1 to 4.
22. The compound of claim 21, wherein z is 2.
23. The compound of claim 1, wherein w is an integer from 0 to 2.
24. The compound of claim 23, wherein w is 0.
25. The compound of claim 1, wherein the compound is:



26. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.
27. A method of inhibiting MDA-9/Syntenin protein activity, said method comprising contacting the MDA-9/Syntenin protein with the compound of claim 1.
28. A method of treating cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of the compound of claim 1.

29. The method of claim 28, wherein said cancer is associated with increased MDA-9/Syntenin gene expression.

30. The method of claim 28, wherein said cancer is breast cancer, hepatocellular carcinoma (HCC), head and neck squamous cell carcinoma (HNSCC), melanoma, brain cancer, glioblastoma, head and neck cancer, oral squamous cell carcinoma, urothelial cancer, uveal melanoma, gastric cancer, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, or neuroblastoma.

31. The method of claim 28, further comprising administering to said subject an anti-cancer agent, wherein the anti-cancer agent is a multi-kinase inhibitor.

32. The method of claim 31, wherein the multi-kinase inhibitor is sorafenib.

33. The method of claim 32, wherein the cancer is hepatocellular carcinoma.

34. A method of preventing metastasis of cancer cells in a subject in need thereof, said method comprising administering to said subject an effective amount of the compound of claim 1.

35. The method of claim 34, wherein said cancer cells are associated with increased MDA-9/Syntenin gene expression.

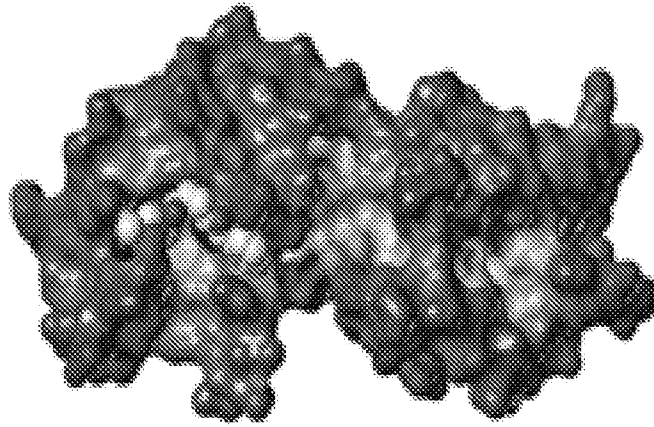
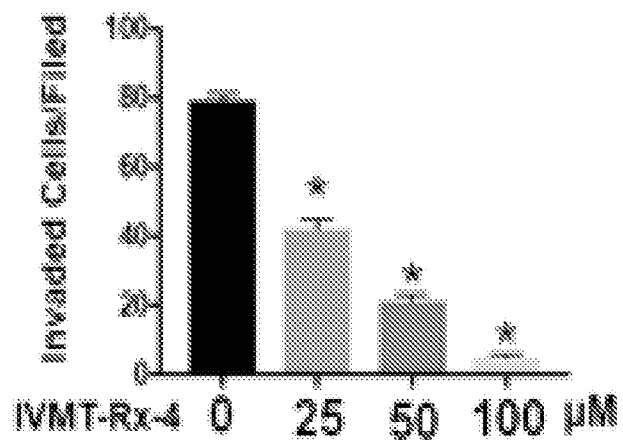
36. The method of claim 34, wherein said cancer cells are breast cancer, hepatocellular carcinoma (HCC) cancer, head and neck squamous cell carcinoma (HNSCC) cancer, oral squamous cell carcinoma, melanoma, brain cancer, glioblastoma, head and neck cancer, urothelial cancer, uveal melanoma, gastric cancer, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, or neuroblastoma cells.

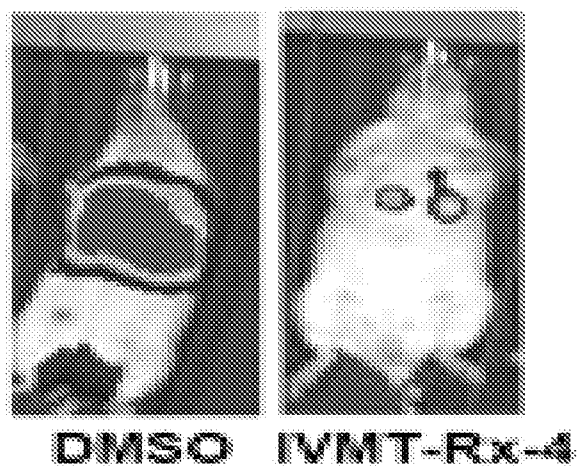
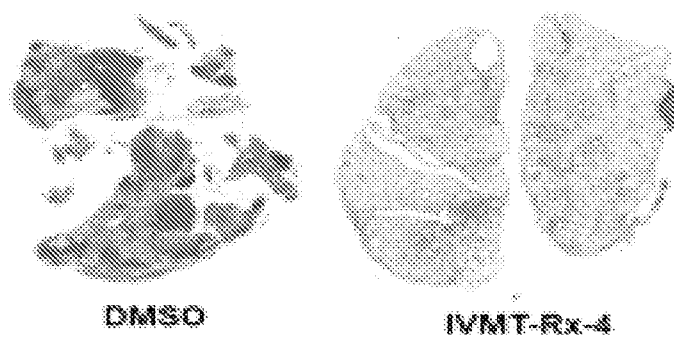
37. The method of claim 34, further comprising administering to said subject an anti-cancer agent, wherein the anti-cancer agent is a multi-kinase inhibitor.

38. The method of claim 37, wherein the multi-kinase inhibitor is sorafenib.

39. The method of claim 28, further comprising administering to said subject an anti-cancer agent, wherein the anti-cancer agent is gemcitabine.

40. The method of claim 34, further comprising administering to said subject an anti-cancer agent, wherein the anti-cancer agent is gemcitabine.

**Fig. 1****Fig. 2A**

**FIG. 2B****FIG. 2C**

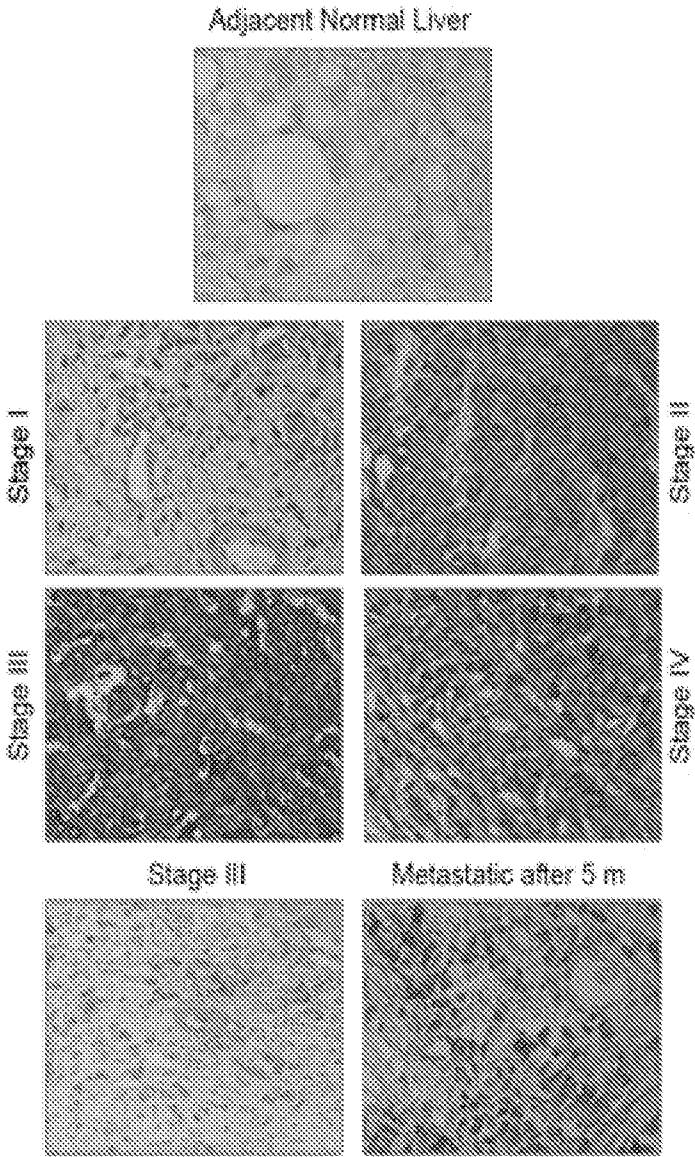


FIG. 3A

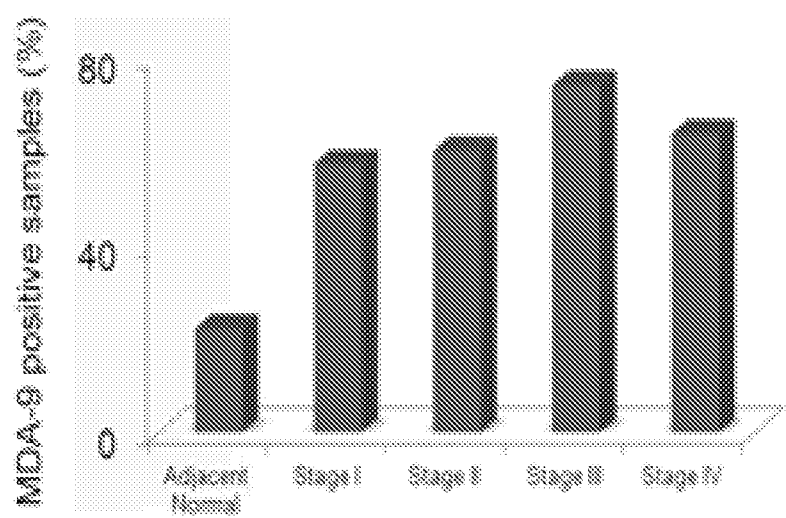


FIG. 3B

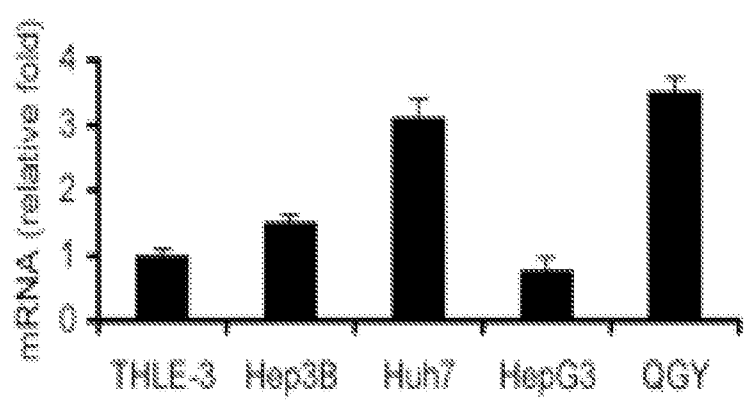


FIG. 3C

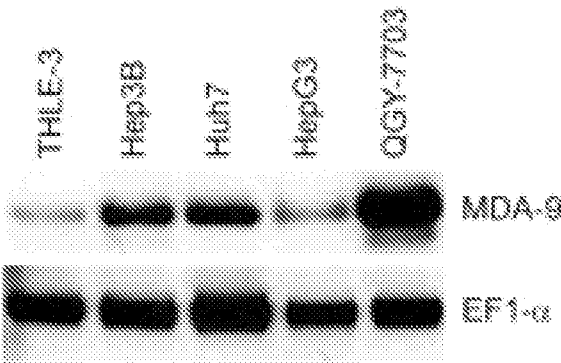


FIG. 3D

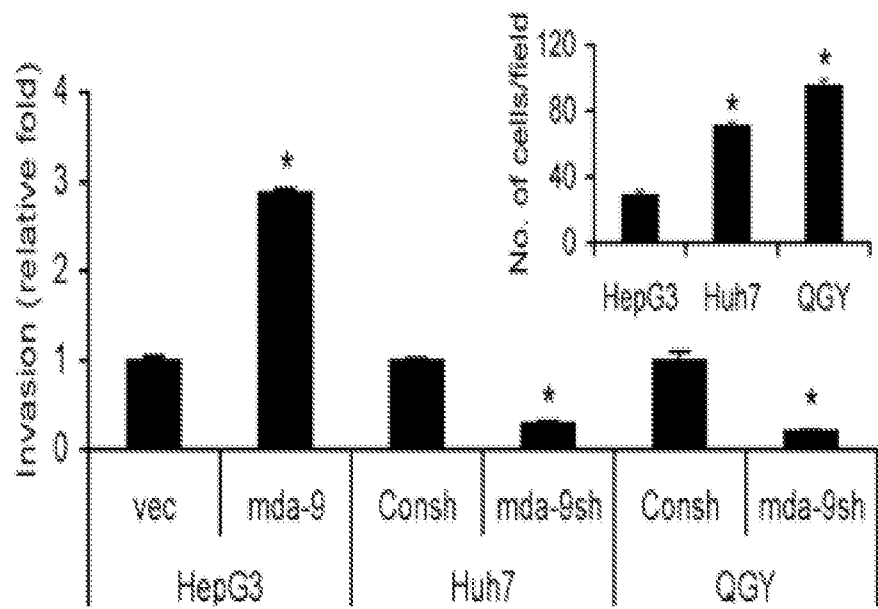


FIG. 4

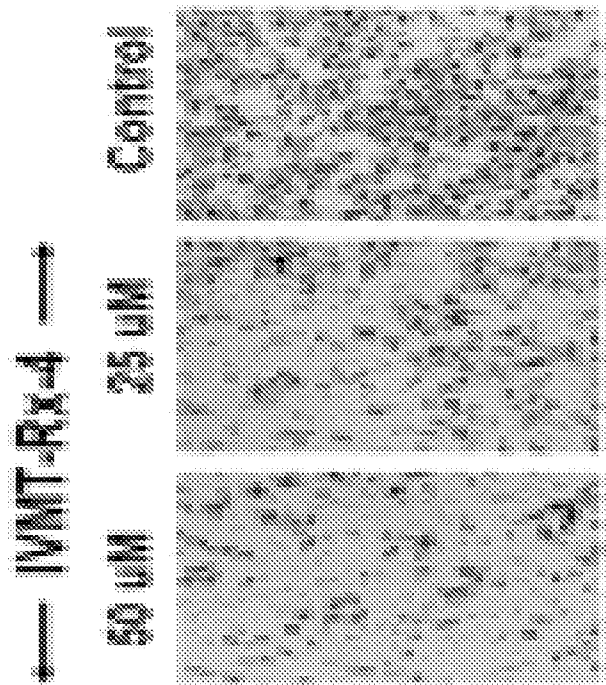


FIG. 5A

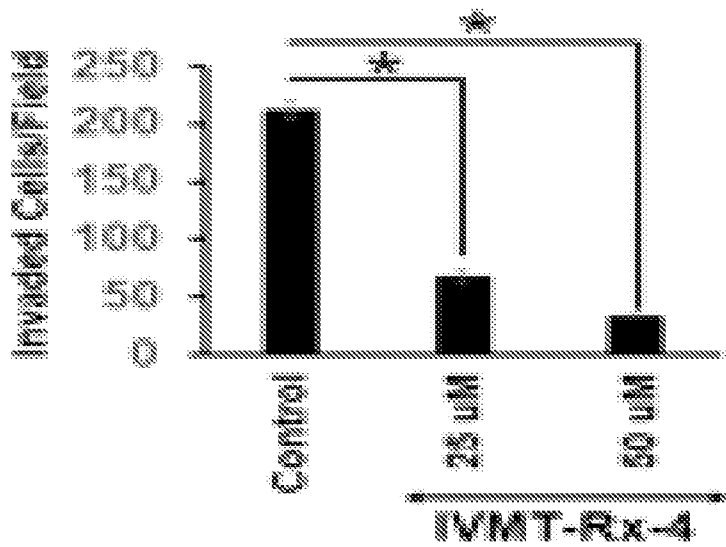
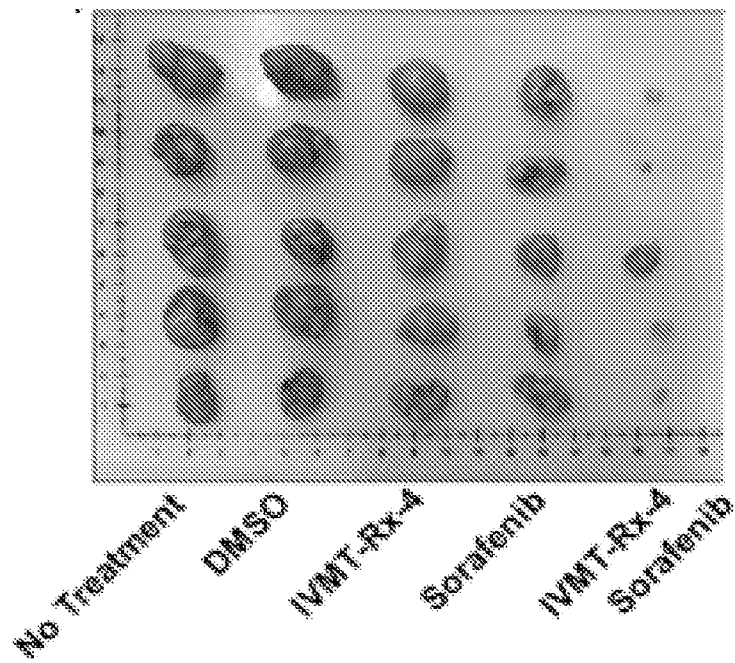
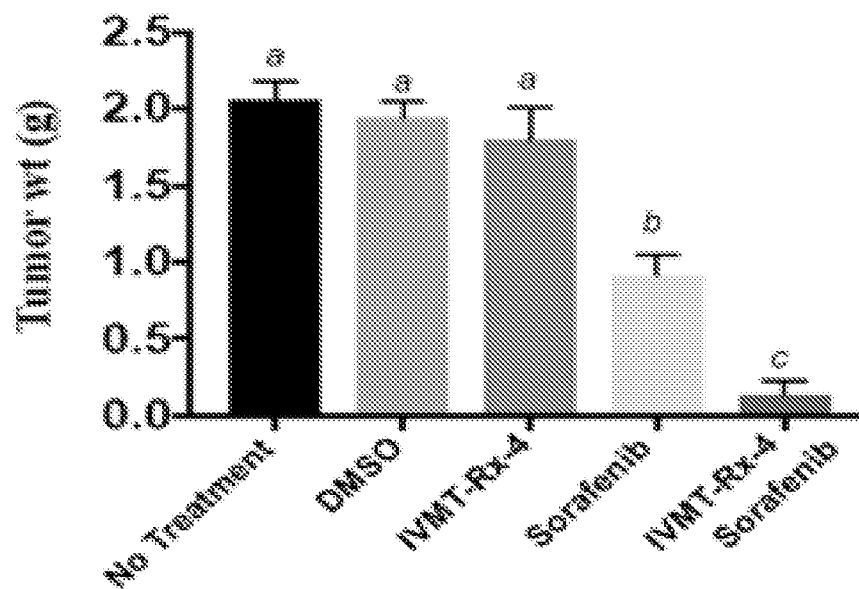


FIG. 5B

**FIG. 6A****FIG. 6B**

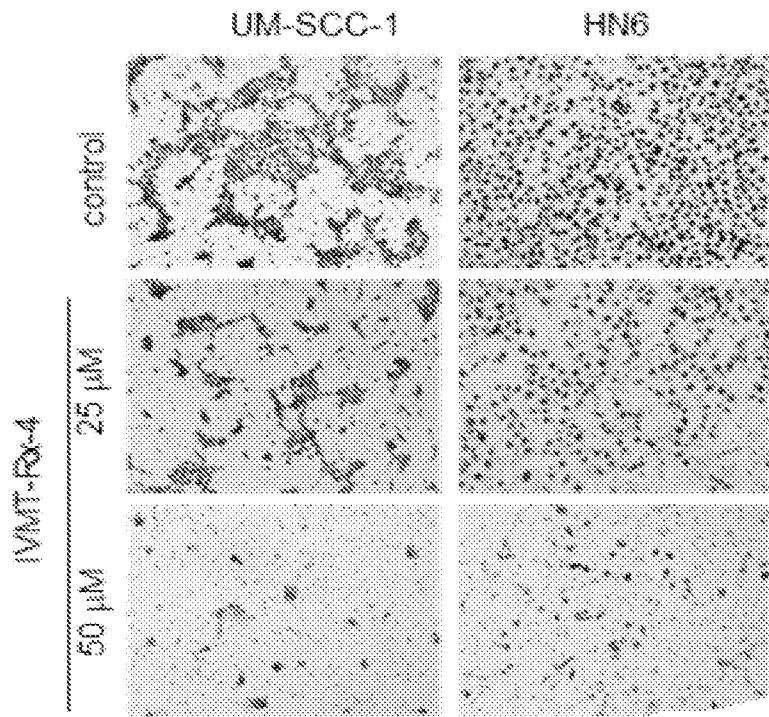


FIG. 7A

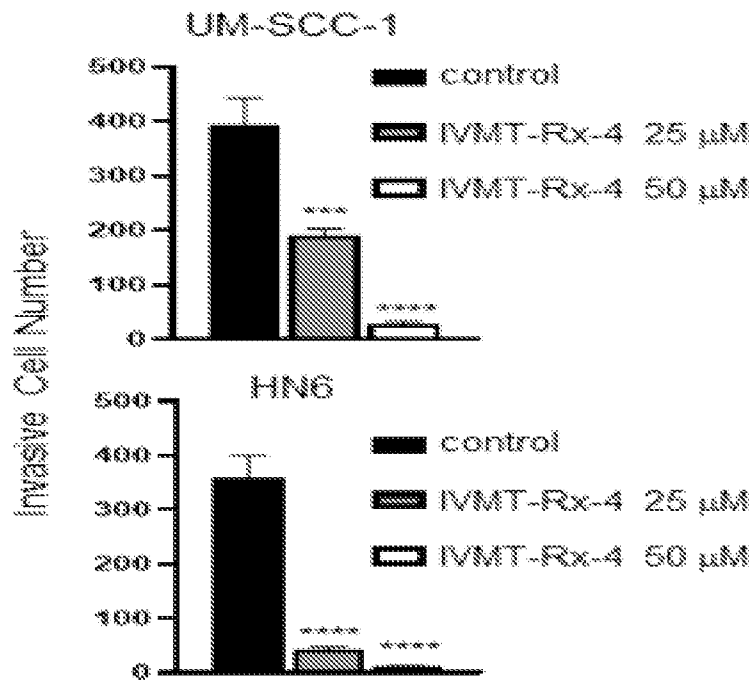
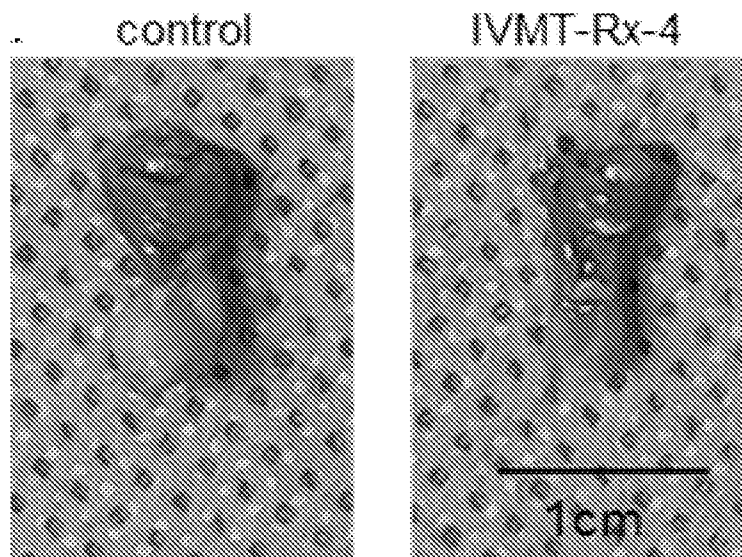
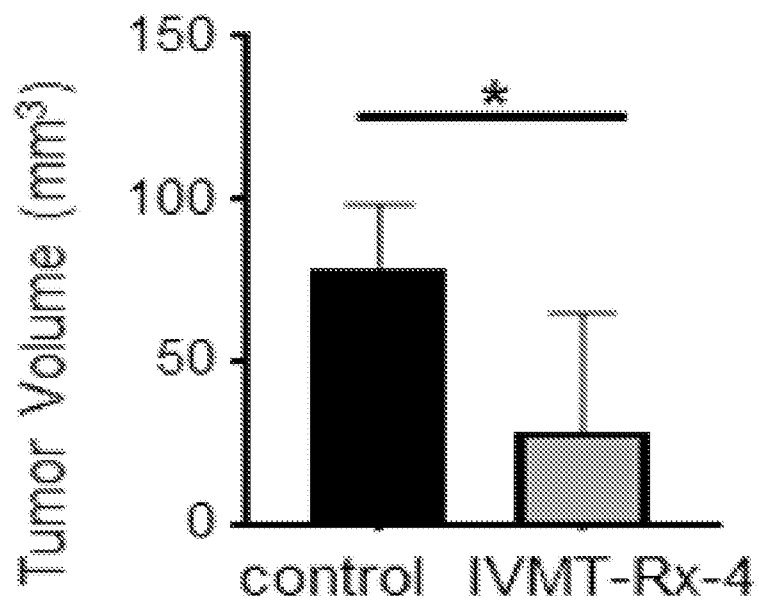
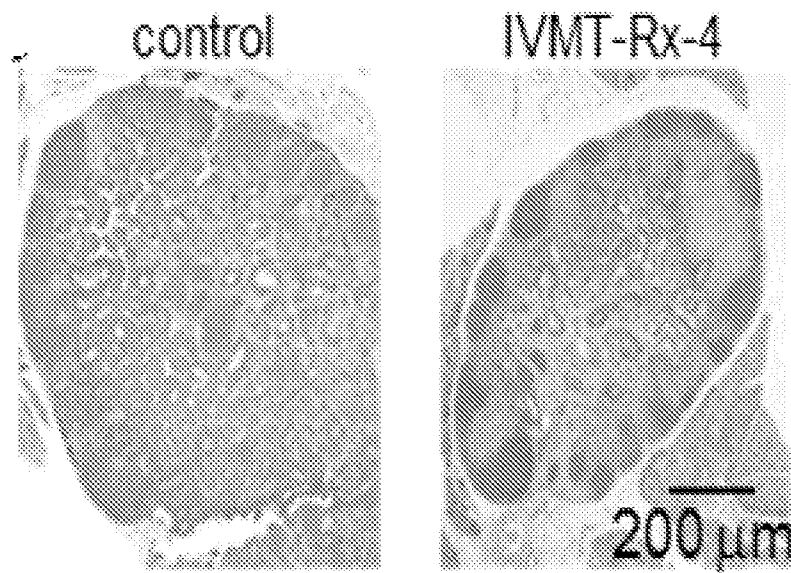
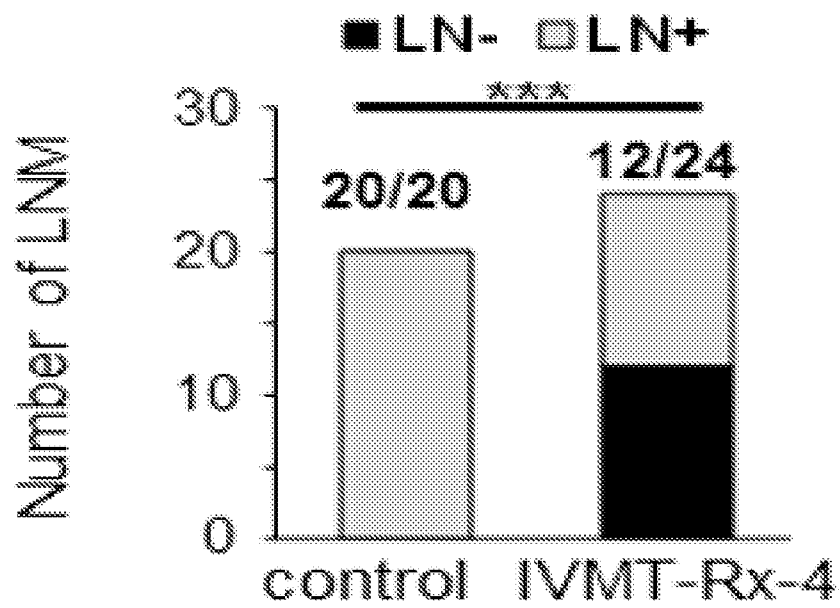


FIG. 7B

**FIG. 8A****FIG. 8B**

**FIG. 8C****FIG. 8D**

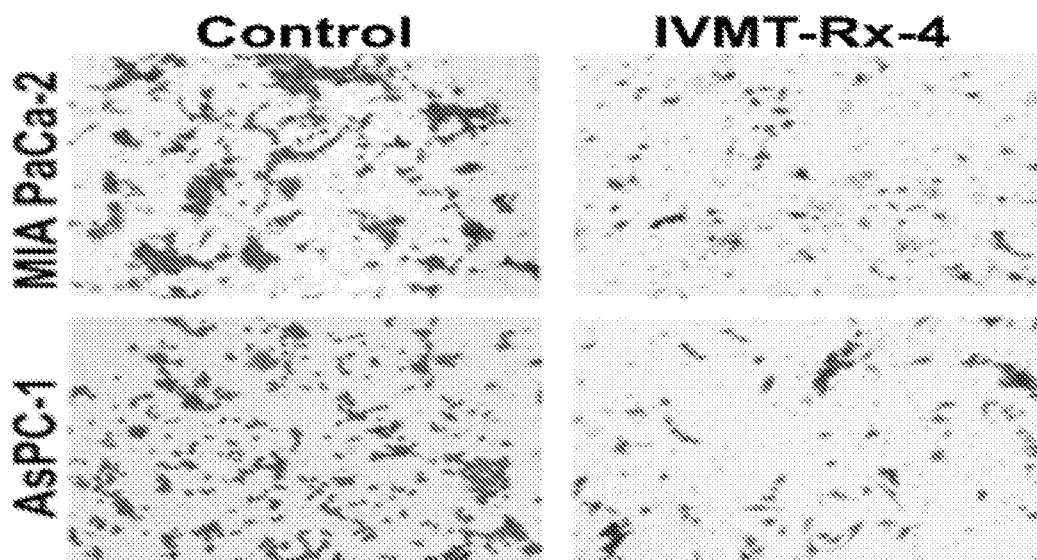


FIG. 9A

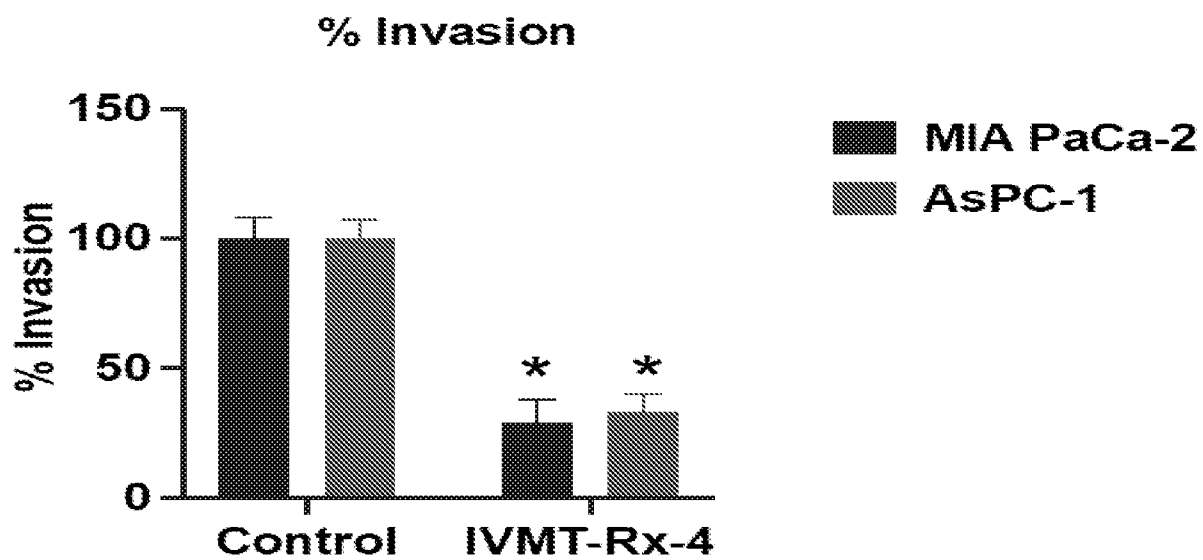


FIG. 9B

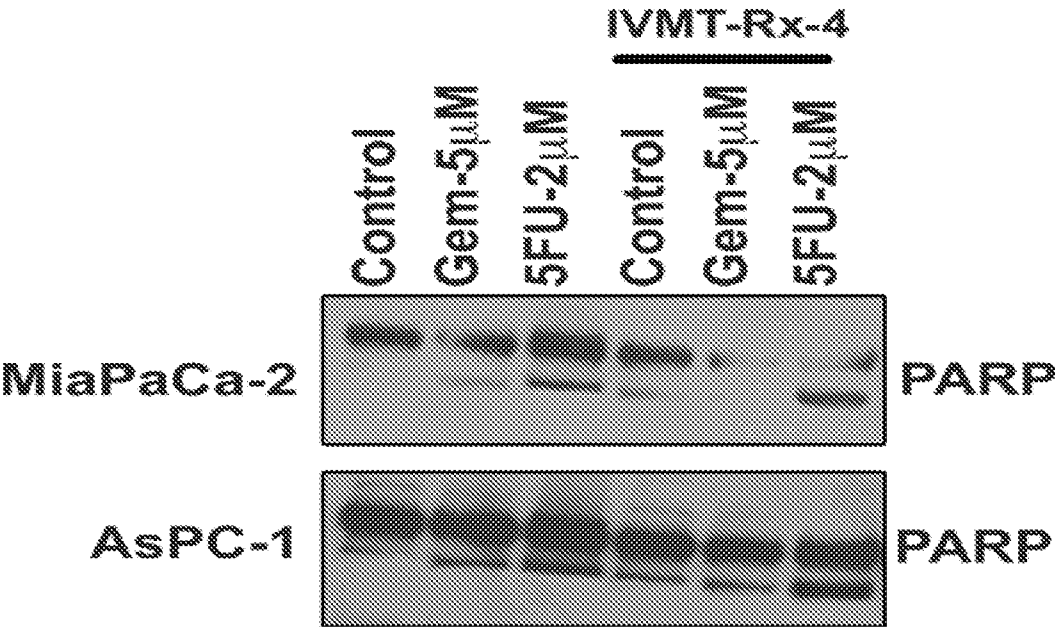


FIG. 10A

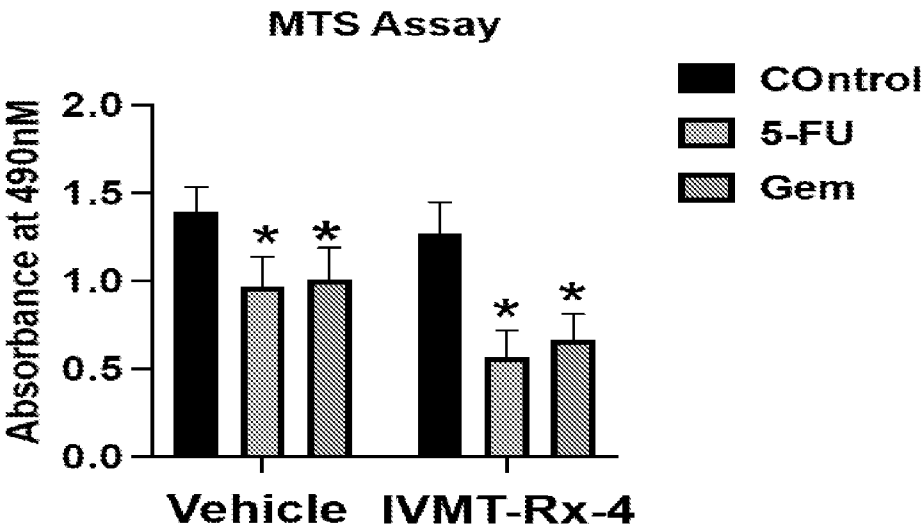


FIG. 10B

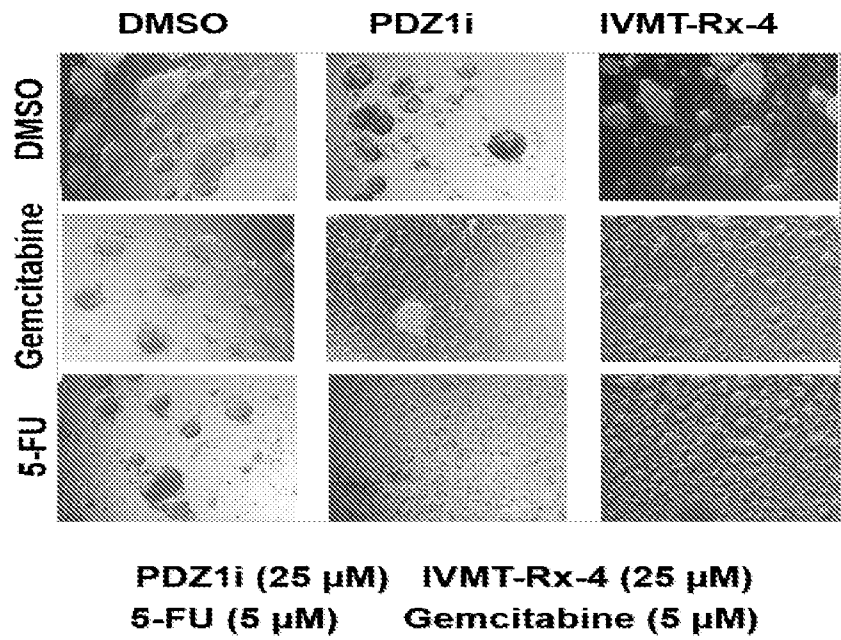


FIG. 11A

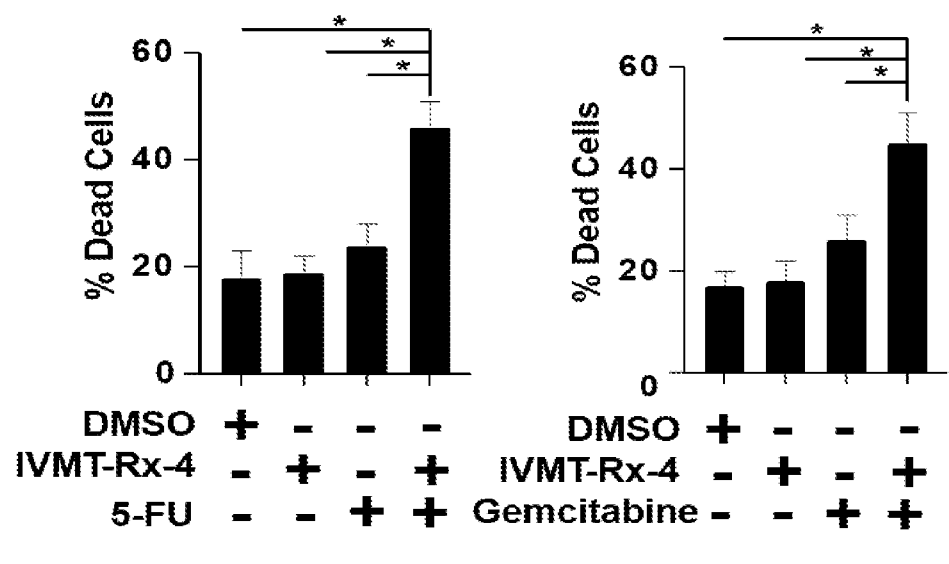


FIG. 11B

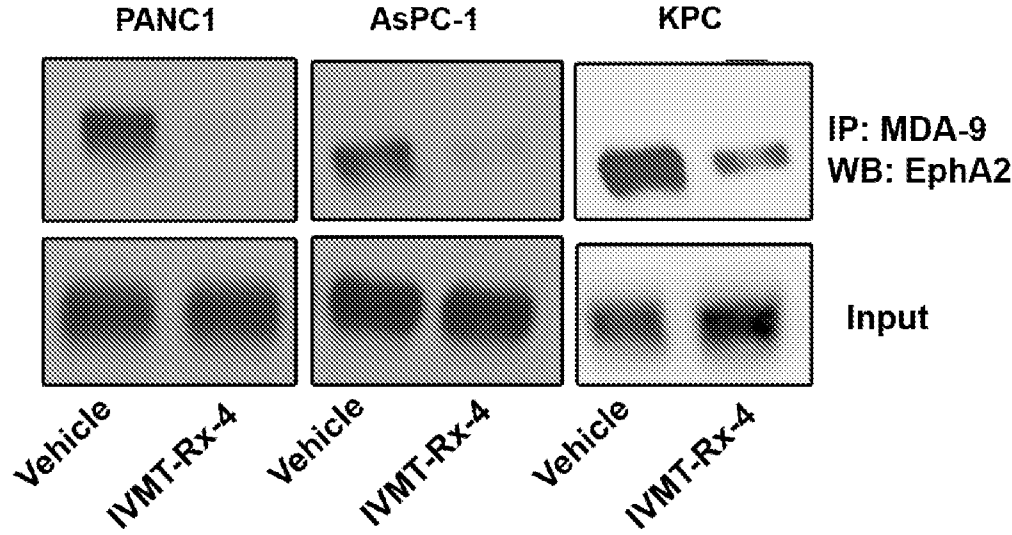


FIG. 12

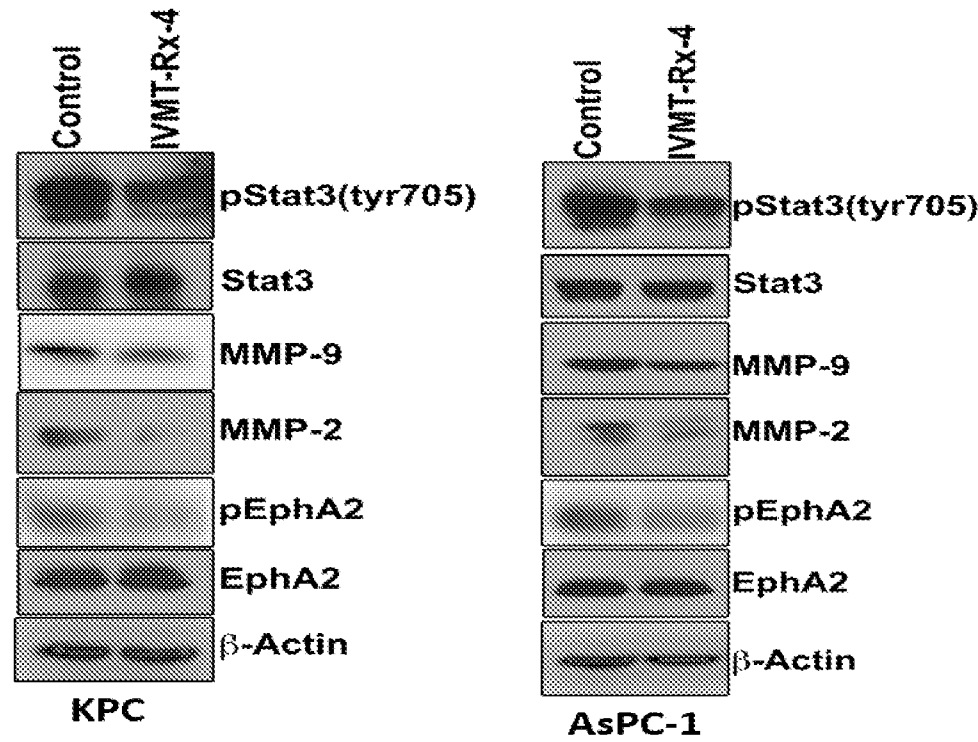


FIG. 13

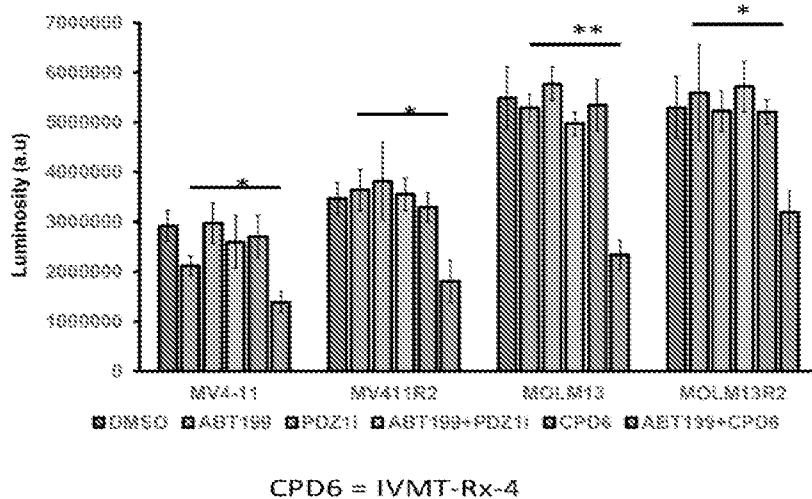


FIG. 14A

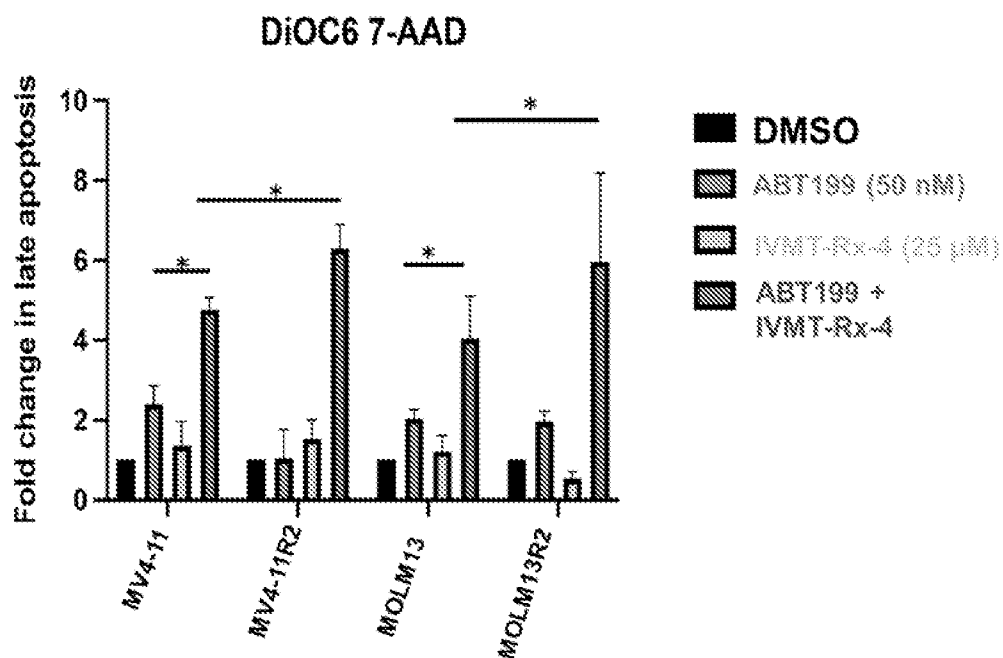


FIG. 14B

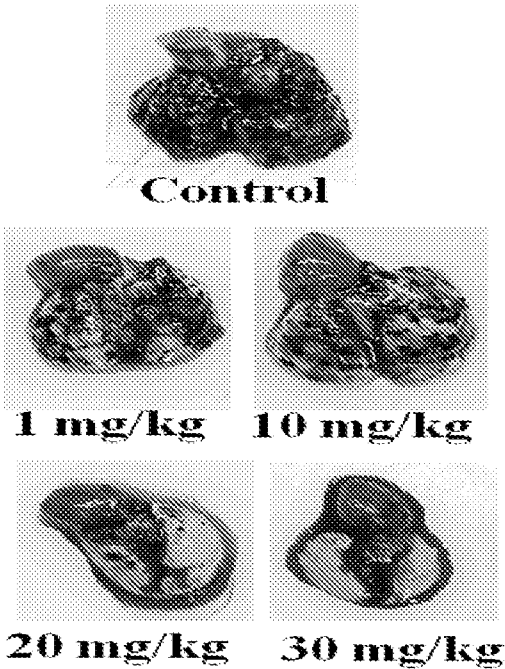


FIG. 15A

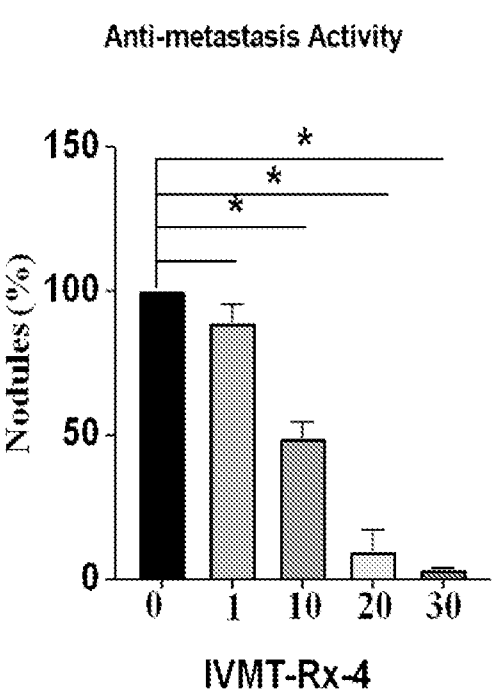


FIG. 15B

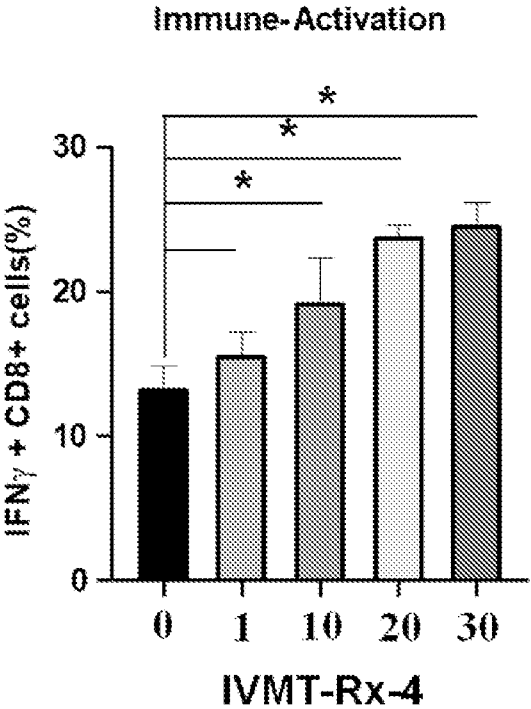
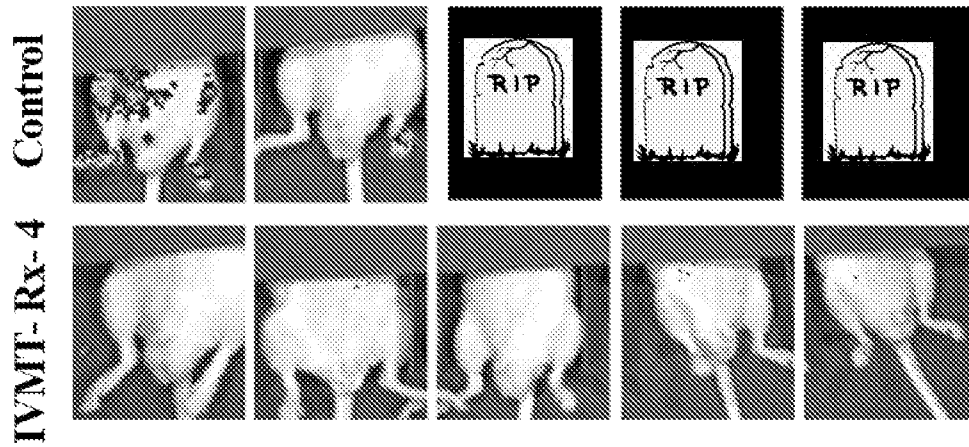
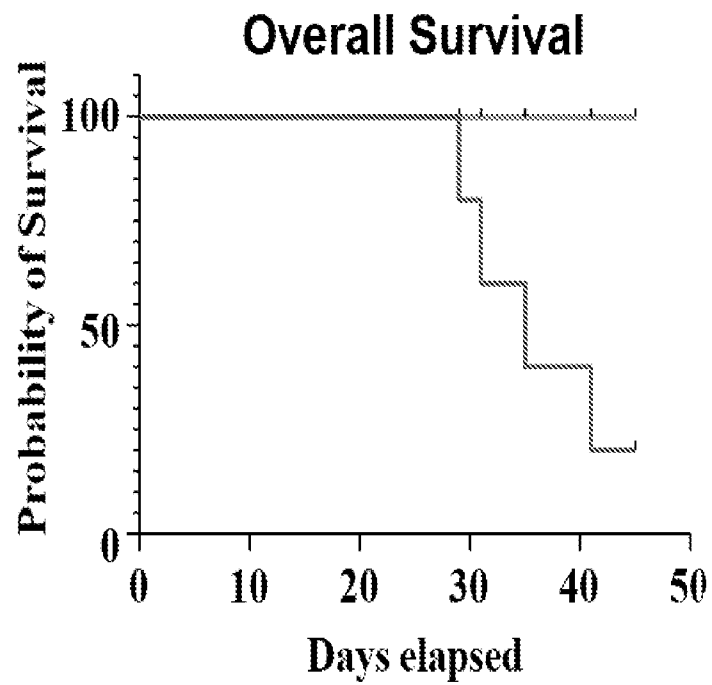


FIG. 15C

Day 36**FIG. 16A****FIG. 16B**

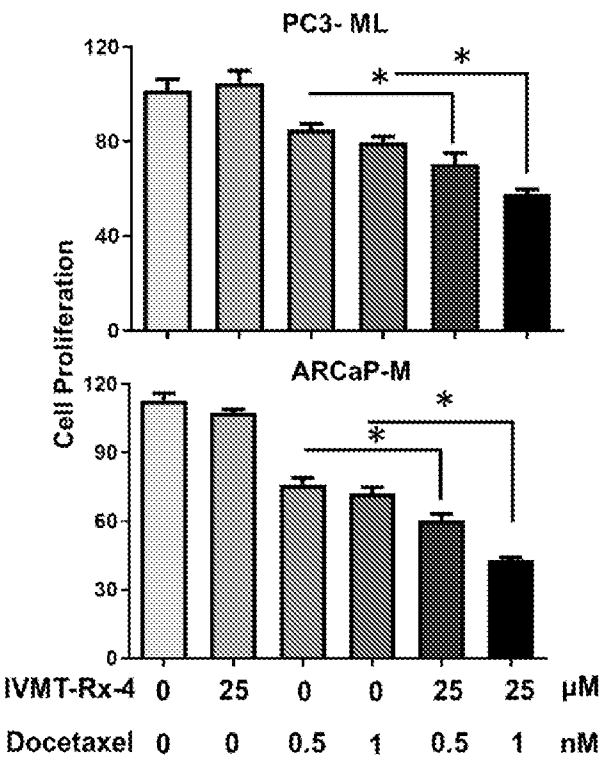


FIG. 17A

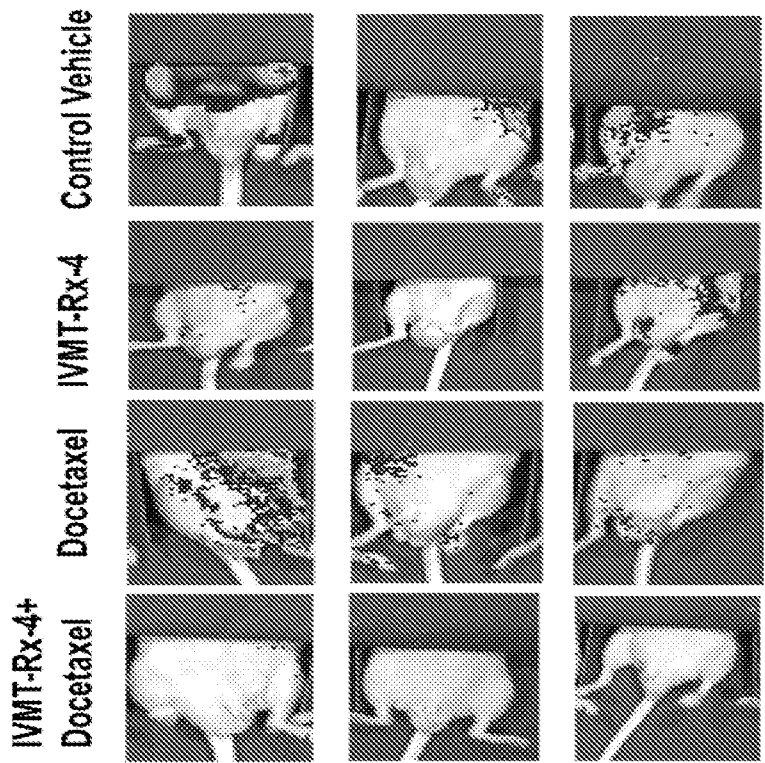
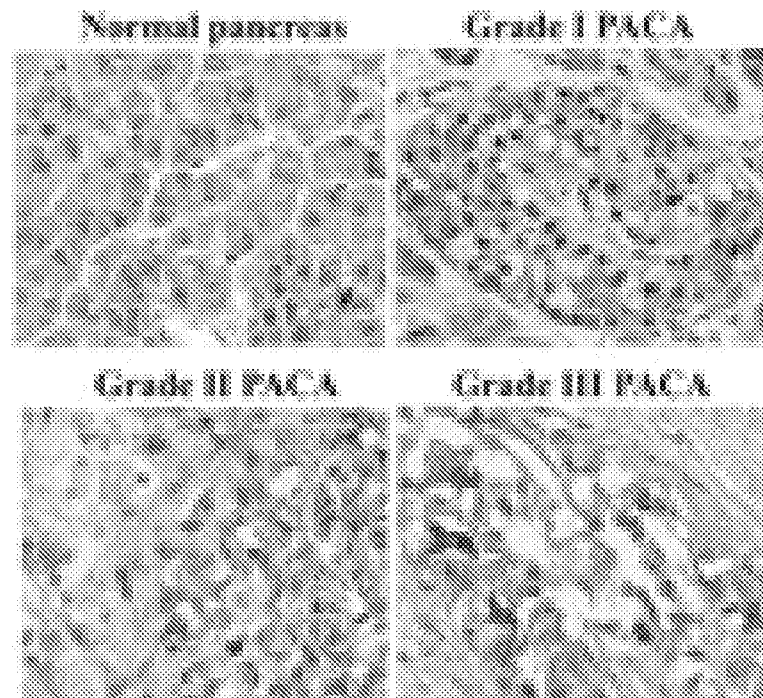
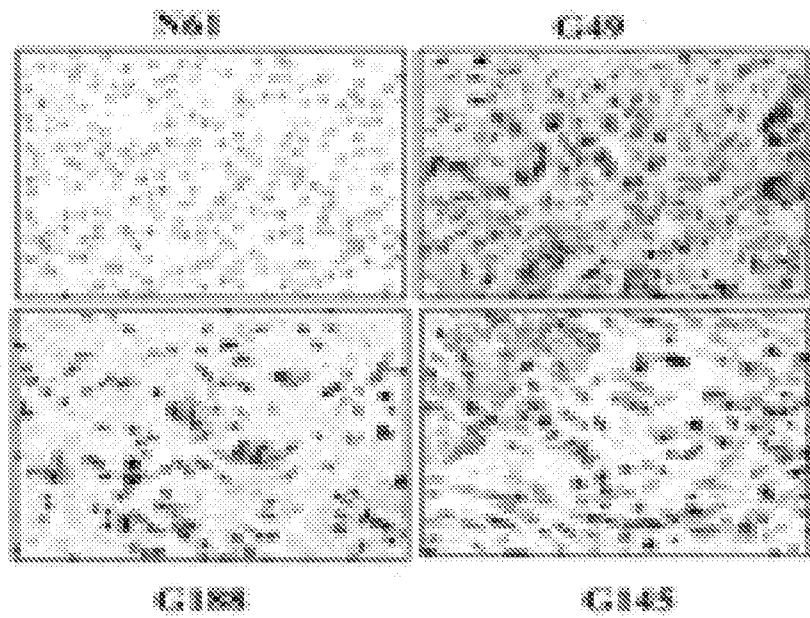


FIG. 17B

**FIG. 18A****FIG. 18B**

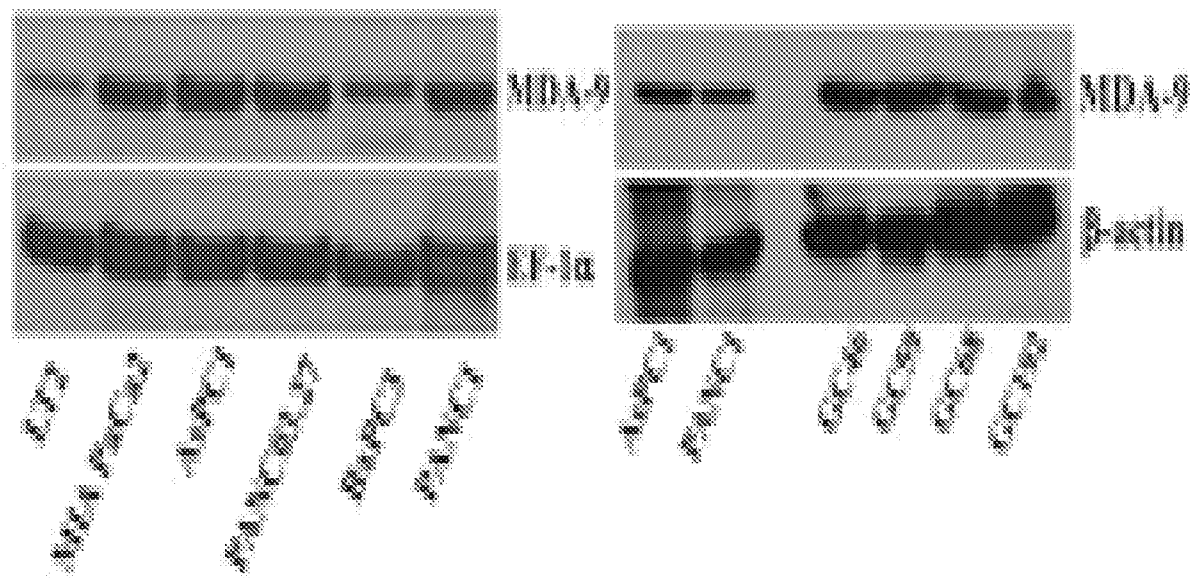


FIG. 18C

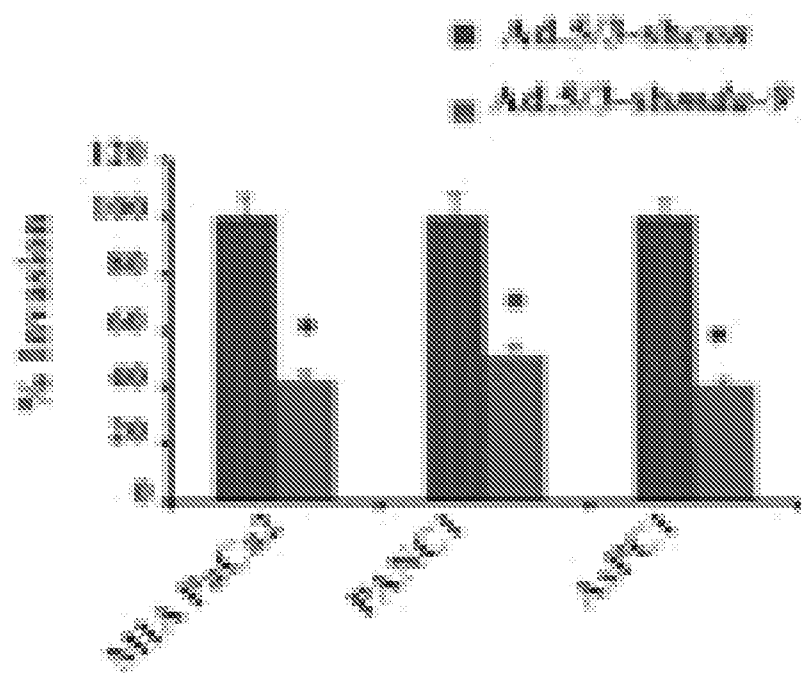
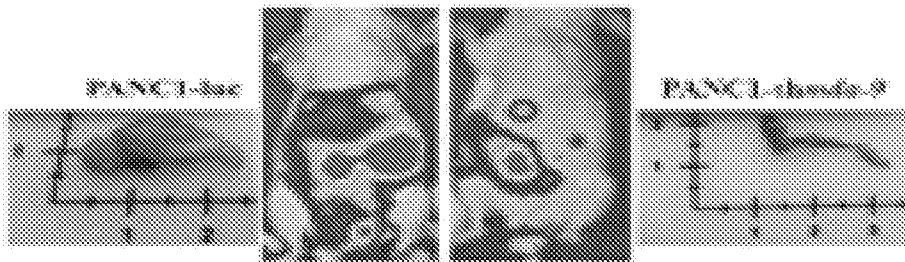
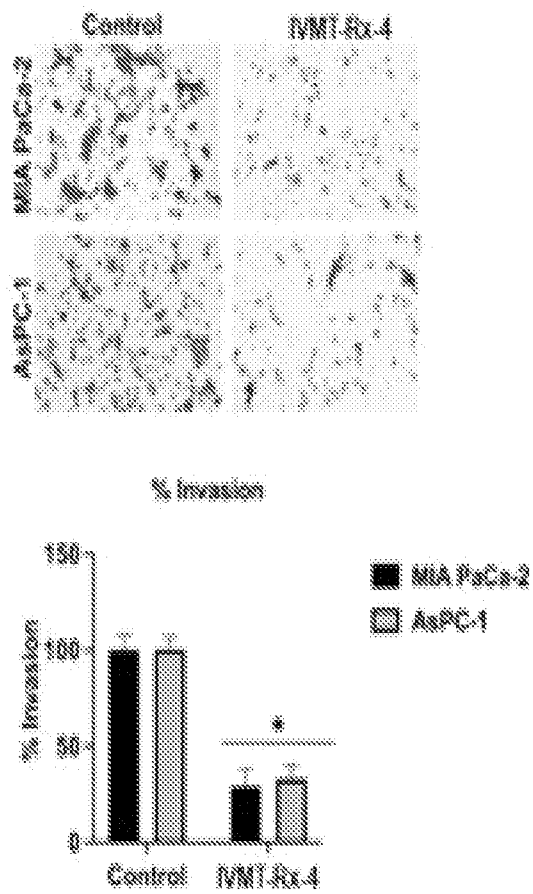


FIG. 18D

**FIG. 18E****FIG. 19A**

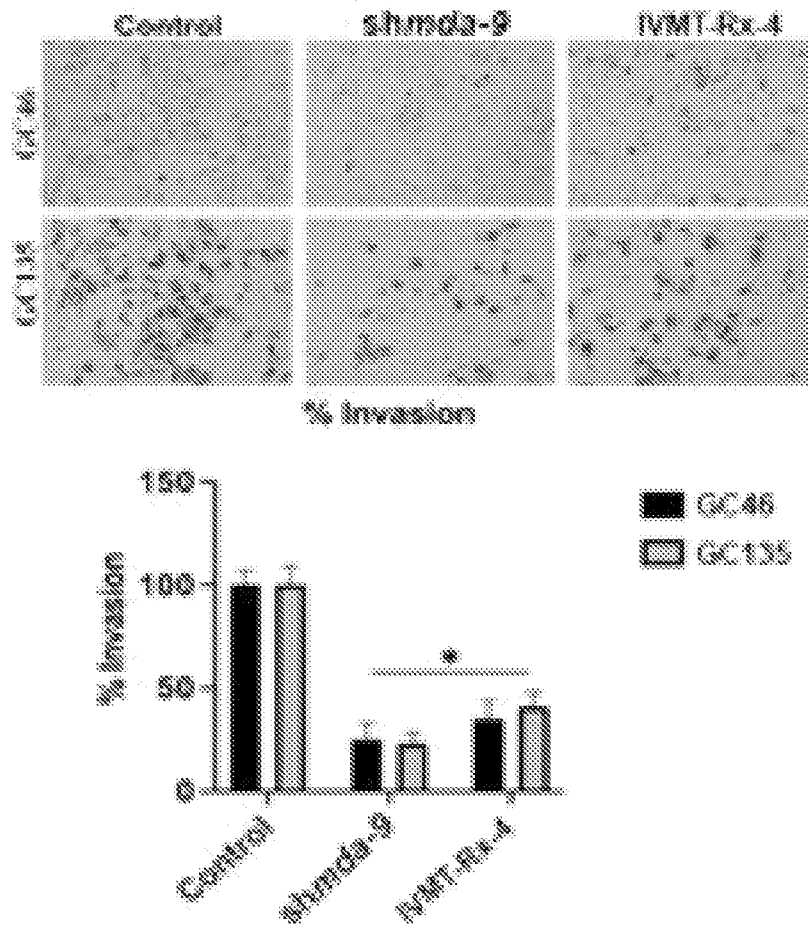


FIG. 19B

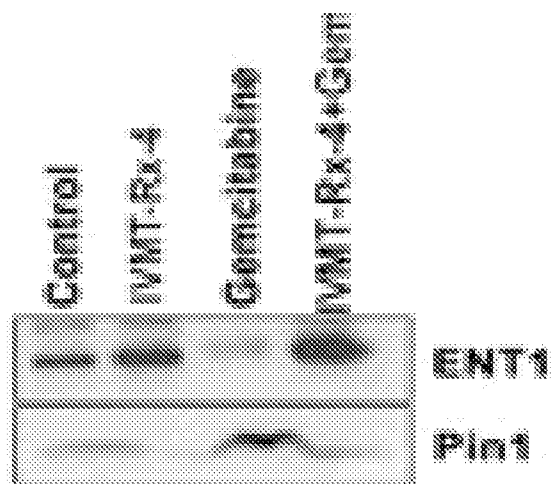


FIG. 20A

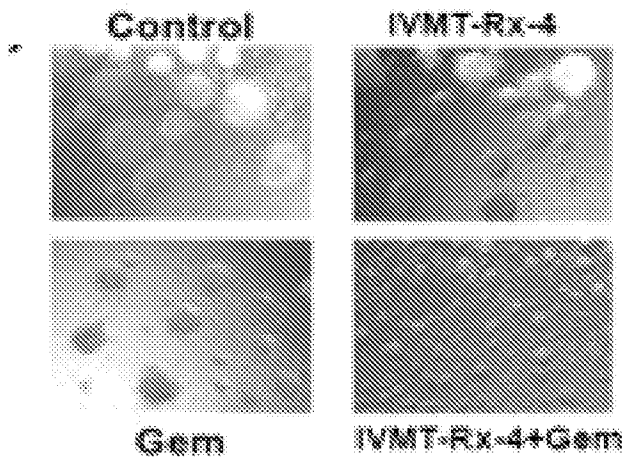


FIG. 20B

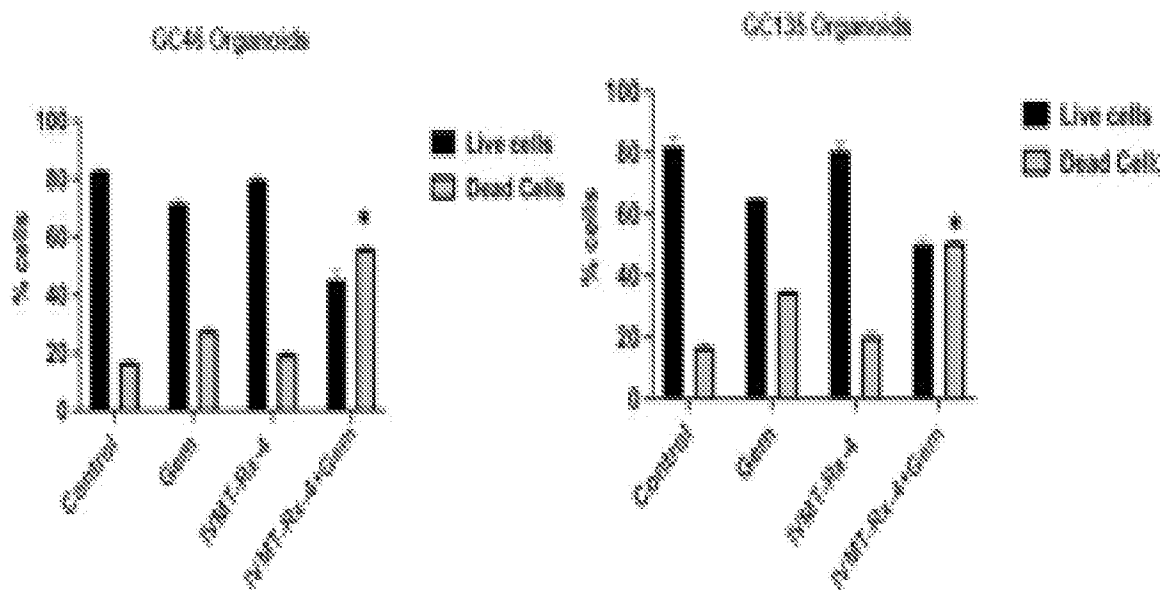


FIG. 20C

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/023834

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 6-10, 12, 13, 16-18, 23, 24, 26-40

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/023834

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/44; A61K 31/4245; A61K 31/7068; A61P 35/04; C07D 271/10 (2022.01)

CPC - A61K 31/44; A61K 31/4245; A61K 31/7068; A61P 35/04; C07D 271/10 (2022.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUBCHEM, Substance Record for SID 416202582, Available Date: 18 August 2020 [retrieved on 27 May 2022]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/416202582 >. entire document	1-3, 6-10, 12, 13, 16-18, 23, 24
Y	US 7,339,026 B2 (FISHER) 04 March 2008 (04.03.2008) entire document	1, 26-29, 34, 35
Y	US 9,889,180 B2 (AGENCY FOR SCIENCE TECHNOLOGY AND RESEARCH) 13 February 2018 (13.02.2018) entire document	1, 26-40
Y	US 9,732,055 B2 (LI et al) 15 August 2017 (15.08.2017) entire document	1, 28, 30-34, 36-40
A	US 8,796,320 B2 (ASAI et al) 05 August 2014 (05.08.2014) entire document	1-3, 6-10, 12, 13, 16-18, 23, 24, 26-40
A	FATHI et al., 1,3,4-oxadiazole/chalcone hybrids: Design, synthesis, and inhibition of leukemia cell growth and EGFR, Src, IL-6 and STAT3 activities, Bioorganic Chemistry, Vol. 84, Author manuscript; available in PMC 20 December 2019 [retrieved on 21 July 2022]. Retrieved from the Internet: <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6923798/ >. Pgs. 1-32	1-3, 6-10, 12, 13, 16-18, 23, 24, 26-40
P, A	WO 2021/127305 A1 (VIRGINIA COMMONWEALTH UNIVERSITY) 24 June 2021 (24.06.2021) entire document	1-3, 6-10, 12, 13, 16-18, 23, 24, 26-40

☐ 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

25 July 2022

Date of mailing of the international search report

AUG 11 2022

Name and mailing address of the ISA/US

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/US2022/023834

Continued from Box No. III Observations where unity of invention is lacking

Claims 1-3, 6-10, 12, 13, 16-18, 23, 24 and 26-40 have been analyzed subject to the restriction that the claims read on a compound having a structure of shown formula (I); or a pharmaceutically acceptable salt thereof, wherein: z is 0; w is 0; R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen; and R6 is absent; pharmaceutical compositions thereof; methods of inhibiting MDA-9/Syntenin protein activity thereof; methods of treating cancer in a subject in need thereof; and methods of preventing metastasis of cancer cells in a subject in need thereof.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-40 are drawn to compounds having a structure of formula (I); pharmaceutical compositions thereof; methods of inhibiting MDA-9/Syntenin protein activity thereof; methods of treating cancer in a subject in need thereof; and methods of preventing metastasis of cancer cells in a subject in need thereof.

The first invention of Group I+ is restricted to a compound having a structure of shown formula (I); or a pharmaceutically acceptable salt thereof, wherein: z is 0; w is 0; R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen; and R6 is absent; pharmaceutical compositions thereof; methods of inhibiting MDA-9/Syntenin protein activity thereof; methods of treating cancer in a subject in need thereof; and methods of preventing metastasis of cancer cells in a subject in need thereof. It is believed that claims 1-3, 6-10, 12, 13, 16-18, 23, 24 and 26-40 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound having a structure of shown formula (I); or a pharmaceutically acceptable salt thereof, wherein: z is 1; w is 0; R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen; and R6 is absent; pharmaceutical compositions thereof; methods of inhibiting MDA-9/Syntenin protein activity thereof; methods of treating cancer in a subject in need thereof; and methods of preventing metastasis of cancer cells in a subject in need thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables z, w, R1, R2, R3, R4, R5, and R6 and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having a core structure of shown formula (I); or a pharmaceutically acceptable salt thereof; a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient; a method of inhibiting MDA-9/Syntenin protein activity, said method comprising contacting the MDA-9/Syntenin protein with a compound; a method of treating cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound; a method of preventing metastasis of cancer cells in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound, these shared technical features do not represent a contribution over the prior art as disclosed by PubChem SID 416202582 and US 7,339,026 B2 to Fisher.

PubChem SID 416202582 teaches a compound having a core structure of shown formula (I); or a pharmaceutically acceptable salt thereof (Pg. 2, see shown structure).

US 7,339,026 B2 to Fisher teaches a pharmaceutical composition comprising a compound and a pharmaceutically acceptable excipient (Col. 5, Lns. 36-43, pharmaceutical composition comprising an amount of the antisense oligonucleotide having a sequence capable of specifically hybridizing to the mRNA of the isolated nucleic acid molecule of an mda-9 gene, wherein the encoded mda-9 protein is a human protein and capable of degrading the hybridized mRNA, effective to prevent expression of a human mda-9 protein and a pharmaceutically acceptable carrier); a method of inhibiting MDA-9/Syntenin protein activity, said method comprising contacting the MDA-9/Syntenin protein with a compound (Col. 5, Lns. 55-59, method of inhibiting expression of a mda-9 gene in a subject comprising introducing a vector containing a nucleic acid molecule which renders the mda-9 gene functionless into the subject under conditions permitting the inhibition of the expression of the mda-9 gene); a method of treating cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound (Col. 5, Lns. 60-63, method of treating a cancer in a subject by administering a pharmaceutical composition comprising an effective amount of the antibody capable of specifically recognizing an mda-9 protein); a method of preventing metastasis of cancer cells in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound (Col. 5, Lns. 60-63, method of treating a cancer in a subject by administering a pharmaceutical composition comprising an effective amount of the antibody capable of specifically recognizing an mda-9 protein; Col. 24, Lns. 15-18, Treatment of metastatic human melanoma cells with the combination of IFN-B and the antileukemic compound MEZ results in an irreversible loss of proliferative ability and terminal cell differentiation).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.