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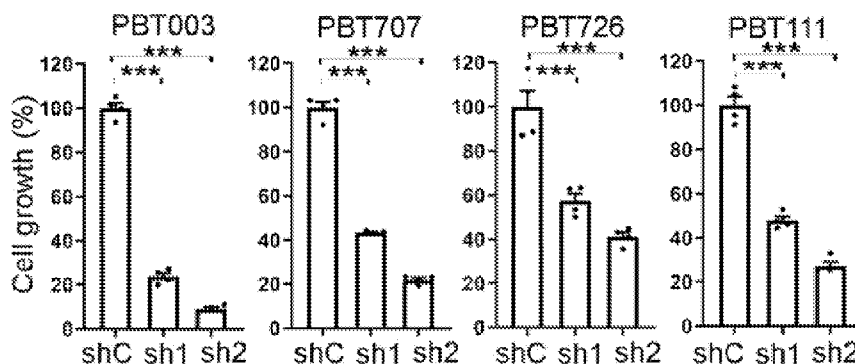


Fig. 2A

(57) Abstract: Disclosed herein are, *inter alia*, compounds inhibiting activity of pseudouridine synthase (PUS) and methods of use thereof for treating PUS associated conditions or disorders.

NOVEL SMALL MOLECULE INHIBITORS OF PUS7 AND USES THEREOF

[0001] This application claims the benefit of priority to U.S. Provisional Application Serial number 63/233,197 filed August 13, 2021. The disclosure of this application is incorporated herein by reference in its entirety and for all purposes.

BACKGROUND

[0002] Over 100 types of posttranscriptional modifications have been discovered in RNA (Machnicka, M.A., *et al. Nucleic acids research* **41**, D262-267 (2013)). Increasing studies have demonstrated that RNA modifications are critical in epigenetic regulation of gene expression in physiology and disease (Nachtergaele, S. & He, C., *Annu Rev Genet* **52**, 349-372 (2018)). Pseudouridine (Ψ), an isomer of uridine, is the most abundant RNA modification (Wu, G., *et al., Wiley Interdiscip Rev RNA* **2**, 571-581 (2011); Charette, M. & Gray, M.W., *IUBMB life* **49**, 341-351 (2000)), therefore called “the fifth RNA nucleotide” (Davis, F.F. & Allen, F.W., *The Journal of biological chemistry* **227**, 907-915 (1957)). The isomerization of uridine to pseudouridine can be catalyzed by either snoRNA-dependent mechanism that requires the box H/ACA ribonucleoproteins or RNA-independent mechanism that involves the stand-alone pseudouridine synthase (PUS) enzymes (Karijolich, J., *et al., Nature reviews. Molecular cell biology* **16**, 581-585 (2015)). These PUS enzymes are divided into six families, including TruA, TruB, TruD, RsuA, RluA, and Pus10 family (Hamma, T. & Ferre-D'Amare, A.R., *Chem Biol* **13**, 1125-1135 (2006); Spenkuch, F., *et al., RNA biology* **11**, 1540-1554 (2014)), among which, PUS7 is the only member of the TruD family (Rintala-Dempsey, A.C. & Kothe, U., *RNA biology* **14**, 1185-1196 (2017)).

[0003] Pseudouridine mainly occurs in noncoding RNAs, such as rRNAs (ribosomal RNAs), tRNAs (transfer RNAs), and snRNAs (small nuclear RNAs), and also in pre-mRNAs, and contributes to critical biological processes such as translation and mRNA splicing (Spenkuch, F., *supra*) With the advance of high-throughput sequencing, recently developed pseudouridine sequencing technologies (Ψ -seq, Pseudo-seq, CeU-seq, Psi-seq and DM- Ψ -seq) revealed prevalent pseudouridine modification in not only tRNA, rRNA, and snRNA, but also mRNA, where it can be dynamic under stress conditions (Carlile, T.M., *et al., Nature* **515**, 143-146

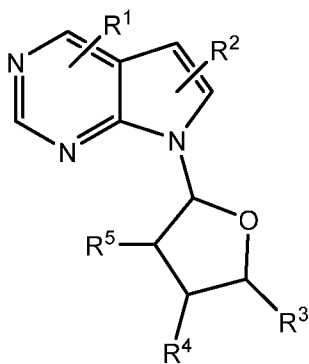
(2014); Li, X., *et al.*, *Nature chemical biology* **11**, 592-597 (2015); Schwartz, S., *et al.*, *Cell* **159**, 148-162 (2014); Lovejoy, A.F., *et al.*, *PloS one* **9**, e110799 (2014); Song, J., *et al.*, *Nature chemical biology* **16**, 160-169 (2020); Lei, Z. & Yi, C. A, *Angew Chem Int Ed Engl* **56**, 14878-14882 (2017)). While RNA pseudouridylation has been implicated in human physiology and diseases (Rintala-Dempsey, *supra*; Guzzi, N., *et al.*, *Cell* **173**, 1204-1216 e1226 (2018); Penzo, M., Guerrieri, *et al.*, *Genes* **8**(2017)(Penzo, M., Guerrieri, A.N., Zacchini, F., Trere, D. & Montanaro, L. RNA Pseudouridylation in Physiology and Medicine: For Better and for Worse. *Genes* **8**(2017)), the biological roles of PUSs remain largely undefined.

[0004] Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults. However, current treatments are only palliative. Despite great efforts in therapeutic development, median survival of GBM patients remains less than 16 months after diagnosis (Johnson, D.R. & O'Neill, B.P., *Journal of neuro-oncology* **107**, 359-364 (2012); Stupp, R., *et al.*, *Lancet Oncol* **10**, 459-466 (2009)). It is believed that glioblastoma stem cells (GSCs) are important for GBM tumor progression and treatment resistance (Cui, Q., *et al.*, *Nature communications* **7**, 10637 (2016); Shi, Y., *et al.*, *Science translational medicine* **10** (2018); Man, J., *et al.*, *Cell stem cell* **22**, 104-118 e106 (2018); Bao, S., *et al.*, *Nature* **444**, 756-760 (2006); Duan, S., *et al.*, *Nature communications* **6**, 10068 (2015); Sancho-Martinez, I., *et al.*, *Nature communications* **7**, 10743 (2016)). Although the role of m⁶A RNA modification in glioblastoma is starting to be revealed (Cui, Q., *et al.*, *Cell reports* **18**, 2622-2634 (2017); Zhang, S., *et al.*, *Cancer cell* **31**, 591-606 e596 (2017); Dixit, D., *et al.*, *Cancer Discov* **11**, 480-499 (2021); Fang, R., *et al.*, *Nature communications* **12**, 177 (2021)), whether and how other RNA modification machinery impacts GBM tumorigenesis remains largely unexplored. Pseudouridine is the most abundant RNA modification and increased levels of pseudouridine has been detected in cancer patients (Waalkes, T.P., *et al.*, *Journal of the National Cancer Institute* **51**, 271-274 (1973); Stockert, J.A., *et al.*, *Am J Clin Exp Urol* **7**, 262-272 (2019)). However, the biological roles of pseudouridine modification and PUS enzymes remain largely undefined in cancer and especially in GBM. There is an urgent need for new treatments of GBM. This invention solves this and other related issues.

SUMMARY

[0005] Provided herein, *inter alia*, are small molecule inhibitors of pseudouridine synthase 7 (PUS7) activity, pharmaceutical compositions comprising these compounds, and the use of these compounds for the treatment of a PUS7 modulated disease or disorder.

[0006] In one aspect, provided herein is a small molecule inhibitor of PUS7 of structural formula (I):



(I), or a pharmaceutically acceptable salt thereof, wherein: R¹ is halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -N₃, -SO_{m1}R^{1A}, -SO_{v1}NR^{1B}R^{1C}, -NHN^{1B}R^{1C}, -ONR^{1B}R^{1C}, -NHC(O)NHN^{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}SO₂R^{1A}, -NR^{1B}C(O)R^{1D}, -NR^{1B}C(O)OR^{1D}, -NR^{1B}OR^{1D}, -OCX¹₃, -OCHX¹₂, -OCH₂X¹, 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; R² is halogen, -CX²₃, -CHX²₂, -CH₂X², -CN, -N₃, -SO_{n2}R^{2A}, -SO_{v2}NR^{2B}R^{2C}, -NHN^{2B}R^{2C}, -ONR^{2B}R^{2C}, -NHC(O)NHN^{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}SO₂R^{2A}, -NR^{2B}C(O)R^{2D}, -NR^{2B}R^{2C}CNOR^{2D}, -NR^{2B}C(O)OR^{2D}, -NR^{2B}OR^{2D}, -OCX²₃, -OCHX²₂, -OCH₂X², 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; R³ is hydrogen, halogen, -CX³₃, -CHX³₂, -CH₂X³, -CN, -N₃, -SO_{n3}R^{3A}, -SO_{v3}NR^{3B}R^{3C}, -NHN^{3B}R^{3C}, -ONR^{3B}R^{3C}, -NHC(O)NHN^{3B}R^{3C}, -NHC(O)NR^{3B}R^{3C}, -N(O)_{m3}, -NH₂, -C(O)R^{3D}, -C(O)OR^{3D}, -C(O)NH₂, -OR^{3A}, -NR^{3B}SO₂R^{3A}, -NR^{3B}C(O)OR^{3D}, -NR^{3B}OR^{3D}, -OCX³₃, -OCHX³₂, -OCH₂X³, 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, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-CN$, $-N_3$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^4_3$, $-OCHX^4_2$, $-OCH_2X^4$, 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, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-CN$, $-N_3$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHN R^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHN R^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^5_3$, $-OCHX^5_2$, $-OCH_2X^5$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} , 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} , and R^{5D} 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} , and R^{5B} and R^{5C} substituents may optionally be joined to form a 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) 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 , X^2 , X^3 , X^4 , and X^5 are independently halogen; $n1$, $n2$, $n3$, $n4$, and $n5$ are independently an integer from 0 to 4; and $m1$, $m2$, $m3$, $m4$, $m5$, $v1$, $v2$, $v3$, $v4$, and $v5$ 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 of pseudouridine synthase 7 (PUS7) activity, said method comprising contacting the PUS7 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).

DETAILED DESCRIPTION OF THE DRAWINGS

[0010] FIGS. 1A-1G. PUS7 is highly expressed in GBM patients. (FIG. 1A) The expression of PUS7 in GBM patients and non-tumor control samples from the REMBRANDT (n=28 non-tumor samples and n=219 GBM samples), TCGA (n=4 non-tumor samples and n=156 GBM samples), and Gravendeel (n=8 non-tumor samples and n=159 GBM samples) datasets. (FIG. 1B) The expression of PUS7 in all glioma patients stratified by IDH mutation status and 1p19q chromosome co-deletion status from the TCGA dataset (n=169 IDH mut 1p19q codel patients, n=258 IDH mut 1p19q noncodel patients, n=229 IDH WT patients). (FIG. 1C) The expression of PUS7 in GBM patients stratified by the status of PUS7 copy number variation (n=26 diploid patients and n=120 gain patients), gain of chromosome 7 and loss of chromosome 10 (n=50 patients for negative group and n=96 patients for positive group), or gain of chromosome 19 and 20 (n=127 patients for negative group and n=19 patients for positive group) in the TCGA dataset. (FIG. 1D) The expression of PUS7 in GBM patients and in non-tumor control samples analyzed by Western blot. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. (FIG. 1E) The expressions of PUS7 in GSCs, NSCs, established GBM lines, and astrocytes (hAS: primary human astrocytes; iPSC1-AS and iPSC2-AS: human iPSC-derived astrocytes) analyzed by Western blot. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. (FIG. 1F) Quantification of PUS7 expression in GBM patients and in non-tumor control samples analyzed by Western blot. n = 9 GBM patients and 10 non-tumor control subjects. p=0.0001. (FIG. 1G) Quantification of the expression level of PUS7 in 4 lines of GSCs, 2 lines of NSCs, 3 established GBM lines, and 3 lines of astrocytes analyzed by Western blot. Error bars are SD of the mean for FIG. 1A-1C. p=0.0212 for GSCs vs NSCs, p=0.0226 for GSCs vs

astrocytes. p value was determined by two-tailed Student's t-test for FIG. 1A-1C. ns: not statistically significant ($p=0.2626$ for gain of chromosome 19 and 20 in C). Error bars represent SE of the mean for FIG. 1F and FIG. 1G. *** $p<0.001$ by one-tailed Student's t-test for FIG. 1F. * $p<0.05$ by One-way ANOVA and Dunnett's multiple comparisons test for FIG. 1 G. See also FIGS. 9A-9H.

[0011] FIGS. 2A-2F. PUS7 regulates GSC growth and self-renewal. (FIG. 2A) Cell growth of GSCs (PBT003, PBT707, PBT726, and PBT111) transduced with lentivirus expressing control shRNA (shC) or PUS7 shRNA (sh-1 and sh-2). $n=4$ cell culture replicates. $p<0.0001$ for PBT003, PBT707, and PBT111; $p=0.0003$ for PBT726-sh1, and $p<0.0001$ for PBT726-sh2. (FIG. 2B) Sphere formation of GSCs transduced with lentivirus expressing control shRNA (shC) or PUS7 shRNA (sh1 and sh2). $n=4$ cell culture replicates. $p<0.0001$ for PBT003; $p=0.0428$ for PBT707-sh1, $p=0.0231$ for PBT707-sh2; $p=0.0002$ for PBT726-sh1, $p<0.0001$ for PBT726-sh2; $p=0.0005$ for PBT111-sh1, and $p=0.0002$ for PBT111-sh2. (FIG. 2C) Limiting dilution assay (LDA) of GSCs transduced with lentivirus expressing control shRNA (shC) or PUS7 shRNA (sh1 and sh2). (FIG. 2D) The growth of GSCs transduced with lentivirus expressing the WT or the mutant PUS7. $n=4$ cell culture replicates. $p=0.0015$ for PBT003-C, $p=0.0067$ for PBT003-Mut; $p<0.0001$ for PBT707 and PBT726; $p=0.0002$ for PBT111-C, and $p=0.0011$ for PBT111-Mut. (FIG. 2E) Sphere formation of GSCs transduced with lentivirus expressing the WT or the mutant PUS7. $n=4$ cell culture replicates. $p<0.0001$ for PBT003; $p=0.0145$ for PBT707-C, $p=0.0018$ for PBT707-Mut; $p=0.0002$ for PBT726-C, $p=0.0007$ for PBT726-Mut; $p=0.0001$ for PBT111-C, and $p<0.0001$ for PBT111-Mut. (FIG. 2F) LDA of GSCs transduced with lentivirus expressing the WT or the mutant PUS7 controls. Error bars are SE of the mean for FIGS. 2A, 2B, 2D and 2E. * $p<0.05$, ** $p<0.01$, and *** $p<0.001$ by One-way ANOVA and Dunnett's multiple comparisons test for FIGS. 2A, 2B, 2D and 2E. p value for the LDA assay in FIGS. 2C and 2F was provided by the ELDA webtool analysis. See also FIGS. 10A-10J and 11A-11B.

[0012] FIGS. 3A-3J. Reduction of PUS7 expression suppresses tumor progression. (FIG. 3A) Schematic of the experimental design, including PBT707 GSC transplantation and bioluminescent imaging of xenografted tumors. (FIG. 3B) Bioluminescent images of brain tumors in NSG mice transplanted with PBT707 GSCs that were transduced with control shRNA (shC) or PUS7 shRNA (shPUS7). (FIG. 3C) Quantification of the bioluminescence intensity of

tumors after PBT707 GSC transplantation. n=7 mice per group. p=0.0025 for week 4, p=0.0284 for week 6. (FIG. 3D) Schematic of the experimental design, including PBT003 GSC transplantation and bioluminescent imaging of xenografted tumors. (FIG. 3E) Bioluminescent images of brain tumors in NSG mice transplanted with PBT003 GSCs that were transduced with shC or shPUS7. (FIG. 3F) Quantification of the bioluminescence intensity of tumors after PBT003 GSC transplantation. n=7 mice for shC control and n=6 mice for shPUS7 group. p=0.0124 for week 4, p=0.0039 for week 5, and p=0.0002 for week 6. (FIGS. 3G, 3H) The survival curve of NSG mice transplanted with PBT707 GSCs (FIG. 3G) or PBT003 GSCs (FIG. 3H) transduced with shC or shPUS7. The X axis represents days after GSC transplantation. n=7 mice for shC control and n=6 mice for shPUS7 group for FIGS. 3G and 3H. (FIG. 3I) Bioluminescent images of brain tumors in NSG mice transplanted with PBT003 GSCs transduced with control sgRNA, or PUS7 sgRNA (PUS7-sg) with the WT or mutant PUS7. (FIG. 3J) Quantification of the bioluminescence intensity of tumors after PBT003 GSC transplantation. n=5 mice per group. p=0.0141 for PUS7-sg + PUS7 Mut group and p=0.9293 (ns) for PUS7-sg + PUS7 WT group for week 6. *p<0.05 by two-way ANOVA and Dunnett's multiple comparisons test. Error bars are SE of the mean for FIGS. 3C, 3F and 3J. *p<0.05, **p<0.01, and ***p<0.001 by one-tailed Student's t test for FIGS. 3C and 3F. Log-rank test for FIGS. 3G and 3H. See also FIGS. 12A-12C.

[0013] FIGS. 4A-4I. PUS7 inhibitors suppress GSC growth. (FIG. 4A) Mass spectrometry (MS)-based PUS7 activity assay for screening PUS7 inhibitors. PseU: pseudouridine. (FIG. 4B) The dose effect of the C17 PUS7 inhibitor on the growth of PBT003 GSCs. A dose range of 0 to 50 μ M was tested. n=4 cell culture replicates. p<0.0001 for all doses tested compared to 0 μ M condition. (FIG. 4C) The effect of the C17 PUS7 inhibitor on the growth of multiple GSC lines (PBT003, PBT707, PBT726, and PBT111) in nM dose range. A dose range of 0 to 400 nM was tested. n=4 cell culture replicates. p=0.0143, 0.0004, and <0.0001 for 4, 40, and 400 nM conditions, respectively, in PBT003; p=0.0001, <0.0001 for 40, 400 nM conditions, respectively, in PBT707; p=0.0005, <0.0001, <0.0001 for 4, 40, and 400 nM conditions, respectively, in PBT726; p<0.0001, <0.0001, and <0.0001 for 4, 40, and 400 nM conditions, respectively, in PBT111. (FIG. 4D) The effect of the C17 PUS7 inhibitor on the growth of NSC006 cells. n=4 cell culture replicates. p<0.0001 for 400 nM condition in NSC006. (FIG. 4E) The growth of PBT707 GSCs treated with the C17 compound and lentivirus

expressing control sgRNA or sgRNA for PUS7. n=4 cell culture replicates. $p < 0.0001$ for all conditions compared to C17 (-) and PUS7-sg (-) condition. ns: $p = 0.6619$. (FIG. 4F) Rescue of the growth inhibitory effect of C17 by the WT but not the mutant PUS7. n=4 cell culture replicates. $p = 0.0004$ for C17 (-) and PUS7(-) vs C17 (+) and PUS7(-), $p = 0.0001$ for C17 (+) and PUS7 (-) vs C17 (+) and WT PUS7 (+), $p = 0.9383$ for C17 (+) and PUS7 (-) vs C17 (+) and Mut PUS7 (+), $p < 0.0001$ for C17 (+) and WT PUS7 (+) vs C17 (+) and Mut PUS7 (+). (FIG. 4G) The dose effect of the C17 analog on the growth of PBT003 GSCs. n=4 cell culture replicates. $p < 0.0001$ for 2, 10, and 50 μM conditions. (FIG. 4H) Pseudouridine levels in GSCs treated by C17 measured by MS. n=3 RNA sample replicates. $p = 0.0035$ for PBT003, $p = 0.0006$ for PBT707, $p = 0.0042$ for PBT726, and $p = 0.0014$ for PBT111. (FIG. 4I) Pseudouridine levels in GSCs treated by the C17 analog measured by MS. n=3 RNA sample replicates. $p = 0.0008$ for PBT003 and $p = 0.0032$ for PBT111. Error bars are SE of the mean. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ by One-way ANOVA and Dunnett's multiple comparisons test FIGS. 4B-4D and 4G, by One-way ANOVA and Tukey's multiple comparisons test for FIGS. 4E-4F, by one-tailed Student's t test for FIGS. 4H and 4I. See also FIGS. 13A-13D.

[0014] FIGS. 5A-5I. The PUS7 inhibitor suppresses tumor progression. (FIG. 5A) Schematic of the experimental design, including PBT003 GSC transplantation, C17 compound treatment, and bioluminescent imaging of xenografted tumors. (FIG. 5B) Bioluminescent images of brain tumors in NSG mice treated with the C17 compound or vehicle control. (FIG. 5C) Quantification of the bioluminescence intensity of tumors in NSG mice treated with C17 or vehicle control. n=5 mice for control and n=8 mice for the C17 group. $p = 0.0323$ for week 6 and $p = 0.0269$ for week 7. (FIG. 5D) Pseudouridine levels in GSC-derived tumors treated by C17 measured by MS. n=3 RNA sample replicates. $p = 0.0398$. (FIG. 5E) The survival curve of NSG mice treated with C17 or vehicle control. The X axis represents days after treatment. n=11 mice per group. (FIG. 5F) Schematic of the experimental design, including PBT707 GSC transplantation, C17 compound treatment, and bioluminescent imaging of xenografted tumors. (FIG. 5G) Bioluminescent images of brain tumors in NSG mice treated with vehicle control or the C17 compound. (FIG. 5H) Quantification of the bioluminescence intensity of tumors in NSG mice treated with vehicle control or the C17 compound. n=5 mice per group. $p = 0.0267$ for week 9. (FIG. 5I) The survival curve of NSG mice treated with vehicle control or the C17 compound. The X axis represents days after treatment. n=5 mice per group. Error bars are SE of the mean

for FIGS. 5C, 5D and 5H. * $p < 0.05$ by one-tailed Student's t test for FIG. 5C, 5D and 5H. Log-rank test for FIGS. 5E and 5I.

[0015] FIGS. 6A-6H. Pseudouridine modification profile in small RNAs. (FIG. 6A) The pseudouridine (pseU) levels in small RNAs and >200 nt RNAs in PBT003 GSCs transduced with lentivirus expressing Cas9 and control sgRNA (C) or PUS7 sgRNA (sg1 and sg2). $n=3$ RNA sample replicates. $p=0.0025$ for sg1 and $p<0.0001$ for sg2. **(FIG. 6B)** Pseudouridine (PseU) sites in tRNAs in GSCs. ns: $p=0.9341$ for sg1 and $p=0.966$ for sg2. **(FIG. 6C)** Schematics of tRNA-Arg-CCG showing pseudouridine sites Ψ 27, Ψ 55 and PUS7-dependent pseudouridine site Ψ 50 (red). **(FIG. 6D)** A representative PUS7-dependent pseudouridine site identified by small RNA DM- Ψ -seq in GSCs. **(FIG. 6E)** PseU sites in tRNAs in GSCs and NSCs. **(FIG. 6F)** A representative PUS7-dependent pseudouridine site in GSCs compared to NSCs. **(FIG. 6G)** KO of PUS7 induces Arg (CGG) codon-dependent increase of translation revealed by firefly luciferase (F-luc) assay. Renilla luciferase (R-luc) was included as a normalization control. $n=3$ cell culture replicates. $p=0.0852$ (ns) for control, $p=0.0011$ for 6x(CGG)Arg, and $p=0.2183$ (ns) for 6x(CGA)Arg. **(FIG. 6H)** The WT but not the mutant (mut) PUS7 could reverse PUS KO-induced Arg (CGG) codon-dependent translation. $n=3$ cell culture replicates. $p=0.0379$ for PUS7 sg (-) and PUS7 (-) vs PUS7 sg (+) and PUS7 (-), $p=0.0415$ for PUS7 sg (+) and PUS7 (-) vs PUS7 sg (+) and WT PUS7 (+), and $p=0.762$ (ns) for PUS7 sg (+) and PUS7 (-) vs PUS7 sg (+) and Mut PUS7 (+). Error bars are SE of the mean for **FIGS. 6A, 6G, and 6H**. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$, and ns: not statistically significant ($p > 0.05$) by One-way ANOVA and Dunnett's multiple comparisons test for **FIGS. 6A and 6H**, by one-tailed Student's t test for **FIG. 6G**. See also **FIGS. 14A-14I**.

[0016] FIGS. 7A-7F. PUS7 regulates IFN pathway in GSC. (FIG. 7A) A putative motif for PUS7-dependent pseudouridine sites in mRNAs in PBT003 GSCs. **(FIG. 7B)** Representative PUS7-dependent pseudouridine sites identified in mRNAs in PBT003 GSCs. **(FIG. 7C)** Gene set enrichment analysis of hallmark pathways enriched in PUS7 KO PBT003 GSCs from RNA-seq. **(FIG. 7D)** Heatmap showing ISG mRNA expression level change in PUS7 KO PBT003 GSCs. **(FIG. 7E)** RT-PCR of ISGs in PUS7 KO PBT707 cells with overexpression of the WT or the mutant PUS7. $n=6$ technical replicates for ISG15 and $n=3$ technical replicates for XAF1. $p<0.0001$ for PUS7 sg (-) and PUS7 (-) vs PUS7 sg (+) and Mut PUS7 (+), $p=0.0009$ for PUS7

sg (+) and WT PUS7 (+) vs PUS7 sg (+) and Mut PUS7 (+) for ISG15; $p=0.0031$ for PUS7 sg (-) and PUS7 (-) vs PUS7 sg (+) and Mut PUS7 (+), and $p=0.0098$ for PUS7 sg (+) and WT PUS7 (+) vs PUS7 sg (+) and Mut PUS7 (+) for XAF1. Error bars are SE of the mean. $**p<0.01$ and $***p<0.001$ by One-way ANOVA and Dunnett's multiple comparisons. **(FIG. 7F)** Correlation analysis of PUS7 expression and ISG gene expression in GBM IDH WT patients from the TCGA dataset. The degree of correlation was indicated by the size and color of the dots with bigger dots of higher intensity indicating a higher degree of correlation. Wells with dots indicate a significant ($p<0.05$) correlation, whereas blank wells indicate a non-significant ($p>0.05$) correlation. See also **FIGS. 15A-15D**.

[0017] FIGS. 8A-8J. PUS7 regulates GSC growth through controlling TYK2-mediated IFN pathway. (FIG. 8A) TMT mass spectrometry analysis of gene expression change at the protein level in PUS7 KO PBT003 GSCs. TYK2 (red dot), a regulator of IFN pathway, was up-regulated in PUS7 (blue dot) KO PBT003 GSCs, among significantly changed proteins (green dots). The IFN-TYK2 pathway was illustrated on the right. **(FIG. 8B)** Heatmap showing TMT mass spectrometry analysis of gene expression change at the protein level in PUS7 KO PBT003 GSCs. **(FIG. 8C)** RT-PCR of TYK2 in PUS7 KO GSCs. $n=3$ technical replicates. ns: not statistically significant ($p=0.3967$ for PBT003 and $p=0.3445$ for PBT707) by one-tailed Student's t test. **(FIG. 8D)** Western blot of TYK2 in PUS7 KO GSCs. The uncropped blot images for the cropped images shown here are in the source data. Repeated three times with similar results. **(FIG. 8E)** Western blot of STAT1 and phosphorylated STAT1 (pSTAT1) in PUS7 KO GSCs. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. **(FIG. 8F)** Codon bias analysis of tRNA usage for TYK2 gene. **(FIG. 8G)** Polysome profiling analysis for TYK2 in PUS7 KO PBT003 GSCs. $n=3$ technical replicates. $p=0.000538$, 0.000069 , and 0.001196 for fractions 10, 11, 12 respectively. **(FIG. 8H)** Western blot of the Flag-tagged WT or mutant TYK2 fragment in PUS7 KO GSCs. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. **(FIG. 8I)** Cell growth of GSCs transduced with lentivirus expressing control sgRNA (-) or sgRNA for TYK2 (TYK2-sg) or STAT1 (STAT1-sg). $n=4$ cell culture replicates. $p=0.0025$ for TYK2-sg in PBT003, $p=0.0101$ for STAT1-sg in PBT003; $p<0.0001$ for TYK2-sg in PBT707, and <0.0001 for STAT1-sg in PBT707. **(FIG. 8J)** Cell growth of GSCs transduced with lentivirus expressing sgRNA for PUS7 and transduced with

lentivirus expressing sgRNA for TYK2 or STAT1. n=3 cell culture replicates for PBT003, n=4 cell culture replicates for PBT707. p=0.0012 for PUS7 sg (-) vs PUS7 sg (+), p=0.004 for PUS7 sg (+) vs PUS7 sg (+) and TYK2 sg (+), p=0.0005 for PUS7 sg (+) vs PUS7 sg (+) and STAT1 sg (+) in PBT003. p<0.0001 for PUS7 sg (-) vs PUS7 sg (+), PUS7 sg (+) vs PUS7 sg (+) and TYK2 sg (+), and PUS7 sg (+) vs PUS7 sg (+) and STAT1 sg (+) in PBT707. Error bars are SE of the mean for **FIGS. 8C, 8G, 8I, and 8J**. *p<0.05, **p<0.01, and ***p<0.001 by One-way ANOVA and Dunnett's multiple comparisons test for **FIGS. 8I and 8J**, by multiple Student's t test for **FIG. 8G**. See also **FIGS. 16A-16G**.

[0018] FIGS. 9A-9H. High level of PUS7 expression correlates with poor prognosis in GBM patients. (FIG. 9A)

The expression of PUS7 in all glioma patients stratified by the IDH mutation status and 1p19q chromosome co-deletion status from the CGGA dataset (n=182 IDH mut 1p19q codeletion patients, n=315 IDH mut 1p19q noncodeletion patients, n=392 IDH WT patients).

(FIG. 9B) The expressions of PUS7 in GBM patients stratified by IDH mutation status or GCIMP status from the CGGA (n=90 Mut patients and n=288 WT patients), TCGA (n=8 Mut patients and n=142 WT patients), Gravendeel (n=33 Mut patients and n=95 WT patients), and Rembrandt (n=11 GCIMP patients and n=208 Non-GCIMP patients) datasets. **(FIGS. 9C-9F)** Kaplan-Meier survival curves with log-rank analysis to assess the correlation between PUS7 expression and overall survival of IDH WT GBM patients in the CGGA dataset (**FIG. 9C**), TCGA dataset (**FIG. 9E**), and Gravendeel dataset (**FIG. 9F**) or non GCIMP GBM patients in the REMBRANDT dataset (**FIG. 9D**). **(FIG. 9G)** The expression of SOX2 and PUS7 in GBM patients and in non-tumor control samples in GBM tissue microarray analyzed by immunohistochemistry (IHC). Scale bar: 10 μ m. **(FIG. 9H)** Quantification of the expression level of PUS7 in GBM patients and in non-tumor control samples analyzed by IHC. n = 34 individuals for GBM patients and 5 individuals for non-tumor control group. Error bars represent SD of the mean for **FIGS. 9A and 9B**. Error bars represent SE of the mean for **FIG. 9H**. Two-tailed Student's t test for **FIGS. 9A and 9B** (ns: not statistically significant. p=0.2844 for CGGA, p=0.1533 for Gravendeel, and p=0.1095 for Rembrandt). **p<0.01 (p=0.002) by one-tailed Student's t-test for **FIG. 9H**.

[0019] FIGS. 10A-10J. PUS7 regulates GSC growth and self-renewal. (FIG. 10A) RT-PCR analysis of PUS7 knock down (KD) in GSCs (PBT003, PBT707, PBT726, PBT111,

PBT017, and PBT030) transduced with lentivirus expressing control shRNA (shC) or PUS7 shRNA (sh1 and sh2). n=3 technical replicates. p=0.0002 for sh1 and p=0.0002 for sh2 in PBT003; p=0.0005 for sh1 and p=0.0004 for sh2 in PBT707; p=0.0008 for sh1 and p=0.0066 for sh2 in PBT726; p=0.0003 for sh1 and p<0.0001 for sh2 in PBT111; p=0.0009 for sh1 and p=0.0004 for sh2 in PBT017; p<0.0001 for sh1 and p<0.0001 for sh2 in PBT030. **(FIG. 10B)** Western blot analysis of PUS7 KD in GSCs (PBT003 and PBT726). The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. **(FIG. 10C)** Cell growth of GSCs (PBT017 and PBT030) transduced with lentivirus expressing control shRNA (shC) or PUS7 shRNA (sh1 and sh2). n=4 cell culture replicates. p<0.0001 for sh1 and p<0.0001 for sh2 in PBT017; p<0.0001 for sh1 and p=0.0013 for sh2 in PBT030. **(FIG. 10D)** Sphere formation of GSCs (PBT017 and PBT030) transduced with lentivirus expressing shC or PUS7 shRNA (sh1 and sh2). n=4 cell culture replicates. p=0.006 for sh1 and p=0.006 for sh2 in PBT017; p=0.0063 for sh1 and p=0.0063 for sh2 in PBT030. **(FIG. 10E)** Western blot analysis of PUS7 in PBT003 GSCs transduced with lentivirus expressing control sgRNA or sgRNA for PUS7 (sg1 and sg2). The uncropped blot images for the cropped images shown here are in the source data. Repeated four times with similar results. **(FIG. 10F)** Cell growth of PBT003 GSCs transduced with lentivirus expressing control sgRNA or sgRNA for PUS7. n=4 cell culture replicates. p=0.0043 for sg1 and p=0.0009 for sg2. **(FIG. 10G)** Sphere formation of PBT003 GSCs transduced with lentivirus expressing control sgRNA or sgRNA for PUS7. n=20 sphere-forming culture replicates. **(FIG. 10H)** Active Caspase 3 (Cas3) analysis of PBT003 GSCs transduced with lentivirus expressing control sgRNA or sgRNA for PUS7. p<0.0001 for sg1 and p<0.0001 for sg2. n=5 cell culture replicates. **(FIG. 10I)** Cell cycle analysis of PBT003 GSCs transduced with lentivirus expressing control sgRNA or sgRNA for PUS7. **(FIG. 10J)** Western blot analysis showing overexpression of the WT and the mutant PUS7 in PBT003 and PBT707 GSCs. The uncropped blot images for the cropped images shown here are in the source data. Repeated three times with similar results. Error bars are SE of the mean for this figure. **p<0.01 and ***p<0.001 by One-way ANOVA and Dunnett's multiple comparisons test for **FIGS. 10A, 10C, 10D, 10F, and 10G**. ns: not statistically significant (p=0.1372) by one-tailed Student's t-test for **FIG. 10H**.

[0020] FIGS. 11A-11B. 3 PUS7 regulates GSC growth in a catalytic activity dependent manner. The WT but not the mutant (Mut) PUS7 rescued PUS KD-induced growth inhibition in

PBT003 (**FIG. 11A**) and PBT707 (**FIG. 11B**) GSCs. n=4 cell culture replicates. $p<0.0001$ for shPUS7 (-) and PUS7 (-) vs shPUS7 (+) and PUS7 (-), $p<0.0001$ for shPUS7 (+) and PUS7 (-) vs shPUS7 (+) and WT PUS7 (+), ns: $p=0.7179$ for shPUS7 (+) and PUS7 (-) vs shPUS7 (+) and Mut PUS7 (+) in PBT003; $p<0.0001$ for shPUS7 (-) and PUS7(-) vs shPUS7 (+) and PUS7(-), $p<0.0001$ for shPUS7 (+) and PUS7 (-) vs shPUS7 (+) and WT PUS7 (+), ns: $p=0.9976$ for shPUS7 (+) and PUS7 (-) vs shPUS7 (+) and Mut PUS7 (+) in PBT707. Error bars are SE of the mean for this figure. *** $p<0.001$ and ns: not statistically significant ($p>0.05$, defined above) by One-way ANOVA and Dunnett's multiple comparisons test for this figure.

[0021] FIGS. 12A-12C. Inhibition of PUS7 suppresses tumor progression. (FIG. 12A)

Bioluminescent images of brain tumors in NSG mice transplanted with PBT003 GSCs that were transduced with control sgRNA (Control-sg) or PUS7 sgRNA (PUS7-sg). (**FIG. 12B**)

Quantification of the bioluminescence intensity of tumors after PBT003 GSC transplantation.

n=5 mice for each group. Error bars represent SE of the mean. * $p<0.05$ ($p=0.037$) by one-tailed Student's t-test. (**FIG. 12C**)

The survival curves of NSG mice transplanted with PBT003 GSCs transduced with control sgRNA or PUS7 sgRNA. n=5 mice for each group. The X axis represents days after GSC transplantation. Log-rank test for mice survival.

[0022] FIGS. 13A-13D. 5 PUS7 inhibitors suppress GSC growth. (FIG. 13A)

Cell growth of PBT003 GSCs treated with the C4 PUS7 inhibitor. n=4 cell culture replicates.

$p=0.0009$ for 10 μM and $p<0.0001$ for 50 μM condition. (**FIG. 13B**) Cell growth of PBT003

GSCs or NSC009 NSCs treated with the C17 PUS7 inhibitor. n=4 cell culture replicates.

$p<0.0001$ for PBT003 and ns: $p=0.2831$ for NSC009. (**FIG. 13C**) IC₅₀ test for C17 compound in

GSCs (PBT003, PBT707, PBT726, and PBT111). For each GSC, n=4 cell culture replicates for

each treatment condition. (**FIG. 13D**) Cell growth of GSC (PBT707, PBT726, and PBT111)

treated with the C17 analog compound. n=4 cell culture replicates. $p=0.0002$, <0.0001 , <0.0001 ,

<0.0001 for 0.4, 2, 10, 50 μM conditions respectively in PBT707; $p<0.0001$ for 2, 10, 50 μM

conditions in PBT726; $p<0.0001$ for 2, 10, 50 μM conditions in PBT111. Error bars are SE of the

mean. *** $p<0.001$ by One-way ANOVA and Dunnett's multiple comparisons test for **FIGS. 13A**

and **13D**. *** $p<0.001$ and ns: not statistically significant ($p>0.05$, defined above) by one-tailed Student's test for **FIG. 13B**.

[0023] FIGS. 14A-14I. The pseudouridine modification profile in GSCs. (FIG. 14A) A representative PUS7-dependent pseudouridine site identified by small RNA DM-Ψ-seq in PBT003 GSCs. **(FIG. 14B)** Validation of the PUS7-dependent pseudouridine site in tRNA-Arg-CCG-2-1 in PUS7 KO PBT003 GSCs by primer extension assay. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. **(FIG. 14C)** A representative PUS7-dependent pseudouridine site in tRNA-Glu-TTC-4-1 in control or C17-treated PBT003 GSCs. **(FIG. 14D)** Pearson correlation analysis for global tRNA abundance in control and PUS7 KO PBT003 GSCs. **(FIG. 14E)** Expression of tRNA-Arg-CCG in control and PUS7 KO PBT003 GSCs examined by Northern blot analysis. U6 was used as a loading control. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. **(FIG. 14F)** Analysis of tRF abundance in control and PUS7 KO PBT003 GSCs. Red dots: tRFs derived from tRNAs with PUS7-dependent pseudouridine sites. The q value was calculated by Cochran Mantel Haenszel test and adjusted by BH methods. **(FIG. 14G)** The OP-puro incorporation analysis of control and PUS7 KO PBT707 GSCs. **(FIG. 14H)** Nascent protein synthesis and total protein level analysis of control and PUS7 KO 293T cells. **(FIG. 14I)** A luciferase reporter assay to test tRNA translation efficiency in control and PUS7 KO PBT707 cells. n=3 cell culture replicates. Error bars are SE of the mean. *p<0.05 (p=0.0251), and ns: not statistically significant [p>0.05, p=0.0921 for control, p=0.0251 for 6x(CGG)Arg, and p=0.1238 for 6x(CGA)Arg] by one-tailed Student's t-test.

[0024] FIGSG. 15A-15D. PUS7 regulates IFN pathway in GSC. (FIG. 15A) Correlation analysis of PUS7 expression and IFN gene signature (IFN alpha response gene signature and IFN gamma response gene signature) analyzed by ssGSEA in GBM patients from the TCGA dataset. **(FIG. 15B)** The growth of PBT003 and PBT707 GSCs treated with IFNα. n=4 cell culture replicates. p=0.0093 for 20 ng/ml and p=0.0002 for 100 ng/ml in PBT003; p=0.0064, <0.0001, <0.0001 for 4, 20, 100 ng/ml conditions, respectively, in PBT707. **(FIG. 15C)** RT-PCR of ISGs in C17 compound-treated PBT003 GSCs. n=3 technical replicates. p=0.0041 for ISG15 and p=0.0015 for XAF1. **(FIG. 15D)** RT-PCR of ISGs in C17 compound-treated tumor derived from PBT003 GSCs. n=3 technical replicates. p=0.0004 for ISG15 and p=0.0001 for XAF1. Error bars are SE of the mean. **p<0.01 and ***p<0.001 by One-way ANOVA and Dunnett's multiple comparisons test for **FIG. 15B**, and by one-tailed Student's t-test for **FIGS. 15C and 15D**.

[0025] FIGS. 16A-16G. PUS7 regulates GSC growth through controlling TYK2-mediated IFN pathway. (FIG. 16A) RT-PCR analysis of WT or mutant TYK2 in PUS7 KO PBT003 GSCs. n=3 technical replicates. p=0.1533 for WT and p=0.0719 for Mut. **(FIG. 16B)** RT-PCR analysis of WT or mutant TYK2 in PUS7 KO PBT707 GSCs. n=3 technical replicates. p=0.0617 for WT and p=0.0625 for Mut. **(FIG. 16C)** Western blot analysis of WT or mutant TYK2 in PUS7 KO PBT707 GSCs. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. **(FIG. 16D)** Western blot analysis of TYK2 in TYK2 KO PBT003 and PBT707 GSCs. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. **(FIG. 16E)** Western blot analysis of STAT1 and phosphorylated STAT1 (pSTAT1) in STAT1 KO PBT003 and PBT707 GSCs. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. **(FIG. 16F)** Western blot of PUS7 and TYK2 in PBT003 GSCs transduced with lentivirus expressing PUS7 sgRNA and/or lentivirus expressing sgRNA for TYK2. The uncropped blot images for the cropped images shown here are in the source data. Repeated twice with similar results. **(FIG. 16G)** The growth of PBT003 and PBT707 GSCs treated by the STAT1 inhibitor fludarabine with or without lentivirus expressing PUS7 sgRNA. n=4 cell culture replicates. p=0.0003 for PUS7sg (-) and STAT1 inhibitor (-) vs PUS7sg (+) and STAT1 inhibitor (-), p=0.0144 for PUS7sg (+) and STAT1 inhibitor (+) vs PUS7sg (+) and STAT1 inhibitor (-) in PBT003; p=0.0004 for PUS7sg (-) and STAT1 inhibitor (-) vs PUS7sg (+) and STAT1 inhibitor (-), p=0.0114 for PUS7sg (+) and STAT1 inhibitor (+) vs PUS7sg (+) and STAT1 inhibitor (-) in PBT707. Error bars are SE of the mean. *p<0.05, ***p<0.001, and ns: not statistically significant (p>0.05) by One-way ANOVA and Dunnett's multiple comparisons test for **FIG. 16G**, and by one-tailed Student's t-test for **FIGS. 16A and 16B**.

[0026] FIGS. 17A-17C. Pyrazofurin and its effect on GSC growth. (FIG. 17A) Structure of pyrazofurin. **(FIG. 17B)** The dose effect of pyrazofurin on the growth of PBT003 and PBT707 GSCs. n=4 cell culture replicates. p<0.0001 for 0.5, 1, 2, 4, and 8 μ M conditions. **(FIG. 17C)** The dose effect of pyrazofurin on the growth of PBT0030, NSC005, and NSC010 GSCs. n=4 cell culture replicates. p<0.0001 for 0.5, 1, 2, 4, and 8 μ M conditions for PBT030 only.

DETAILED DESCRIPTION

I. Definitions

[0027] 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.

[0028] 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 $-\text{OCH}_2-$.

[0029] 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.

[0030] 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.

[0031] 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.

[0032] 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.

[0033] 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.

[0034] 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. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems are bridged monocyclic rings or fused bicyclic rings. In embodiments, bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form $(CH_2)_w$, where w is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. In embodiments, fused bicyclic cycloalkyl ring systems contain a monocyclic cycloalkyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. In embodiments, the bridged or fused bicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkyl ring. In embodiments, cycloalkyl groups are optionally substituted with one or two groups which are independently oxo or thia. In embodiments, the fused bicyclic cycloalkyl is a 5 or 6 membered monocyclic cycloalkyl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused bicyclic cycloalkyl is optionally substituted by one or two groups which are independently oxo or thia. In embodiments, multicyclic cycloalkyl ring systems are a monocyclic cycloalkyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a

phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. In embodiments, the multicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the base ring. In embodiments, multicyclic cycloalkyl ring systems are a monocyclic cycloalkyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, and a monocyclic heterocyclyl. Examples of multicyclic cycloalkyl groups include, but are not limited to tetradecahydrophenanthrenyl, perhydrophenothiazin-1-yl, and perhydrophenoxazin-1-yl.

[0035] 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. In embodiments, monocyclic cycloalkenyl ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups are unsaturated (i.e., containing at least one annular carbon carbon double bond), but not aromatic. Examples of monocyclic cycloalkenyl ring systems include cyclopentenyl and cyclohexenyl. In embodiments, bicyclic cycloalkenyl rings are bridged monocyclic rings or a fused bicyclic rings. In embodiments, bridged monocyclic rings contain a monocyclic cycloalkenyl ring where two non adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form $(CH_2)_w$, where w is 1, 2, or 3). Representative examples of bicyclic cycloalkenyls include, but are not limited to, norbornenyl and bicyclo[2.2.2]oct 2 enyl. In embodiments, fused bicyclic cycloalkenyl ring systems contain a monocyclic cycloalkenyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. In embodiments, the bridged or fused bicyclic cycloalkenyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkenyl ring. In embodiments, cycloalkenyl groups are optionally substituted with one or two groups which are independently oxo or thia. In embodiments, multicyclic cycloalkenyl rings contain a monocyclic cycloalkenyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic

cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two ring systems independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. In embodiments, the multicyclic cycloalkenyl is attached to the parent molecular moiety through any carbon atom contained within the base ring. In embodiments, multicyclic cycloalkenyl rings contain a monocyclic cycloalkenyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two ring systems independently selected from the group consisting of a phenyl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, and a monocyclic heterocyclyl.

[0036] In embodiments, a heterocycloalkyl is a heterocyclyl. The term “heterocyclyl” as used herein, means a monocyclic, bicyclic, or multicyclic heterocycle. The heterocyclyl monocyclic heterocycle is a 3, 4, 5, 6 or 7 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S where the ring is saturated or unsaturated, but not aromatic. The 3 or 4 membered ring contains 1 heteroatom selected from the group consisting of O, N and S. The 5 membered ring can contain zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The 6 or 7 membered ring contains zero, one or two double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S. The heterocyclyl monocyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the heterocyclyl monocyclic heterocycle. Representative examples of heterocyclyl monocyclic heterocycles include, but are not limited to, azetidiny, azepanyl, aziridiny, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazoliny, imidazolidiny, isothiazoliny, isothiazolidiny, isoxazoliny, isoxazolidiny, morpholiny, oxadiazoliny, oxadiazolidiny, oxazoliny, oxazolidiny, piperaziny, piperidiny, pyranyl, pyrazoliny, pyrazolidiny, pyrroliny, pyrrolidiny, tetrahydrofuranyl, tetrahydrothienyl, thiadiazoliny, thiadiazolidiny, thiazoliny, thiazolidiny, thiomorpholiny, 1,1-dioxidothiomorpholiny (thiomorpholine sulfone), thiopyranyl, and trithianyl. The heterocyclyl bicyclic heterocycle is a monocyclic heterocycle fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycle, or a monocyclic heteroaryl. The heterocyclyl bicyclic heterocycle is connected to the parent molecular moiety through any

carbon atom or any nitrogen atom contained within the monocyclic heterocycle portion of the bicyclic ring system. Representative examples of bicyclic heterocyclyls include, but are not limited to, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, indolin-1-yl, indolin-2-yl, indolin-3-yl, 2,3-dihydrobenzothien-2-yl, decahydroquinolinyl, decahydroisoquinolinyl, octahydro-1H-indolyl, and octahydrobenzofuranyl. In embodiments, heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia. In certain embodiments, the bicyclic heterocyclyl is a 5 or 6 membered monocyclic heterocyclyl ring fused to a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the bicyclic heterocyclyl is optionally substituted by one or two groups which are independently oxo or thia. Multicyclic heterocyclyl ring systems are a monocyclic heterocyclyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. The multicyclic heterocyclyl is attached to the parent molecular moiety through any carbon atom or nitrogen atom contained within the base ring. In embodiments, multicyclic heterocyclyl ring systems are a monocyclic heterocyclyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, and a monocyclic heterocyclyl. Examples of multicyclic heterocyclyl groups include, but are not limited to 10H-phenothiazin-10-yl, 9,10-dihydroacridin-9-yl, 9,10-dihydroacridin-10-yl, 10H-phenoxazin-10-yl, 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl, 1,2,3,4-tetrahydropyrido[4,3-g]isoquinolin-2-yl, 12H-benzo[b]phenoxazin-12-yl, and dodecahydro-1H-carbazol-9-yl.

[0037] 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.

[0038] 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.

[0039] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term “heteroaryl” refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, 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.

[0040] 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.

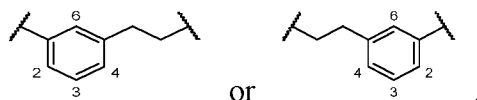
[0041] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other 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.

[0042] The symbol “~” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0043] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0044] 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”).

[0045] 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:



[0046] 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2CH_3$, $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $\square NHNH_2$, $\square ONH_2$, $\square NHC(O)NHNH_2$, substituted or unsubstituted C_1 - C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0047] 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.

[0048] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, $-OR'$, $=O$, $=NR'$, $=N-OR'$, $-NR'R''$, $-SR'$, $-halogen$, $-SiR'R''R'''$, $-OC(O)R'$, $-C(O)R'$, $-CO_2R'$, $-CONR'R''$, $-OC(O)NR'R''$, $-NR'C(O)R'$, $-NR'-C(O)NR'R''$, $-NR'C(O)_2R'$, $-NR-C(NR'R''R''')=NR'''$, $-NR-C(NR'R'')=NR'''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R''$, $-NRSO_2R'$, $-NR'NR'R''$, $-ONR'R''$, $-NR'C(O)NR''NR'''R''''$, $-CN$, $-NO_2$, $-NR'SO_2R''$, $-NR'C(O)R''$, $-NR'C(O)-OR''$, $-NR'OR''$, in a number ranging from zero to $(2m'+1)$, where m' is the total number of carbon atoms in such radical. R , R' , R'' , R''' , and R'''' each preferably

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

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0054] A “substituent group,” as used herein, means a group selected from the following moieties:

- (A) oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-N_3$, 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., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 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, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, 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, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, 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, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, 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).

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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).

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] Certain compounds of the present disclosure possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] “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.

[0074] 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 $\text{C}_1\text{-C}_{20}$ alkyl, or unsubstituted 2 to 20 membered heteroalkyl,” the group may contain one or more unsubstituted $\text{C}_1\text{-C}_{20}$ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0075] 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 R^{13} substituents are present, each R^{13} substituent may be distinguished as R^{13A} , R^{13B} , R^{13C} , R^{13D} , etc., wherein each of R^{13A} , R^{13B} , R^{13C} , R^{13D} , etc. is defined within the scope of the definition of R^{13} and optionally differently.

[0076] 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.

[0077] 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).

[0078] 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.

[0079] 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).

[0080] 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 K_d 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.

[0081] 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, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers.

[0082] 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, 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, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (*e.g.*, Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including AML, ALL, and CML), or multiple myeloma. 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, 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, 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, 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, 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.

[0083] 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.

[0084] 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.

[0085] 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 telangiectatic sarcoma.

[0086] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

[0087] 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, cerebriiform 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, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

[0088] The term “glioblastoma” or “glioblastoma multiforme” refers to an aggressive malignant brain tumor that develops in the brain or spinal cord from astrocytes. The term “glioma” refers to a malignant brain tumor that develops in the brain or spinal cord from glial cells.

[0089] The term “myelodysplastic syndrome” refers to a group of disorders resulting from poorly formed or dysfunctional blood cells. Conditions related to myelodysplastic syndrome include but are not limited to acute myeloid leukemia, myeloproliferative neoplasm, multiple myeloma, myelofibrosis, sideroblastic anemia, chronic myeloid leukemia, and leukemia. The term “acute myeloid leukemia” refers to a type of blood and bone marrow cancer which effects white blood cells. The term “myeloproliferative neoplasm” refers to a group of rare blood cancers in which excess red blood cells, white blood cells or platelets are produced in the bone

marrow. The term “multiple myeloma” refers to cancer of mature plasma cells in the bone marrow. The term “myelofibrosis” refers to a bone marrow disorder in which excessive scar tissue forms in the bone marrow and disrupts body’s normal production of blood cells. The term “sideroblastic anemia” refers to a form of anemia in which the bone marrow produces ringed erythrocytes due to iron accumulation in their nucleus. The term “chronic myeloid leukemia” refers to a type of white blood cancer that is caused due to an acquired genetic defect. The term “leukemia” refers to a cancer that affects production and function of blood cells.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] The terms “anti-cancer agent” and “anticancer agent” are used in accordance with their plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (*e.g.*, cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (*e.g.*, mechloroethamine, cyclophosphamide, chlorambucil, melphalan), ethylenimine and methylmelamines (*e.g.*, hexamethylmelamine, thiotepa), alkyl sulfonates (*e.g.*, busulfan), nitrosoureas (*e.g.*, carmustine, lomustine, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (*e.g.*, 5- azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (*e.g.*, methotrexate), or pyrimidine analogs (*e.g.*, fluorouracil, floxouridine, Cytarabine), purine analogs (*e.g.*, mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (*e.g.*, vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (*e.g.*, irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.*, doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin,

bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin), anthracenedione (*e.g.*, mitoxantrone), substituted urea (*e.g.*, hydroxyurea), methyl hydrazine derivative (*e.g.*, procarbazine), adrenocortical suppressant (*e.g.*, mitotane, aminoglutethimide), epipodophyllotoxins (*e.g.*, etoposide), antibiotics (*e.g.*, daunorubicin, doxorubicin, bleomycin), enzymes (*e.g.*, L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (*e.g.* U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (*e.g.*, rituxan), gossypol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor;

cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone;
 dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine;
 dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron;
 doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine;
 edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue;
 estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane;
 fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone;
 fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine;
 gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors;
 gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide;
 hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat;
 imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor
 inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol,
 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide;
 kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate;
 leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon;
 leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue;
 lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin;
 lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium
 texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol;
 maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone;
 meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim;
 mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide;
 mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim;
 monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium
 cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-
 based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract;
 myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip;
 naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic
 acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide
 antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone;

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

Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; broprimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II (including recombinant interleukin II, or rIL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedpa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine;

thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; tricyclic phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinic sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZZ-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armada/Kyowa Hakko), AM-132 (Armada), AM-138 (Armada/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta

Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desacetyeleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), immunotherapy (e.g., cellular immunotherapy, antibody therapy, cytokine therapy, combination immunotherapy, *etc.*), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In , ^{90}Y , or ^{131}I , *etc.*), immune checkpoint inhibitors (e.g., CTLA4 blockade, PD-1 inhibitors, PD-L1 inhibitors, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbix™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-

380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0094] 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.

[0095] **[0001]** “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.

[0096] "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.

[0097] 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.

[0098] The terms “Patient”, “patient in need thereof”, “subject”, 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. In embodiments, a patient in need thereof is human. In embodiments, a subject is human. In embodiments, a subject in need thereof is human.

[0099] A “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).

[0100] 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.

[0101] 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.

[0102] 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.

[0103] 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.

[0104] As used herein, the term "administering" is used in accordance with its plain and ordinary meaning and includes 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.

[0105] 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.

[0106] 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).

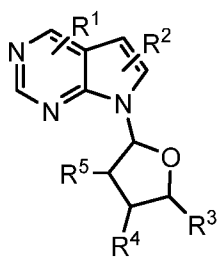
[0107] As used herein, the term “pseudouridine synthase 7 (PUS7) is a nuclear protein involved in stem cell development and intellectual disabilities, and is a novel interactor of SIRT1. The binding regions of PUS7 are predicted and analyzed based on molecular docking studies.

[0108] 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 .

[0109] 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

[0110] In an aspect, provided herein is a compound having the formula (I):

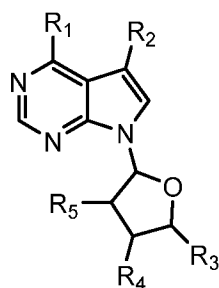


(I), or a pharmaceutically acceptable salt thereof.

[0111] R¹ is hydrogen, halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -N₃, -SO_{n1}R^{1A}, -SO_{v1}NR^{1B}R^{1C}, -NHN^{1B}R^{1C}, -ONR^{1B}R^{1C}, -NHC(O)NHN^{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}SO₂R^{1A}, -NR^{1B}C(O)R^{1D}, -NR^{1B}C(O)OR^{1D}, -NR^{1B}OR^{1D}, -OCX¹₃, -OCHX¹₂, -OCH₂X¹, 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. R² is halogen, -CX²₃, -CHX²₂, -CH₂X², -CN, -N₃, -SO_{n2}R^{2A}, -SO_{v2}NR^{2B}R^{2C}, -NHN^{2B}R^{2C}, -ONR^{2B}R^{2C}, -NHC(O)NHN^{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}SO₂R^{2A}, -NR^{2B}C(O)R^{2D}, -NR^{2B}C(O)OR^{2D}, -NR^{2B}OR^{2D}, -OCX²₃, -OCHX²₂, -OCH₂X², 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. R³ is hydrogen, halogen, -CX³₃, -CHX³₂, -CH₂X³, -CN, -N₃, -SO_{n3}R^{3A}, -SO_{v3}NR^{3B}R^{3C}, -NHN^{3B}R^{3C}, -ONR^{3B}R^{3C}, -NHC(O)NHN^{3B}R^{3C}, -NHC(O)NR^{3B}R^{3C}, -N(O)_{m3}, -NH₂, -C(O)R^{3D}, -C(O)OR^{3D}, -C(O)NH₂, -OR^{3A}, -NR^{3B}SO₂R^{3A}, -NR^{3B}C(O)R^{3D}, -NR^{3B}OR^{3D}, -OCX³₃, -OCHX³₂, -OCH₂X³, 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. R⁴ is hydrogen, halogen, -CX⁴₃, -CHX^{4.1}₂, -CH₂X^{4.1}, -CN, -N₃, -SO_{n4}R^{4A}, -SO_{v4}NR^{4B}R^{4C}, -NHN^{4B}R^{4C}, -ONR^{4B}R^{4C}, -NHC(O)NHN^{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}SO₂R^{4A}, -NR^{4B}C(O)R^{4D}, -NR^{4B}C(O)OR^{4D}, -NR^{4B}OR^{4D}, -OCX⁴₃, -OCHX⁴₂, -OCH₂X⁴, 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, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-CN$, $-N_3$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHN R^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHN R^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^5_3$, $-OCHX^5_2$, $-OCH_2X^5$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^{1A} , 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} , and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, 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} , and R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a 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) or 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) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^1 , X^2 , X^3 , X^4 , and X^5 are independently halogen (i.e., $-Cl$, $-Br$, $-I$ or $-F$). n_1 , n_2 , n_3 , n_4 , and n_5 are independently an integer from 0 to 4; m_1 , m_2 , m_3 , m_4 , m_5 , v_1 , v_2 , v_3 , v_4 , and v_5 are independently 1 or 2.

[0112] In embodiments, provided herein is a compound having the formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof. In

embodiments, R^1 , R^2 , R^3 , R^4 , and R^5 are described herein, including embodiments.

[0113] In embodiments, R^1 is halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCHX^1_2$, $-OCH_2X^1$, $-CN$, $-N_3$, $-SO_{nl}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHN R^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHN R^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{ml}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, 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.

[0114] In embodiments, R^1 is halogen (e.g., -F, -Cl, Br, -I), $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCHX^1_2$, $-OCH_2X^1$, $-CN$, $-S(O)_2R^{1A}$, $-SR^{1A}$, $-S(O)R^{1A}$, $-SO_2NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_2$, $-NR^{1A}R^{1B}$, $-NHN R^{1A}R^{1B}$, $-C(O)R^{1A}$, $-C(O)-OR^{1A}$, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHN R^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$, $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, (e.g., $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-N_3$, $-CN$, $-SH$, $-SCH_3$, $-SO_2H$, $-SO_2CH_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-NHC(O)NH_2$, $-NHC(O)NHCH_3$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, $-C(O)OCH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-OH$, $-OCH_3$, $-NHSO_2H$, $-NHSO_2CH_3$, $-NHC(O)H$, $-NCH_3C(O)H$, $-NHC(O)OH$, $-NCH_3C(O)OH$, $-NHOH$, $-NCH_3OH$, or $-NCH_3OCH_3$), 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 is independently -F, -Cl, -Br, or -I.

[0115] In embodiments, R^1 is -F, -Cl, Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -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).

[0116] In embodiments, R^1 is -F, -Cl, Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -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).

[0117] In embodiments, R^1 is 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^{11} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{11} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{11} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{11} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{11} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{11} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0118] In embodiments, R^1 is 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 $-OCH_2I$.

[0119] In embodiments, R^1 is R^{11} -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^1 is R^{11} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^1 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^1 is R^{11} -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^1 is R^{11} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^1 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^1 is R^{11} -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^1 is R^{11} -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).

[0120] 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, -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).

[0121] 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.

[0122] In embodiments, R¹¹ is R¹²-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹¹ is R¹²-substituted (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹¹ is unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹¹ is 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 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 unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹¹ is R¹²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹¹ is R¹²-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹¹ is unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹¹ is 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 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 unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹¹ is R¹²-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹¹ is R¹²-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹¹ is unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹¹ is 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 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 unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0123] R^{12} 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^{13} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{13} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{13} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{13} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{13} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{13} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0124] In embodiments, R^{12} 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 $-OCH_2I$.

[0125] In embodiments, R^{12} is R^{13} -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^{12} is R^{13} -substituted (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{12} is unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{12} is R^{13} -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^{12} is R^{13} -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 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 R^{13} -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^{12} is R^{13} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{12} is unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{12} is 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 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 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 R^{13} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{12} is R^{13} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{12} is unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{12} is 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 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 unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0126] R^{13} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, 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).

[0127] In embodiments, R^{13} 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 $-OCH_2I$.

[0128] In embodiments, R^{13} 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).

[0129] The definitions of R^{1A} , R^{1B} , R^{1C} , and R^{1D} are the same as the definition of R^1 . The definitions of R^{11A} , R^{11B} , R^{11C} , and R^{11D} are the same as the definition of R^{11} . The definitions of R^{12A} , R^{12B} , R^{12C} , and R^{12D} are the same as the definition of R^{12} . The definitions of R^{13A} , R^{13B} , R^{13C} , and R^{13D} are the same as the definition of R^{13} .

[0130] In embodiments, R^{1A} is independently hydrogen, 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^{11A} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{11A} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{11A} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{11A} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{11A} -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} aryl, C_{10} aryl, or phenyl), or R^{11A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0131] In embodiments, R^{11A} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{12A} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{12A} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{12A} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{12A} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{12A} -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} aryl, C_{10} aryl, or phenyl), or R^{12A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0132] In embodiments, R^{12A} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{13A} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{13A} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{13A} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{13A} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{13A} -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} aryl, C_{10} aryl, or phenyl), or R^{13A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0133] In embodiments, R^{13A} 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).

[0134] In embodiments, R^{1B} is independently 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^{11B} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{11B} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{11B} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{11B} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{11B} -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} aryl, C_{10} aryl, or

phenyl), or R^{11B}-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, R^{11B} 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^{12B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{12B}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{12B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{12B}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{12B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{12B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0136] In embodiments, R^{12B} 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^{13B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{13B}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{13B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower

substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{13B}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{13B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{13B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0137] In embodiments, R^{13B} 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).

[0138] In embodiments, R^{1C} is independently hydrogen, 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^{11C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{11C}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{11C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{11C}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered

heterocycloalkyl), R^{11C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{11C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0139] In embodiments, R^{11C} 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, R^{12C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{12C}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{12C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{12C}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{12C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{12C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0140] In embodiments, R^{12C} 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, R^{13C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{13C}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{13C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{13C}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{13C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{13C}-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, R^{13C} 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).

[0142] In embodiments, R^{1D} is independently 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, R^{11D}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{11D}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{11D}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{11D}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{11D} -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} aryl, C_{10} aryl, or phenyl), or R^{11D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0143] In embodiments, R^{11D} 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^{12D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{12D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{12D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{12D} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{12D} -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} aryl, C_{10} aryl, or phenyl), or R^{12D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0144] In embodiments, R^{12D} 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^{13D} -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 alkyl,

C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{13D}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{13D}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{13D}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{13D}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{13D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0145] In embodiments, R^{13D} 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, R¹ is -COOH, -NH₂, substituted or unsubstituted C₁-C₃ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R¹ is -COOH. In embodiments, R¹ is -NH₂. In embodiments, R¹ is substituted or unsubstituted C₁-C₃ alkyl. In embodiments, R¹ is unsubstituted methyl. In embodiments, R¹ is unsubstituted ethyl. In embodiments, R¹ is unsubstituted propyl. In embodiments, R¹ is unsubstituted n-propyl. In embodiments, R¹ is unsubstituted isopropyl. In embodiments, R¹ is substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0147] In embodiments, R² is halogen, -CX²₃, -CHX²₂, -CH₂X², -CN, -N₃, -SO_{n2}R^{2A}, -SO_{v2}NR^{2B}R^{2C}, -NHN^{2B}R^{2C}, -ONR^{2B}R^{2C}, -NHC(O)NHN^{2B}R^{2C}, -NHC(O)NR^{2B}R^{2C}, -N(O)_{m2},

$-\text{NR}^{2\text{B}}\text{R}^{2\text{C}}$, $-\text{C}(\text{O})\text{R}^{2\text{D}}$, $-\text{C}(\text{O})\text{OR}^{2\text{D}}$, $-\text{C}(\text{O})\text{NR}^{2\text{B}}\text{R}^{2\text{C}}$, $-\text{OR}^{2\text{A}}$, $-\text{NR}^{2\text{B}}\text{SO}_2\text{R}^{2\text{A}}$, $-\text{NR}^{2\text{B}}\text{C}(\text{O})\text{R}^{2\text{D}}$, $-\text{NR}^{2\text{B}}\text{C}(\text{O})\text{OR}^{2\text{D}}$, $-\text{NR}^{2\text{B}}\text{OR}^{2\text{D}}$, $-\text{OCX}^2_3$, $-\text{OCHX}^2_2$, $-\text{OCH}_2\text{X}^2$, 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.

[0148] In embodiments, R^2 is halogen (e.g., -F, -Cl, Br, -I), $-\text{CX}^2_3$, $-\text{CHX}^2_2$, $-\text{CH}_2\text{X}^2$, $-\text{OCX}^2_3$, $-\text{OCHX}^2_2$, $-\text{OCH}_2\text{X}^2$, -CN, $-\text{S}(\text{O})_2\text{R}^{2\text{A}}$, $-\text{SR}^{2\text{A}}$, $-\text{S}(\text{O})\text{R}^{2\text{A}}$, $-\text{SO}_2\text{NR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{N}(\text{O})_2$, $-\text{NR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{NHNR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{C}(\text{O})\text{R}^{2\text{A}}$, $-\text{C}(\text{O})-\text{OR}^{2\text{A}}$, $-\text{C}(\text{O})\text{NR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{C}(\text{O})\text{NHNR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{OR}^{2\text{A}}$, $-\text{NR}^{2\text{A}}\text{SO}_2\text{R}^{2\text{B}}$, $-\text{NR}^{2\text{A}}\text{C}(\text{O})\text{R}^{2\text{B}}$, $-\text{NR}^{2\text{A}}\text{C}(\text{O})\text{OR}^{2\text{B}}$, $-\text{NR}^{2\text{A}}\text{OR}^{2\text{B}}$, $-\text{N}_3$, (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, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHC}(\text{O})\text{NHCH}_3$, -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, 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^2 is independently -F, -Cl, -Br, or -I.

[0149] In embodiments, R^2 is -F, -Cl, Br, -I, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CCl}_3$, $-\text{CHCl}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CBr}_3$, $-\text{CHBr}_2$, $-\text{CH}_2\text{Br}$, $-\text{Cl}_3$, $-\text{CHI}_2$, $-\text{CH}_2\text{I}$, $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHF}_2$, -

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).

[0150] In embodiments, R² is -F, -Cl, Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -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).

[0151] In embodiments, R^2 is 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^{21} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{21} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{21} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{21} -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).

[0152] In embodiments, R^2 is 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 $-OCH_2I$.

[0153] 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).

[0154] R^{21} is halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, 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).

[0155] In embodiments, R^{21} is 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 $-OCH_2I$.

[0156] In embodiments, R^{21} is 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 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 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 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 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 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 R^{22} -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^{21} is R^{22} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{21} is unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{21} is 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 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 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 R^{22} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{21} is R^{22} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{21} is unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{21} is 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 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 unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0157] R^{22} is halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{23} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 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., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 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., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{23} -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^{22} is 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 $-OCH_2I$.

[0159] In embodiments, R^{22} is R^{23} -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^{22} is R^{23} -substituted (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{22} is unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{22} is R^{23} -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^{22} is R^{23} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{22} is unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{22} is R^{23} -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^{22} is R^{23} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{22} is unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{22} is R^{23} -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^{22} is R^{23} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{22} is unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{22} is R^{23} -substituted

or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R²² is R²³-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R²² is unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R²² is R²³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R²² is R²³-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R²² is unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0160] R²³ is 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).

[0161] In embodiments, R²³ is 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.

[0162] In embodiments, R²³ is 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).

[0163] The definitions of R^{2A}, R^{2B}, R^{2C}, and R^{2D} are the same as the definition of R². The definitions of R^{21A}, R^{21B}, R^{21C}, and R^{21D} are the same as the definition of R²¹. The definitions of R^{22A}, R^{22B}, R^{22C}, and R^{22D} are the same as the definition of R²². The definitions of R^{23A}, R^{23B}, R^{23C}, and R^{23D} are the same as the definition of R²³.

[0164] In embodiments, R^{2A} is hydrogen, 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^{21A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{21A}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{21A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{21A}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{21A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{21A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0165] In embodiments, R^{21A} is 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^{22A}-substituted (e.g., substituted with a substituent group, a size-limited

substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{22A}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{22A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{22A}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{22A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{22A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0166] In embodiments, R^{22A} is 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^{23A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{23A}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{23A}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{23A}-substituted 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^{23A} is 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).

[0168] In embodiments, R^{2B} 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, R^{21B} -substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{21B} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{21B} -substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{21B} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{21B} -substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{21B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0169] In embodiments, R^{21B} is 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, R^{22B} -substituted (e.g., substituted with a substituent group, a size-limited

substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{22B}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{22B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{22B}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{22B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{22B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0170] In embodiments, R^{22B} is 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, R^{23B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{23B}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{23B}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{23B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0171] In embodiments, R^{23B} is 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).

[0172] In embodiments, R^{2C} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -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, -OCH₂I, R^{21C} -substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{21C} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{21C} -substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{21C} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{21C} -substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{21C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0173] In embodiments, R^{21C} is halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -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, -OCH₂I, R^{22C} -substituted (e.g., substituted with a substituent group, a size-limited

substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{22C}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{22C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{22C}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{22C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{22C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0174] In embodiments, R^{22C} is 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^{23C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{23C}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{23C}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{23C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0175] In embodiments, R^{23C} is 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).

[0176] In embodiments, R^{2D} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -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, -OCH₂I, R^{21D} -substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{21D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{21D} -substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{21D} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{21D} -substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{21D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0177] In embodiments, R^{21D} is halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -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, -OCH₂I, R^{22D} -substituted (e.g., substituted with a substituent group, a size-limited

substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{22D}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{22D}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{22D}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{22D}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{22D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0178] In embodiments, R^{22D} is 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^{23D}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{23D}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23D}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{23D}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23D}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{23D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0179] In embodiments, R^{23D} is 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).

[0180] In embodiments, R^2 is $-\text{COOH}$, $-\text{NH}_2$, substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^2 is $-\text{COOH}$. In embodiments, R^2 is $-\text{NH}_2$. In embodiments, R^2 is substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl. In embodiments, R^2 is unsubstituted methyl. In embodiments, R^2 is unsubstituted ethyl. In embodiments, R^2 is unsubstituted propyl. In embodiments, R^2 is unsubstituted isopropyl. In embodiments, R^2 is substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^2 is $-\text{CH}_2\text{NH}_2$. In embodiments, R^2 is $\text{C}(\text{NOH})\text{NH}_2$.

[0181] In embodiments, R³ is hydrogen, halogen, -CX³₃, -CHX³₂, -CH₂X³, -CN, -N₃, -SO_{n3}R^{3A}, -SO_{v3}NR^{3B}R^{3C}, -NHN^{3B}R^{3C}, -ONR^{3B}R^{3C}, -NHC(O)NHN^{3B}R^{3C}, -NHC(O)NR^{3B}R^{3C}, -N(O)_{m3}, -NH₂, -C(O)R^{3D}, -C(O)OR^{3D}, -C(O)NH₂, -OR^{3A}, -NR^{3B}SO₂R^{3A}, -NR^{3B}C(O)OR^{3D}, -NR^{3B}OR^{3D}, -OCX³₃, -OCHX³₂, -OCH₂X³, 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.

[0182] In embodiments, R³ is hydrogen, halogen (e.g., -F, -Cl, Br, -I), -CX³₃, -CHX³₂, -CH₂X³, -OCX³₃, -OCHX³₂, -OCH₂X³, -CN, -S(O)₂R^{3A}, -SR^{3A}, -S(O)R^{3A}, -SO₂NR^{3A}R^{3B}, -NHC(O)NR^{3A}R^{3B}, -N(O)₂, -NR^{3A}R^{3B}, -NHNR^{3A}R^{3B}, -C(O)R^{3A}, -C(O)-OR^{3A}, -C(O)NR^{3A}R^{3B}, -C(O)NHNR^{3A}R^{3B}, -OR^{3A}, -NR^{3A}SO₂R^{3B}, -NR^{3A}C(O)R^{3B}, -NR^{3A}C(O)OR^{3B}, -NR^{3A}OR^{3B}, -N₃, (e.g., -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -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, 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). X³ is independently – F, –Cl, –Br, or –I.

[0183] In embodiments, R³ is hydrogen, –F, –Cl, Br, –I, –CF₃, –CHF₂, –CH₂F, –CCl₃, –CHCl₂, –CH₂Cl, –CBr₃, –CHBr₂, –CH₂Br, –CI₃, –CHI₂, –CH₂I, –OCF₃, –OCCl₃, –OCBr₃, –OCI₃, –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).

[0184] In embodiments, R³ is hydrogen, -F, -Cl, Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -Cl₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -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).

[0185] 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, -OCI₃, -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).

[0186] In embodiments, R^3 is hydrogen, 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 $-OCH_2I$.

[0187] In embodiments, R^3 is R^{31} -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^3 is R^{31} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^3 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^3 is R^{31} -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^3 is R^{31} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^3 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., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^3 is R^{31} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^3 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^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., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^3 is R^{31} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^3 is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} 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).

[0188] R^{31} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{32} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 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., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 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., C_6 - C_{10} aryl, C_{10} 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).

[0189] In embodiments, R^{31} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0190] In embodiments, R^{31} is 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 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 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 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 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 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 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 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 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 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 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 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 R^{32} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{31} is R^{32} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{31} is unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{31} is 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 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 unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0191] 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).

[0192] 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 $-OCH_2I$.

[0193] In embodiments, R^{32} is R^{33} -substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R^{32} is R^{33} -substituted (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R^{32} is unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R^{32} is 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 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 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 R^{33} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{32} is R^{33} -substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{32} is unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{32} is R^{33} -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^{32} is R^{33} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{32} is unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{32} is R^{33} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{32} is R^{33} -substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{32} is unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{32} is R^{33} -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^{32} is R^{33} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{32} is unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0194] R^{33} is independently halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -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, -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).

[0195] In embodiments, R³³ is independently halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -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.

[0196] 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).

[0197] The definitions of R^{3A}, R^{3B}, R^{3C}, and R^{3D} are the same as the definition of R³. The definitions of R^{31A}, R^{31B}, R^{31C}, and R^{31D} are the same as the definition of R³¹. The definitions of R^{32A}, R^{32B}, R^{32C}, and R^{32D} are the same as the definition of R³². The definitions of R^{33A}, R^{33B}, R^{33C}, and R^{33D} are the same as the definition of R³³.

[0198] In embodiments, R^{3A} is Hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -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, -OCH₂I, R^{31A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆

alkyl, or C₁-C₄ alkyl), R^{31A}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{31A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{31A}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{31A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{31A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0199] In embodiments, R^{31A} is 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^{32A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{32A}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{32A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{32A}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{32A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{32A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0200] In embodiments, R^{32A} 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^{33A} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{33A} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{33A} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{33A} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{33A} -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} aryl, C_{10} aryl, or phenyl), or R^{33A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0201] In embodiments, R^{33A} 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).

[0202] In embodiments, R^{3B} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-$

OCH₂Br, -OCH₂I, R^{31B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{31B}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{31B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{31B}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{31B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{31B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0203] In embodiments, R^{31B} is 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, R^{32B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{32B}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{32B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{32B}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{32B}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{32B}-

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^{32B} is 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^{33B} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{33B} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{33B} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{33B} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{33B} -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} aryl, C_{10} aryl, or phenyl), or R^{33B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0205] In embodiments, R^{33B} is 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).

[0206] In embodiments, R^{3C} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$,

-NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{31C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{31C}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{31C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{31C}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{31C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{31C}-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^{31C} is 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, R^{32C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{32C}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{32C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{32C}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{32C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or

lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{32C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0208] In embodiments, R^{32C} is 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, R^{33C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{33C}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{33C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{33C}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{33C}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{33C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0209] In embodiments, R^{33C} is 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).

[0210] In embodiments, R^{3D} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{31D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{31D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{31D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{31D} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{31D} -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} aryl, C_{10} aryl, or phenyl), or R^{31D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0211] In embodiments, R^{31D} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{32D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{32D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{32D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{32D} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{32D} -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} aryl, C_{10} aryl, or phenyl), or R^{32D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0212] In embodiments, R^{32D} is independently halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{33D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{33D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{33D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{33D} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{33D} -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} aryl, C_{10} aryl, or phenyl), or R^{33D} -substituted 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^{33D} is 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).

[0214] In embodiments, R^3 is substituted or unsubstituted C_1 - C_3 alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^3 is substituted C_1 - C_3 alkyl. In embodiments, R^3 is unsubstituted C_1 - C_3 alkyl. In embodiments, R^3 is substituted 2 to 4 membered heteroalkyl. In embodiments, R^3 is unsubstituted 2 to 4 membered heteroalkyl.

[0215] In embodiments, R^4 is hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-CN$, $-N_3$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^4_3$, $-OCHX^4_2$, $-OCH_2X^4$, 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.

[0216] In embodiments, R^4 is hydrogen, halogen (e.g., $-F$, $-Cl$, Br , $-I$), $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCHX^4_2$, $-OCH_2X^4$, $-CN$, $-S(O)_2R^{4A}$, $-SR^{4A}$, $-S(O)R^{4A}$, $-SO_2NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_2$, $-NR^{4A}R^{4B}$, $-NHN R^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHN R^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, (e.g., $-CF_3$, $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CHCl_2$, $-CH_2Cl$, $-CBr_3$, $-CHBr_2$, $-CH_2Br$, $-Cl_3$, $-CHI_2$, $-CH_2I$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-N_3$, $-CN$, $-SH$, $-SCH_3$, $-SO_2H$, $-SO_2CH_3$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-NHC(O)NH_2$, $-NHC(O)NHCH_3$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-C(O)H$, $-C(O)CH_3$, $-C(O)OH$, $-C(O)OCH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-OH$, $-OCH_3$, $-NHSO_2H$, $-NHSO_2CH_3$, $-NHC(O)H$, $-NCH_3C(O)H$, $-NHC(O)OH$, $-NCH_3C(O)OH$, $-NHOH$, $-NCH_3OH$, or $-NCH_3OCH_3$), 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., 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). X⁴ is independently – F, –Cl, –Br, or –I.

[0217] In embodiments, R⁴ is hydrogen, –F, –Cl, Br, –I, –CF₃, –CHF₂, –CH₂F, –CCl₃, –CHCl₂, –CH₂Cl, –CBr₃, –CHBr₂, –CH₂Br, –Cl₃, –CHI₂, –CH₂I, –OCF₃, –OCCL₃, –OCBr₃, –OCI₃, –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).

[0218] In embodiments, R⁴ is hydrogen, –F, –Cl, Br, –I, –CF₃, –CHF₂, –CH₂F, –CCl₃, –CHCl₂, –CH₂Cl, –CBr₃, –CHBr₂, –CH₂Br, –Cl₃, –CHI₂, –CH₂I, –OCF₃, –OCCL₃, –OCBr₃, –OCI₃, –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).

[0219] 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).

[0220] 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, or -OCH₂I.

[0221] In embodiments, R⁴ is R⁴¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁴ is R⁴¹-substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁴ is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁴ is R⁴¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁴ is R⁴¹-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁴ 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., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^4 is R^{41} -substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^4 is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ 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., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^4 is R^{41} -substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^4 is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ 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).

[0222] R^{41} is 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^{42} -substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ 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., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ 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., C₆-C₁₀ aryl, C₁₀ 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).

[0223] In embodiments, R^{41} is 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 $-OCH_2I$.

[0224] In embodiments, R^{41} is 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 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 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 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 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 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 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 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 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 R^{42} -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^{41} is R^{42} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{41} is unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{41} is R^{42} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{41} is R^{42} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{41} is unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{41} is R^{42} -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^{41} is R^{42} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{41} is unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0225] R^{42} is 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^{43} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{43} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{43} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{43} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{43} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{43} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0226] In embodiments, R^{42} is 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 $-OCH_2I$.

[0227] In embodiments, R^{42} is R^{43} -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^{42} is R^{43} -substituted (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{42} is unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{42} is R^{43} -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^{42} is R^{43} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{42} is unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{42} is R^{43} -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^{42} is R^{43} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{42} is unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{42} is R^{43} -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^{42} is R^{43} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{42} is unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{42} is R^{43} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{42} is R^{43} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{42} is unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{42} is R^{43} -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^{42} is R^{43} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{42} is unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0228] R^{43} is halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, 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).

[0229] In embodiments, R^{43} is halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0230] In embodiments, R^{43} is 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).

[0231] The definitions of R^{4A} , R^{4B} , R^{4C} , and R^{4D} are the same as the definition of R^4 . The definitions of R^{41A} , R^{41B} , R^{41C} , and R^{41D} are the same as the definition of R^{41} . The definitions of R^{42A} , R^{42B} , R^{42C} , and R^{42D} are the same as the definition of R^{42} . The definitions of R^{43A} , R^{43B} , R^{43C} , and R^{43D} are the same as the definition of R^{43} .

[0232] In embodiments, R^{4A} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{41A} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{41A} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{41A} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{41A} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{41A} -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} aryl, C_{10} aryl, or phenyl), or R^{41A} -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^{41A} is 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^{42A} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{42A} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{42A} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{42A} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{42A} -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} aryl, C_{10} aryl, or phenyl), or R^{42A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0234] In embodiments, R^{42A} is 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^{43A} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{43A} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{43A} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{43A} -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

heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{43A} -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} aryl, C_{10} aryl, or phenyl), or R^{43A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0235] In embodiments, R^{43A} is 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).

[0236] In embodiments, R^{4B} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{41B} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{41B} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{41B} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{41B} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{41B} -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} aryl, C_{10} aryl, or phenyl), or R^{41B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0237] In embodiments, R^{41B} is 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^{42B} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{42B} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{42B} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{42B} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{42B} -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} aryl, C_{10} aryl, or phenyl), or R^{42B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0238] In embodiments, R^{42B} is 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^{43B} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{43B} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{43B} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{43B} -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

heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{43B} -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} aryl, C_{10} aryl, or phenyl), or R^{43B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0239] In embodiments, R^{43B} is 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).

[0240] In embodiments, R^{4C} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{41C} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{41C} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{41C} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{41C} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{41C} -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} aryl, C_{10} aryl, or phenyl), or R^{41C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0241] In embodiments, R^{41C} is 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^{42C} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{42C} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{42C} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{42C} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{42C} -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} aryl, C_{10} aryl, or phenyl), or R^{42C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0242] In embodiments, R^{42C} is 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^{43C} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{43C} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{43C} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{43C} -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

heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{43C} -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} aryl, C_{10} aryl, or phenyl), or R^{43C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0243] In embodiments, R^{43C} is 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).

[0244] In embodiments, R^{4D} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{41D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{41D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{41D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{41D} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{41D} -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} aryl, C_{10} aryl, or phenyl), or R^{41D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0245] In embodiments, R^{41D} is 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^{42D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{42D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{42D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{42D} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{42D} -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} aryl, C_{10} aryl, or phenyl), or R^{42D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0246] In embodiments, R^{42D} is 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^{43D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{43D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{43D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{43D} -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

heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{43D} -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} aryl, C_{10} aryl, or phenyl), or R^{43D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0247] In embodiments, R^{43D} is 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).

[0248] In embodiments, R^4 is $-\text{COOH}$, $-\text{OH}$, substituted or unsubstituted C_1 - C_3 alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^4 is $-\text{COOH}$. In embodiments, R^4 is $-\text{OH}$. In embodiments, R^4 is substituted or unsubstituted C_1 - C_3 alkyl. In embodiments, R^4 is substituted C_1 - C_3 alkyl. In embodiments, R^4 is unsubstituted C_1 - C_3 alkyl. In embodiments, R^4 is substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^4 is substituted 2 to 4 membered heteroalkyl. In embodiments, R^4 is unsubstituted 2 to 4 membered heteroalkyl.

[0249] In embodiments, R^5 is hydrogen, halogen, $-\text{CX}^5_3$, $-\text{CHX}^5_2$, $-\text{CH}_2\text{X}^5$, $-\text{CN}$, $-\text{N}_3$, $-\text{SO}_{n5}\text{R}^{5A}$, $-\text{SO}_{v5}\text{NR}^{5B}\text{R}^{5C}$, $-\text{NHN}^{5B}\text{R}^{5C}$, $-\text{ONR}^{5B}\text{R}^{5C}$, $-\text{NHC}(\text{O})\text{NHN}^{5B}\text{R}^{5C}$, $-\text{NHC}(\text{O})\text{NR}^{5B}\text{R}^{5C}$, $-\text{N}(\text{O})_{m5}$, $-\text{NR}^{5B}\text{R}^{5C}$, $-\text{C}(\text{O})\text{R}^{5D}$, $-\text{C}(\text{O})\text{OR}^{5D}$, $-\text{C}(\text{O})\text{NR}^{5B}\text{R}^{5C}$, $-\text{OR}^{5A}$, $-\text{NR}^{5B}\text{SO}_2\text{R}^{5A}$, $-\text{NR}^{5B}\text{C}(\text{O})\text{R}^{5D}$, $-\text{NR}^{5B}\text{C}(\text{O})\text{OR}^{5D}$, $-\text{NR}^{5B}\text{OR}^{5D}$, $-\text{OCX}^5_3$, $-\text{OCHX}^5_2$, $-\text{OCH}_2\text{X}^5$, 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.

[0250] In embodiments, R^5 is hydrogen, halogen (e.g., $-\text{F}$, $-\text{Cl}$, Br , $-\text{I}$), $-\text{CX}^5_3$, $-\text{CHX}^5_2$, $-\text{CH}_2\text{X}^5$, $-\text{OCX}^5_3$, $-\text{OCHX}^5_2$, $-\text{OCH}_2\text{X}^5$, $-\text{CN}$, $-\text{S}(\text{O})_2\text{R}^{5A}$, $-\text{SR}^{5A}$, $-\text{S}(\text{O})\text{R}^{5A}$, $-\text{SO}_2\text{NR}^{5A}\text{R}^{5B}$, $-\text{NHC}(\text{O})\text{NR}^{5A}\text{R}^{5B}$, $-\text{N}(\text{O})_2$, $-\text{NR}^{5A}\text{R}^{5B}$, $-\text{NHN}^{5A}\text{R}^{5B}$, $-\text{C}(\text{O})\text{R}^{5A}$, $-\text{C}(\text{O})\text{-OR}^{5A}$, $-\text{C}(\text{O})\text{NR}^{5A}\text{R}^{5B}$,

$-\text{C}(\text{O})\text{NHN}^{\text{5A}}\text{R}^{\text{5B}}$, $-\text{OR}^{\text{5A}}$, $-\text{NR}^{\text{5A}}\text{SO}_2\text{R}^{\text{5B}}$, $-\text{NR}^{\text{5A}}\text{C}(\text{O})\text{R}^{\text{5B}}$, $-\text{NR}^{\text{5A}}\text{C}(\text{O})\text{OR}^{\text{5B}}$, $-\text{NR}^{\text{5A}}\text{OR}^{\text{5B}}$, $-\text{N}_3$,
 (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^5 is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$.

[0251] In embodiments, R^5 is hydrogen, $-\text{F}$, $-\text{Cl}$, 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., 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., 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).

[0252] In embodiments, R⁵ is hydrogen, -F, -Cl, Br, -I, -CF₃, -CHF₂, -CH₂F, -CCl₃, -CHCl₂, -CH₂Cl, -CBr₃, -CHBr₂, -CH₂Br, -CI₃, -CHI₂, -CH₂I, -OCF₃, -OCCl₃, -OCBr₃, -OCI₃, -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).

[0253] In embodiments, R⁵ is hydrogen, 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, R⁵¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R⁵¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R⁵¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R⁵¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6

membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R⁵¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R⁵¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0254] In embodiments, R⁵ is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -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.

[0255] In embodiments, R⁵ is R⁵¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁵ is R⁵¹-substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁵ is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R⁵ is R⁵¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁵ is R⁵¹-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁵ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R⁵ is R⁵¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁵ is R⁵¹-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁵ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R⁵ is R⁵¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁵ is R⁵¹-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁵ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁵ is R⁵¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁵ is R⁵¹-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁵ is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁵ is R⁵¹-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).

[0256] 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).

[0257] In embodiments, R^{51} is 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 $-OCH_2I$.

[0258] In embodiments, R^{51} is R^{52} -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^{51} is R^{52} -substituted (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{51} is unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{51} is R^{52} -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^{51} is R^{52} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{51} is unsubstituted

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

[0259] R^{52} is 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^{53} -substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ 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., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ 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., C₆-C₁₀ aryl, C₁₀ 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).

[0260] In embodiments, R^{52} is 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 $-OCH_2I$.

[0261] In embodiments, R^{52} is 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 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 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 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 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 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 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 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 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 R^{53} -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^{52} is R^{53} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{52} is unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{52} is R^{53} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{52} is R^{53} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{52} is unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{52} is R^{53} -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^{52} is R^{53} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{52} is unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0262] R^{53} is halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, 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).

[0263] In embodiments, R^{53} is halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, or $-OCH_2I$.

[0264] In embodiments, R^{53} is 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).

[0265] The definitions of R^{5A} , R^{5B} , R^{5C} , and R^{5D} are the same as the definition of R^5 . The definitions of R^{51A} , R^{51B} , R^{51C} , and R^{51D} are the same as the definition of R^{51} . The definitions of R^{52A} , R^{52B} , R^{52C} , and R^{52D} are the same as the definition of R^{52} . The definitions of R^{53A} , R^{53B} , R^{53C} , and R^{53D} are the same as the definition of R^{53} .

[0266] In embodiments, R^{5A} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$,

-NHSO₂H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCCl₃, -OCBr₃, -OCl₃, -OCHF₂, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -OCH₂Cl, -OCH₂Br, -OCH₂I, R^{51A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{51A}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{51A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{51A}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{51A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{51A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0267] In embodiments, R^{51A} is 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^{52A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{52A}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{52A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{52A}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{52A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or

lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{52A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0268] In embodiments, R^{52A} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -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, -OCH₂I, R^{53A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{53A}-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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{53A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{53A}-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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{53A}-substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{53A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0269] In embodiments, R^{53A} is 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).

[0270] In embodiments, R^{5B} 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^{51B} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{51B} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{51B} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{51B} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{51B} -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} aryl, C_{10} aryl, or phenyl), or R^{51B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0271] In embodiments, R^{51B} is 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^{52B} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{52B} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{52B} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{52B} -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

heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{52B} -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} aryl, C_{10} aryl, or phenyl), or R^{52B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0272] In embodiments, R^{52B} is 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^{53B} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{53B} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{53B} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{53B} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{53B} -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} aryl, C_{10} aryl, or phenyl), or R^{53B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0273] In embodiments, R^{53B} is 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).

[0274] In embodiments, R^{51C} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{51C} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{51C} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{51C} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{51C} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{51C} -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} aryl, C_{10} aryl, or phenyl), or R^{51C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0275] In embodiments, R^{52C} is halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-N_3$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NH SO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, R^{52C} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{52C} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{52C} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{52C} -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

heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{52C} -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} aryl, C_{10} aryl, or phenyl), or R^{52C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0276] In embodiments, R^{52C} is 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^{53C} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{53C} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{53C} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{53C} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{53C} -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} aryl, C_{10} aryl, or phenyl), or R^{53C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0277] In embodiments, R^{53C} is 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).

[0278] In embodiments, R^{5D} is hydrogen, 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^{51D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{51D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{51D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{51D} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{51D} -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} aryl, C_{10} aryl, or phenyl), or R^{51D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0279] In embodiments, R^{51D} is 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^{52D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{52D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{52D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{52D} -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

heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{52D} -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} aryl, C_{10} aryl, or phenyl), or R^{52D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0280] In embodiments, R^{52D} is 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^{53D} -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 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{53D} -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 heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{53D} -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 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{53D} -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 heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{53D} -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} aryl, C_{10} aryl, or phenyl), or R^{53D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0281] In embodiments, R^{53D} is 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).

[0282] In embodiments, R^5 is $-\text{COOH}$, $-\text{OH}$, substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^5 is $-\text{COOH}$. In embodiments, R^5 is $-\text{OH}$. In embodiments, R^5 is substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl. In embodiments, R^5 is substituted $\text{C}_1\text{-C}_3$ alkyl. In embodiments, R^5 is unsubstituted $\text{C}_1\text{-C}_3$ alkyl. In embodiments, R^5 is substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^5 is substituted 2 to 4 membered heteroalkyl. In embodiments, R^5 is unsubstituted 2 to 4 membered heteroalkyl.

[0283] 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.

[0284] 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.

[0285] 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.

[0286] 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.

[0287] 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.

[0288] In embodiments, m_1 is 1 or 2. In embodiments, m_1 is 1. In embodiments, m_1 is 2.

[0289] In embodiments, m_2 is 1 or 2. In embodiments, m_2 is 1. In embodiments, m_2 is 2.

[0290] In embodiments, m_3 is 1 or 2. In embodiments, m_3 is 1. In embodiments, m_3 is 2.

[0291] In embodiments, m_4 is 1 or 2. In embodiments, m_4 is 1. In embodiments, m_4 is 2.

- [0292] In embodiments, m5 is 1 or 2. In embodiments, m5 is 1. In embodiments, m5 is 2.
- [0293] In embodiments, v1 is 1 or 2. In embodiments, v1 is 1. In embodiments, v1 is 2.
- [0294] In embodiments, v2 is 1 or 2. In embodiments, v2 is 1. In embodiments, v2 is 2.
- [0295] In embodiments, v3 is 1 or 2. In embodiments, v3 is 1. In embodiments, v3 is 2.
- [0296] In embodiments, v4 is 1 or 2. In embodiments, v4 is 1. In embodiments, v4 is 2.
- [0297] In embodiments, v5 is 1 or 2. In embodiments, v5 is 1. In embodiments, v5 is 2.
- [0298] X¹ is halogen. In embodiments, halogen is -F, -Cl, -Br, -I. In embodiments, X¹ is -F. In embodiments, X¹ is -Cl. In embodiments, X¹ is -Br. In embodiments, X¹ is -I.
- [0299] X² is halogen. In embodiments, halogen is -F, -Cl, -Br, -I. In embodiments, X² is -F. In embodiments, X² is -Cl. In embodiments, X² is -Br. In embodiments, X² is -I.
- [0300] X³ is halogen. In embodiments, halogen is -F, -Cl, -Br, -I. In embodiments, X³ is -F. In embodiments, X³ is -Cl. In embodiments, X³ is -Br. In embodiments, X³ is -I.
- [0301] X⁴ is halogen. In embodiments, halogen is -F, -Cl, -Br, -I. In embodiments, X⁴ is -F. In embodiments, X⁴ is -Cl. In embodiments, X⁴ is -Br. In embodiments, X⁴ is -I.
- [0302] X⁵ is halogen. In embodiments, halogen is -F, -Cl, -Br, -I. In embodiments, X⁵ is -F. In embodiments, X⁵ is -Cl. In embodiments, X⁵ is -Br. In embodiments, X⁵ is -I.
- [0303] 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).

[0304] 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.

[0305] 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.

[0306] 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.

[0307] 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.

[0308] 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} , and R^{5D} 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.

[0309] In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0310] In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently unsubstituted alkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0311] In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} are independently unsubstituted heteroalkyl. In embodiments, $R^1, R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^2, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^3, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^4, R^{4A}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^5, R^{5A}, R^{5B}, R^{5C},$ and R^{5D} 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} , and R^{5D} , 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} , and R^{5D} are independently an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered).

[0312] 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} , and R^{5D} 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} , and R^{5D} 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} , and R^{5D} 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} , and R^{5D} 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} , and R^{5D} are independently substituted 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} , and R^{5D} are independently unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0313] 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} , and R^{5D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl. 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} , and R^{5D} are

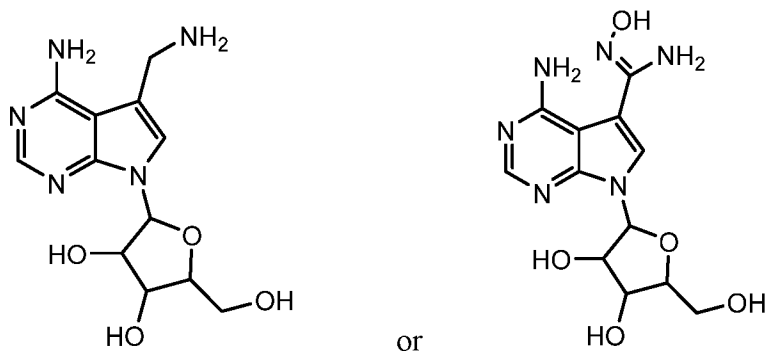
independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl. In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A}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

[0314] 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} , and R^{5D} are independently substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or 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} , and R^{5D} 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} , and R^{5D} 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} , and R^{5D} are independently substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ 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} , and R^{5D} are independently substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ 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} , and R^{5D} are independently an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

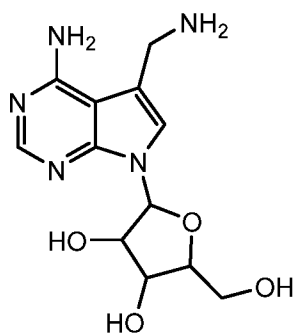
[0315] In embodiments, R^1 , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^2 , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^3 , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^4 , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^5 , R^{5A} , R^{5B} , R^{5C} , and R^{5D} are independently substituted (e.g.,

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} , and R^{5D} 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} , and R^{5D} 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} , and R^{5D} 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} , and R^{5D} 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} , and R^{5D} are independently an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

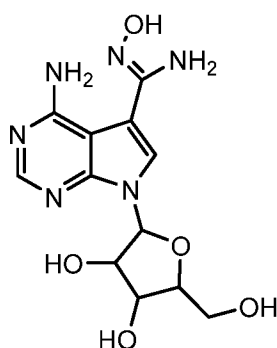
[0316] In embodiments, the compound is:



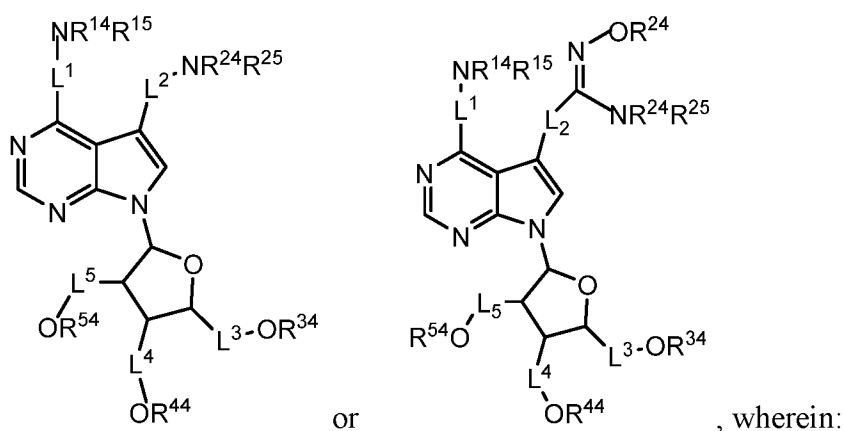
[0317] In embodiments, the compound is:



[0318] In embodiments, the compound is:



[0319] In embodiments, the compound is:



R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently hydrogen, 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; and

L^1 , L^2 , L^3 , L^4 , and L^5 are independently a bond or unsubstituted C_1 - C_5 alkyl.

[0320] In embodiments, L^1 , L^2 , L^3 , L^4 , and L^5 are independently a bond. In embodiments, L^1 , L^2 , L^3 , L^4 , and L^5 are independently an unsubstituted C_1 - C_5 alkyl.

[0321] In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently a 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).

[0322] In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) alkyl. In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroalkyl. In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) cycloalkyl. In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heterocycloalkyl. In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) aryl. In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently a substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) heteroaryl.

[0323] In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently an unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄). In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently an unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered). In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently an unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆). In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered). In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently an unsubstituted aryl (e.g., C₆-C₁₀, C₆, or phenyl). In embodiments, R^{14} , R^{15} , R^{24} , R^{25} , R^{34} , R^{44} , and R^{54} are independently an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0324] 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).

[0325] In embodiments, the compound has the formula as described elsewhere herein, for example within a table, claim or example.

III. Pharmaceutical compositions

[0326] In an aspect, there is provided a pharmaceutical composition, including a compound as described herein, including embodiments, e.g., structural Formula (I) or (Ia) and a pharmaceutically acceptable excipient.

[0327] 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.

[0328] 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.

[0329] The pharmaceutical compositions containing the active ingredient (e.g., an inhibitor of Wnt/catenin signaling pathway, 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.

[0330] 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(methylmethacrolate) 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.

[0331] 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.

[0332] 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.

[0333] 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.

[0334] 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.

[0335] 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.

[0336] 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).

[0337] 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.

[0338] 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.

[0339] 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.

[0340] 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).

[0341] 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.

[0342] 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

[0343] In an aspect, there is provided a method of inhibiting of pseudouridine synthase 7 (PUS7) activity, said method comprising contacting the PUS7 with the compound described herein, including embodiments (e.g., structural Formula (I) or (Ia), or a pharmaceutically acceptable salt thereof).

[0344] In an aspect, there is provided a method of treating a PUS7 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 (Ia), or a pharmaceutically acceptable salt thereof).

[0345] 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), (Ia), or a pharmaceutically acceptable salt thereof). In embodiments, the cancer is associated with increased PUS7 gene expression. In embodiments, the cancer is associated with increased PUS7 activity.

[0346] 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, 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, 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, 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, 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.

[0347] 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.

[0348] In embodiments, the cancer is prostate cancer, glioblastoma, glioma, myelodysplastic syndrome, leukemia, stomach cancer, colorectal cancer, endometrial cancer, breast cancer, pancreatic cancer, kidney cancer, mesothelioma, or sarcoma.

[0349] 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.

[0350] 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.

[0351] 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.

[0352] 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 oral administration. In embodiments, the administration is parenteral administration.

[0353] 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.

[0354] 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.

[0355] 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.

[0356] 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.

[0357] In embodiments, the compounds contemplated by the present disclosure may be administered (e.g., orally) 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 an oral agent, the compositions can be provided in the form of tablets, capsules and the like containing from 0.05 to 1000 milligrams of the active ingredient, particularly 0.05, 0.1, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 125.0, 150.0, 175.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient. A pharmaceutically acceptable carrier(s), diluent(s) and/or excipient(s) may be present in an amount of from about 0.1 g to about 2.0 g.

[0358] In embodiments, the dosage of the desired compound is contained in a “unit dosage form”. 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

[0359] In another aspect, provided herein is a kit including a compound described herein (i.e., compound of structural formula (I) or (Ia)) 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.

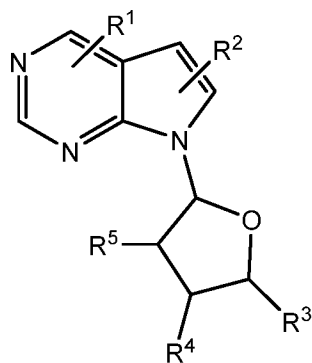
[0360] A kit may include one or more of the compounds disclosed herein (e.g., provided in a sterile container), which may be in the form of a pharmaceutical composition suitable for administration to a subject. In embodiments, the compound has the structure of Formulae (I), (Ia), or a pharmaceutically 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).

[0361] 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).

[0362] 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.

EMBODIMENTS

[0363] Embodiment 1. A compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof,

wherein:

[0364] R¹ is halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -N₃, -SO_{n1}R^{1A}, -SO_{v1}NR^{1B}R^{1C}, -NHNR^{1B}R^{1C}, -ONR^{1B}R^{1C}, -NHC(O)NHNR^{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}SO₂R^{1A}, -NR^{1B}C(O)R^{1D}, -NR^{1B}C(O)OR^{1D}, -NR^{1B}OR^{1D}, -OCX¹₃, -OCHX¹₂, -OCH₂X¹, 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;

[0365] R² is halogen, -CX²₃, -CHX²₂, -CH₂X², -CN, -N₃, -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}SO₂R^{2A}, -NR^{2B}C(O)R^{2D}, -NR^{2B}R^{2C}CNOR^{2D}, -NR^{2B}C(O)OR^{2D}, -NR^{2B}OR^{2D}, -OCX²₃, -OCHX²₂, -OCH₂X², 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;

[0366] R³ is hydrogen, halogen, -CX³₃, -CHX³₂, -CH₂X³, -CN, -N₃, -SO_{n3}R^{3A}, -SO_{v3}NR^{3B}R^{3C}, -NHNR^{3B}R^{3C}, -ONR^{3B}R^{3C}, -NHC(O)NHNR^{3B}R^{3C}, -NHC(O)NR^{3B}R^{3C}, -N(O)_{m3}, -NH₂, -C(O)R^{3D}, -C(O)OR^{3D}, -C(O)NH₂, -OR^{3A}, -NR^{3B}SO₂R^{3A}, -NR^{3B}C(O)OR^{3D}, -NR^{3B}OR^{3D}, -OCX³₃, -OCHX³₂, -OCH₂X³, 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, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-CN$, $-N_3$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^4_3$, $-OCHX^4_2$, $-OCH_2X^4$, 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;

[0367] R^5 is hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-CN$, $-N_3$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHN R^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHN R^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^5_3$, $-OCHX^5_2$, $-OCH_2X^5$, 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;

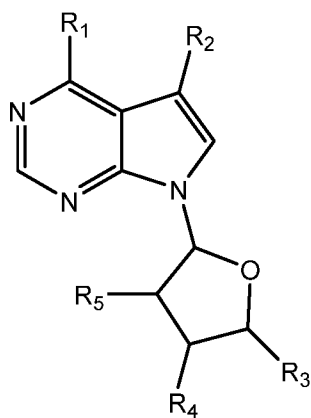
[0368] R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, substituted or unsubstituted 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} , and R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

[0369] X^1 , X^2 , X^3 , X^4 , and X^5 are independently halogen;

[0370] n_1 , n_2 , n_3 , n_4 , and n_5 are independently an integer from 0 to 4; and

[0371] m_1 , m_2 , m_3 , m_4 , m_5 , v_1 , v_2 , v_3 , v_4 , and v_5 are independently 1 or 2.

[0372] Embodiment 2. The compound of embodiment 1 having the formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof.

[0373] Embodiment 3. The compound of embodiment 1 or 2, wherein R^1 is $-\text{COOH}$, NH_2 , substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0374] Embodiment 4. The compound of any one of embodiments 1 to 3, wherein R^1 is $-\text{COOH}$, or $-\text{NH}_2$.

[0375] Embodiment 5. The compound of any one of embodiments 1 to 4, wherein R^1 is $-\text{NH}_2$.

[0376] Embodiment 6. The compound of embodiment 1 or 2, wherein R^2 is $-\text{COOH}$, $-\text{NH}_2$, substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0377] Embodiment 7. The compound of any one of embodiments 1 to 6, wherein R^2 is substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0378] Embodiment 8. The compound of any one of embodiments 1 to 7, wherein R^2 is $-\text{CH}_2\text{NH}_2$.

[0379] Embodiment 9. The compound of any one of embodiments 1 to 7, wherein R^2 is $\text{C}(\text{NOH})\text{NH}_2$.

[0380] Embodiment 10. The compound of embodiment 1 or 2, wherein R^3 is unsubstituted $\text{C}_1\text{-C}_3$ alkyl or unsubstituted 2 to 4 membered heteroalkyl.

[0381] Embodiment 11. The compound of any one of embodiments 1 to 10, wherein R^3 is unsubstituted 2 membered heteroalkyl.

[0382] Embodiment 12. The compound of any one of embodiments 1 to 10, wherein R^3 is CH_2OH .

[0383] Embodiment 13. The compound of embodiment 1 or 2, wherein R^4 is $-COOH$, $-OH$, substituted or unsubstituted C_1-C_3 alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0384] Embodiment 14. The compound of any one of embodiments 1 to 13, wherein R^4 is $-OH$, substituted or unsubstituted C_1-C_3 alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.

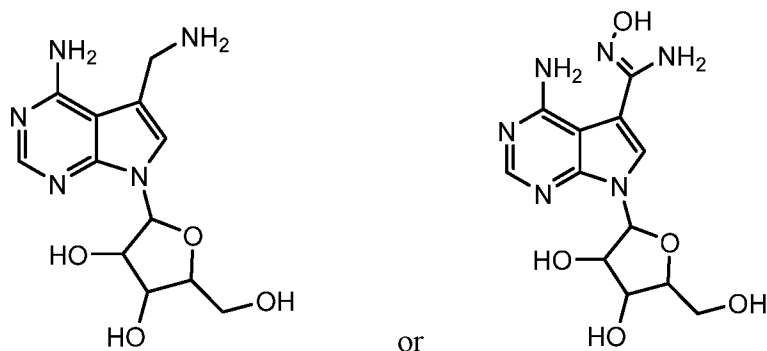
[0385] Embodiment 15. The compound of any one of embodiments 1 to 14, wherein R^4 is $-OH$.

[0386] Embodiment 16. The compound of embodiment 1 or 2, wherein R^5 is $-COOH$, $-OH$, substituted or unsubstituted C_1-C_3 alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0387] Embodiment 17. The compound of any one of embodiments 1 to 16, wherein R^5 is $-OH$, substituted or unsubstituted C_1-C_3 alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0388] Embodiment 18. The compound of any one of embodiments 1 to 17, wherein R^5 is $-OH$.

[0389] Embodiment 19. The compound of any one of embodiments 1 to 18, wherein the compound is:



[0390] Embodiment 20. A pharmaceutical composition comprising a compound of any one of embodiments 1 to 19 and a pharmaceutically acceptable excipient.

[0391] Embodiment 21. A method of inhibiting pseudouridine synthase 7 (PUS7) activity, said method comprising contacting the PUS7 with the compound of any one of embodiments 1 to 19.

[0392] Embodiment 22. 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 19.

[0393] Embodiment 23. The method of embodiment 22, wherein said cancer is associated with increased PUS7 gene expression or increased PUS7 activity.

[0394] Embodiment 24. The method of embodiment 21 or 22, wherein said cancer is prostate cancer, glioblastoma, glioma, myelodysplastic syndrome, leukemia, stomach cancer, colorectal cancer, endometrial cancer, breast cancer, pancreatic cancer, kidney cancer, mesothelioma, or sarcoma.

[0395] Embodiment 25. The method of any one of embodiments 22-24, further comprising administering to said subject an anti-cancer agent.

[0396] Embodiment 26. The method of embodiment 25, wherein the anti-cancer agent is a mitotic inhibitor or a histone deacetylase (HDAC) inhibitor.

EXAMPLES

[0397] The analysis of PUS enzymes in GBM revealed statistically significant association between PUS expression and GBM patient median survival in GBM datasets. Such association prompted to explore the role of PUS7 in GBM tumorigenesis. By manipulating PUS7 expression in GSCs through gene knockdown, knockout and overexpression, it was demonstrated that PUS7 plays an important role in GBM tumorigenesis. Through RNA, protein and pseudouridine profiling, it was shown that PUS7 controls GSC growth through codon-specific translational control of key regulators of GSCs via PUS7-dependent tRNA modification. Also identified were chemical inhibitors of PUS7 and the effect of these chemicals in GSC growth and tumorigenicity was determined.

METHODS

Cell culture

[0398] GSCs were derived from newly diagnosed grade IV GBM patients. GSCs and NSCs were maintained in spheres in DMEM-F12 medium supplemented with 2 mM L-glutamine, 27.4 mM HEPES, B27, 20 ng ml⁻¹ EGF, 20 ng ml⁻¹ FGF and 5 µg ml⁻¹ heparin as described (Cui, Q., *et al.*, *supra*). Established GBM cells were maintained in DMEM medium supplemented with 2 mM L-glutamine and 10% FBS. All cultures were mycoplasma-free as confirmed using MycoAlert PLUS Mycoplasma Detection Kit (Lonza). GSCs or NSCs were treated with PUS7 inhibitors at indicated concentration for 72 h. GSCs were treated with IFNα at indicated doses for 6 days.

Human Subjects Research

[0399] Specimens without identifiers from leftover surgical tissues were used in this study. The information was evaluated and determined to not involve human subjects research by City of Hope Institutional Review Board (IRB).

Animals

[0400] All animal-related work was performed under the IACUC protocol 05050 approved by the City of Hope Institutional Animal Care and Use Committee. Mice were housed in rooms with 20 to 24 °C room temperature, 30-70 % humidity, and a 12/12 hours light/dark cycle.

Plasmid DNA

[0401] shRNAs were cloned into the pHIV7-GFP lentiviral vector. sgRNAs were cloned into lentiCRISPR v2 vector (Addgene plasmid # 52961) or lentiCRISPR v2-Blast vector (Addgene plasmid # 83480). The WT or mutant PUS7 (D256A) (Behm-Ansmant, I., *et al*, *RNA (New York, N.Y)* **9**, 1371-1382 (2003)) was cloned into the CSC lentiviral vector. The reporter plasmids were prepared by inserting 6 x CGG or 6 x CGA sequences before the firefly luciferase coding region in the pmirGlo luciferase expression vector (Promega) to obtain the 6 x Arg (CGG) or the 6 x Arg (CGA) reporter plasmid. The TYK2 fragment plasmids were cloned by replacing the eGFP sequences in the pLENTI-DDK-puro-eGFP vector (Addgene plasmid #123299) with the WT or mutant TYK2 fragment (aa 100 - aa 264).

Viral preparation and transduction

[0402] Lentiviruses were prepared using 293T cells as described (Shi, Y., *et al.*, *Nature* **427**, 78-83 (2004)). GSCs were transduced by incubating with lentivirus and 4 µg ml⁻¹ polybrene (AmericanBio) for 24 h. The sgRNA-expressing lentivirus transduced cells were selected with 5 µg ml⁻¹ blasticidin (Gibco) or 2 µg ml⁻¹ puromycin (Gibco).

GBM database analysis

[0403] Data from the CGGA, the Rembrandt, the TCGA and the Gravendeel datasets were accessed through the GlioVis portal (Bowman, R.L., *et al.*, *Neuro-oncology* **19**, 139-141 (2017)), (<http://gliovis.bioinfo.cnio.es/>). The detailed setting for patient survival and gene expression analyses is listed in Supplemental Tables 1 and 2. Raw data for patient survival and gene expression analyses downloaded from the GlioVis portal is included in Supplemental Table 12. For PUS7 and ISG correlation analysis, IDH wild type GBM patient data from TCGA GBM HG-U133A dataset were used. The single-sample GSEA (ssGSEA) analysis was performed using the

Gene Set Variation Analysis (GSVA) package 1.40.0 (Bowman, R.L., et al., *Neuro-oncology* **19**, 139-141 (2017).

Immunohistochemistry

[0404] Immunohistochemistry analysis was performed on GBM tissue microarray (US Biomax, GL806f) using antibodies for SOX2 and PUS7. The intensity of the PUS7 signal was quantified on a relative scale from 1 to 3 (1=low, 2=medium, and 3=high).

RT-PCR and Western blot

[0405] RT-PCR and Western blot were performed as described (Cui, Q., *et al.*, *supra*).- Bio-Rad's Image Lab 6.0 was used for Western blot data analysis.

Cell growth, sphere formation and limiting dilution assays

[0406] GSC growth, sphere formation and limiting dilution assays were performed as described (Cui, Q., *et al.*, *supra*). For growth, GSCs were seeded at 5×10^4 cells per well in 24-well plates and cultured for 7 days. Cell growth was monitored by cell counting using a hemocytometer. For sphere formation, GSCs were seeded at 1 cell per well in 96-well plates or 100 cells per well in 48-well plates and cultured for 2 weeks. Spheres were counted under microscope. For limiting dilution assay, GSCs were seeded into 96-well plates at 1, 5, 10, 20, 50 and 100 cells per well. The number of sphere-forming wells was recorded in two weeks. The limiting dilution analysis was performed using the extreme limiting dilution analysis software at <http://bioinf.wehi.edu.au/software/elda>.

Cell cycle analysis

[0407] The cell cycle analysis was performed using FxCycle™ PI/RNase Staining Solution. Propidium iodide staining of DNA content in fixed cells was analyzed by flow cytometry to determine the cell cycle status.

GSC transplantation and PUS7 inhibitor treatment

[0408] One week after viral transduction, 2×10^5 GSCs were transplanted into the frontal lobes of mouse brain (AP +0.6 mm, ML +1.6 mm and DV -2.6 mm) by stereotaxic intracranial injection. For PUS7 inhibitor treatment, one week after GSC transplantation, tumors were detected by bioluminescence imaging and mice were treated with 5 μ l of 400 nM PUS7 inhibitor C17 in PBS per mouse, corresponding to a dose of 25.9 ng/Kg C17 for a 25 g mouse for PBT003 cells, or 5 μ l of 1 μ M C17 in PBS per mouse, corresponding to a dose of 64.9 ng/Kg C17 for a 25 g mouse for PBT707 cells, or vehicle control, by intratumoral injection once a week for four weeks using the same coordinates for GSC transplantation. Tumor growth was monitored by bioluminescence imaging every other week for six to nine weeks. The bioluminescence intensity was quantified using Spectral Instruments Imaging-AMIView 1.7.061. Mice were euthanized when one or more of the early euthanasia criteria (failure to eat food/ drink water for 24 h; failure to make normal postural adjustments/ display normal behavior; obvious distress such as posture hunched, unresponsive; weight loss > 20%) were met. The survival of mice was recorded.

Virtual screen for PUS7 inhibitor

[0409] The virtual screen was performed using in-house developed LiVS (Ligand Virtual Screening Pipeline) as described (Su, R., *et al.*, *Cancer cell* **38**, 79-96 e11 (2020)). The PUS7 catalytic center was used as a pocket for the virtual screening. A small molecule compound library containing the NCI-DTP (developmental therapeutics program) compounds and the FDA-approved drugs was used to identify inhibitor hits for PUS7. The available compounds from the top 100 hits were validated.

In vitro PUS7 activity assay

[0410] For PUS7 activity assay, 100 μ M candidate compound was added to 1 μ g PUS7 recombinant protein, 0.5 μ g in vitro T7 transcribed tRNA-Glu substrates, 20 U rRNasin, 100 mM Tris-HCl pH 8.0, 100 mM Ammonium acetate, 2 mM DTT, 0.1 mM EDTA, and 5 mM $MgCl_2$, in 25 μ l reaction, and incubated at 37 °C for 1 h. RNA was purified by ethanol precipitation and subjected to MS analysis to quantify pseudouridine level. The small molecule screening information is summarized in Supplemental Table 13.

MS analysis for pseudouridine levels

[0411] Quantification of pseudouridine level in RNA samples was performed as described (Li, X., *et al.*, *supra*) with modifications. Briefly, 200 ng RNA samples were digested with 1 U nuclease P1 at 42 °C for 1-6 hours. Then 2.5 µl MES buffer (pH 6.5), 0.25 µl rSAP (1,000 U/ml), and 2.25 µl nuclease-free water were added, and incubated at 37 °C overnight. Ψ/U levels were analyzed using LC-MS/MS (Agilent 6490 QQQ or AB SCIEX QTRAP 5500).

Small RNA DM-Ψ-seq

[0412] Small RNA was extracted using MEGAclear Transcription Clean-Up Kit (Invitrogen). For library preparation, small RNA fraction was demethylated by AlkB protein, recovered by phenol chloroform extraction, labeled by CMC and then treated with Na₂CO₃. RNA was labeled with CMC as described (Li, X., *et al.*, *supra*; Song, J., *et al.*, *supra*) with modifications. Briefly, 10 µg RNAs were fragmented into 150-200 nt fragments. RNA was recovered by ethanol precipitation and denatured at 80 °C for 5 min. 5 µg denatured RNA was added to 100 µl BEU buffer with or without 0.2M CMC. The CMC reaction was carried out at 37 °C for 20 min, followed by ethanol precipitation. Recovered RNA was re-dissolved in 50 µl Na₂CO₃ buffer, incubated at 37 °C for 6 h, followed by ethanol precipitation. Library preparation was performed according to the eCLIP protocol as described (Van Nostrand, E.L., *et al.*, *Nature methods* **13**, 508-514 (2016)). with modifications. RNA samples were dephosphorylated with CIP. 3' adaptor ligation was performed with RNA T4 ligase 2 truncated KQ, followed by 5' deadenylase and RecJf treatment. Reverse transcription was performed with Superscript III reverse transcriptase, and cDNA was treated with 1 µl RNase H. 5' linker ligation was performed with T4 RNA ligase 1 high concentration. cDNA was amplified by PCR. The PCR products were purified and sequenced on Illumina Hiseq 2000 or X10.

Primer extension and Northern blot

[0413] Primer extension and Northern blot were performed as described (Song, J., *et al.*, *supra*; Li, X., *et al.*, *Molecular cell* **68**, 993-1005 e1009 (2017)). For primer extension, CMC-labeled small RNA fractions were mixed with biotin-labelled RT primer, followed by reverse transcription. RT products were separated on Urea-PAGE, transferred to Nylon membrane, and

detected by chemiluminescent nucleic acid detection module (Thermo). For Northern blot, RNA samples were separated on Urea-PAGE, transferred to Nylon membrane, and hybridized with DIG-labeled probe. The membrane was washed and blocked using DIG Wash and Block Buffer Set (Roche).

Expression analysis of tRNA-derived fragments (tRFs)

[0414] The reads number of tRFs was calculated from the FASTQ files and combined with the aligned information from the aligned file to determine the abundance and location of tRFs. Only tRFs with reads number >100 was used for analysis. Differential expression analysis of tRFs in control and PUS7 KO GSCs (three biological replicates per condition) was performed using the DESeq2 R package (version 1.16.1). tRFs with an adjusted p value < 0.01 and fold change (KO/WT) > 2 were assigned as differentially expressed.

Transcriptome-wide Ψ sequencing

[0415] CMC is used for transcriptome-wide Ψ profiling as described (Carlile, T.M., *et al.*, *Nature* **515**, 143-146 (2014); Li, X., *et al.*, *Nature chemical biology* **11**, 592-597 (2015)). 500 ng poly A⁺ RNA samples were fragmented, labeled by CMC, and then treated with Na₂CO₃. Library preparation was similar to that described in small RNA DM- Ψ -seq. Ψ sequencing of rRNA was performed similarly.

Identification of Ψ sites on tRNA, rRNA, and mRNA

[0416] For small RNA DM- Ψ -seq data, transcriptome-wide or rRNA Ψ seq data, a random barcode of 10 nt was added to the 5' end of Reads 2 to remove PCR duplication, so only Reads 2 in raw sequencing data were used for further analysis. The adapter sequences were trimmed by Cutadapt (Version 2.10). The minimum quality threshold was set to 20, and the minimum length required for reads after trimming was 30 nt. The remaining reads were further processed by removing the first 10 nt random barcode in the 5' end, and then mapped with Bowtie aligner (Version 1.2.2), with parameters set as “*bowtie -a --best --strata --chunkmbs 2000*”.

[0417] For identification of Ψ in small RNA, we considered position i to be a Ψ site with the following criteria: (1) CMC coverage > 50; (2) stop Reads number > 5 in CMC sample; (3) stop

rate (SR) < 1% in BEU sample; (4) SR (CMC-BEU) difference > 4%; (5) SR fold change (CMC/BEU) > 4; (6) the adjusted p value of matched sample < 0.05; (7) the Ψ site appears in all three independent replicates. For identification of PUS7-dependent Ψ in small RNA dataset, we consider position i to be a PUS7-dependent Ψ site with the following criteria: (1) Position i was considered a Ψ site in WT GSCs; (2) SR (WT_{CMC} – PUS7KO_{CMC}) difference > 4%; (3) SR fold change (WT_{CMC} / PUS7KO_{CMC}) > 1.5; and (4) adjusted p value < 0.05. In some cases, conditions 2 and 3 were not met at the same time.

[0418] For identification of Ψ in rRNAs, we considered position i to be a Ψ site with the following criteria: (1) coverage (CMC) > 200; (2) CMC stop rate > 5%; (3) SR Fold Change (CMC/BEU) > 2; (4) SR difference (CMC-BEU) > 3%; (5) adjusted p value < 0.05; and (6) the Ψ site must appear in at least two replicates.

[0419] For identification of Ψ on mRNAs, we considered position i to be a Ψ site with the following criteria: (1) CMC coverage > 50; (2) CMC stop rate > 6%; (3) SR (CMC-BEU) difference > 5; (4) SR Fold Change (CMC/BEU) > 5; (5) adjusted p value < 0.05; and (6) the Ψ site appears in at least two replicates. For identification of PUS7-dependent Ψ sites, we consider position i to be true with the following criteria: (1) position i was considered a Ψ site in WT GSCs; (2) the difference of SR between the WT-CMC (+) samples and the matched PUS7KO-CMC (+) samples must be at least 5%.

Motif discovery and GO enrichment analysis

[0420] For analysis of sequence consensus, a 10-nt sequence next to each Ψ site was retrieved. These sequences were subjected to DREME algorithm in MEME suite (Version 5.1.1) for discovery of enriched motives (Bailey, T.L., *et al.*, *Nucleic acids research* **37**, W202-208 (2009)). The shuffled input sequences were used as the background to eliminate potential false positive caused by nucleotide composition. GO enrichment analyses were performed using a cluster Profiler (version 3.14.3) (Yu, G., *et al.*, *OMICS* **16**, 284-287 (2012)).

TMT-based quantitative proteomics analysis

[0421] Proteins were reduced and alkylated with TCEP and iodoacetamide and precipitated in 10% trichloroacetic acid, then digested overnight with Trypsin/ LysC (protein : protease ratio

= 80:1). Resulting peptides were purified and labeled with TMT reagents. High pH reverse phase chromatography was performed using a Thermo Ultimate 3000 HPLC system (Thermo) with a 250 mm Zorbax extend C18 column (Agilent, ID 4.6 mm, particle size 5 μ m) and one hour gradient from 97% ammonium bicarbonate, pH 8, 3% to 40% acetonitrile. 96 fractions were collected and combined into 24 fractions. These fractions were analyzed on an Orbitrap Fusion Lumos mass spectrometer with a 5 mm C18 PepMap 100 μ -precolumn (ID 300 μ m), a 75 μ m by 50 cm PepMap RSLC C18 analytical column (Thermo), and an Easy-Spray ion source (Thermo Scientific). Peptides were eluted. MS3 quant spectra were acquired in the Orbitrap, while MS2 fragment spectra were acquired in the linear trap.

RNA-seq

[0422] Total RNAs isolated from control or PUS7 KO PBT003 GSCs were subjected to RNA-seq. Library construction of 300 ng total RNA from each sample was made using KAPA mRNA HyperPrep Kit (Illumina Platforms). Libraries were purified using AxyPrep Mag PCR Clean-up kit. Sequencing was performed on an Illumina® HiSeq 2500 (Illumina) instrument using the TruSeq SR Cluster Kit V4-cBot-HS to generate 51 bp single-end reads. The raw counts of each gene were generated by running HTSeq (v0.6.1p1) against GRCh37 GTF file (Ensembl release 87). RPKM (Reads Per Kilobase of transcript, per Million mapped reads) was calculated using the count data and gene length. Gene set enrichment analysis (Subramanian, A., *et al.*, *PNAS USA*, **102**, 15545-15550 (2005); Mootha, V.K., *et al.*, *Nature genetics* **34**, 267-273 (2003)) was performed for differentially expressed genes from RNA-seq using the GSEA 4.1.0 software and the MSigDB version v7.2.

OP-puro incorporation analysis

[0423] The Op-puro incorporation assay was performed using the Click-iT Plus OPP Alexa Fluor™ 647 Protein Synthesis Assay Kit. Data were analyzed by Flowjo 10.7.1.

Nascent protein synthesis analysis

[0424] Nascent protein synthesis was performed as described (Li, X., *et al.*, *supra*) with modifications. Cells in log phase were pre-treated with methionine-free DMEM medium, followed by L-azidohomoalanine (AHA) labeling. Total proteins were quantified, and then

labeled with Cy3. The Cy3-labeled proteins were separated using gradient SDS-PAGE. Protein gels were stained with silver stain kit.

Codon bias analysis

[0425] The global frequency of a specific codon was obtained by calculating the codon frequency of each gene annotated by Refseq, and the codon frequency of the TYK2 was calculated. The ranking of the codon frequency of the TYK2 among that of the global transcriptome was indicated. The other codons encoding the same amino acid were used as controls.

Luciferase Reporter Assay

[0426] Control or PUS7 KO GSCs were transfected with luciferase reporter plasmids using Lipofectamine 3000. After 48 h, cells were assayed by Dual-Luciferase Reporter Assay System. The renilla luciferase was used as a normalization control.

Polysome profiling analysis

[0427] We followed the procedure reported previously for polysome fractionation (Wang, X., *et al.*, *Cell* **161**, 1388-1399 (2015)) with the following modifications. (1) GSCs were treated with 100 µg/ml CHX for 7 min, flash frozen in liquid N₂ and stored at -80 degree. (2) The lysis buffer contains 100 µg/ml CHX. Total RNAs were isolated by using the Direct-zol RNA Microprep with on-column DNase-I digestion. RT-PCR was performed to determine TYK2 expression in each fractionation.

Statistics and reproducibility

[0428] Unpaired Student's t-test was used for statistical analysis between two groups, One-way ANOVA test was used for statistical analysis of more than two groups using GraphPad Prism 8 software with default setting. The method of statistical analysis was indicated in each figure legend. Values were presented as *p<0.05, **p<0.01, ***p<0.001 with exact p values shown in the legend of each figure. Error bars are s.e. of the mean unless stated otherwise. Log-rank test was used for animal survival analysis. Experiments were performed with sample size n greater than or equal to 3 replicates and results from representative experiments were confirmed

in at least two independent experiment repeats and multiple cell lines. For animal study, 6-12-week-old male and female NSG mice (from the Jackson Laboratory) were used in age- and gender-matched manner. A sample size determination (n greater than or equal to 5 mice) was calculated using t-test for two-group independent samples to reach power of 0.8 and the significance level of 0.05 based on our preliminary study. $p < 0.05$ was considered statistically significant. When monitoring tumor growth, investigators were blinded to the group allocation during bioluminescence imaging and aware of group allocation when assessing the outcome. For other experiments, sample size was determined empirically based on our preliminary or previous studies, experiments were not randomized, and the Investigators were not blinded to allocation during experiments and outcome assessment. No data were excluded from analyses.

Data availability

[0429] Data that support the findings of this invention have been deposited in the Gene Expression Omnibus (GEO) under accession code GSE147382 for RNA-seq data and GSE147342 for pseudouridine-seq data. Human data were derived from the CGGA, the Rembrandt, the TCGA and the Gravendeel datasets. Data derived from these resources is available in the GlioVis portal (<http://gliovis.bioinfo.cnio.es/>). tRNA sequences from GtRNAdb and human genome sequences from GCF_000001405.25_GRCh37.p13 were used for this invention.

Example 1. High PUS7 expression in GBM patients predicts poor prognosis

[0430] To reveal the functional relevance of PUS enzymes in GBM, the expression of PUS in the Chinese Glioma Genome Atlas (CGGA) database (Zhao, Z., *et al.*, *Sci Data* **4**, 170024 (2017)), the Repository for Molecular Brain Neoplastic Data (REMBRANDT) database (Gusev, Y., *et al.*, *Sci Data* **5**, 180158 (2018)), the Cancer Genome Atlas (TCGA) database (Brennan, C.W., *et al.*, *Cell* **155**, 462-477 (2013)), and the Gravendeel dataset (Gravendeel, L.A., *et al.*, *Cancer research* **69**, 9065-9072 (2009)) was examined. Among all the PUS enzymes, the expression of PUS7 is most strongly associated with the progression of GBM. PUS7 is the only PUS that exhibits statistically significant association between PUS expression and GBM patient median survival in three out of four datasets examined, with $p=0.0039$ in the CGGA database, $p=0.0345$ in the REMBRANDT database, and $p=0.0161$ in the Gravendeel dataset (Supplemental

table 1). Upregulated expression of PUS7 predicts worse survival in GBM patients (Supplemental table 1). Although the association did not reach statistical significance in TCGA, the same trend of association between higher PUS7 expression and worse GBM patient median survival was observed in the other databases that were analyzed. The expression level of PUS7 is much higher in GBM patients than that in non-tumor control subjects (FIG. 1A and supplemental table 2). Moreover, it was found that the PUS7 expression level is associated with the IDH status in all glioma patients but not GBM only patients, with low expression of PUS7 in glioma patients that have IDH mutation, which are often associated with better patient survival (Cohen, A.L., *et al.*, *Curr Neurol Neurosci Rep* **13**, 345 (2013); Labussiere, M., *et al.*, *Neurology* **74**, 1886-1890 (2010)) (FIGS. 1B, 9A and 9B). After excluding IDH mutant patients from the population of GBM patients, there is still a statistically significant association between higher PUS7 expression and worse patient median survival in GBM patients in the CGGA and Rembrandt datasets (FIGS. 9C and 9D). Although the association did not reach statistical significance in TCGA and Gravendeel datasets, the same trend of association between higher PUS7 expression and worse GBM patient median survival was observed in these datasets (FIGS. 9E and 9F). In addition, there is a statistically significant association of PUS7 expression with gain of chromosome 7 and loss of chromosome 10 status. Increased PUS7 expression is associated with gain of PUS7 copy number variations, but not gain of chromosome 19/20 status in GBM patients (FIG. 1C), indicating a correlation between PUS7 expression and chromosome abnormality in GBM.

[0431] Consistent with increased PUS7 mRNA expression in GBM patients as shown in the datasets (FIG. 1A), the protein level of PUS7 is elevated considerably in GBM patient tissues, compared to non-tumor control tissues, as revealed by Western blot (FIGS. 1D and 1F) and immunohistochemistry (IHC) analysis of GBM tissue microarray (FIGS. 9G and 9H). A portion (32.86%) of PUS7-positive cells in GBM tissues also expressed the GSC marker SOX2 (FIG. 9G), suggesting that these cells could be GSCs. The remaining PUS7-positive cells could include cells expressing other GSC markers (Suva, M.L., *et al.*, *Cell* **157**, 580-594 (2014); Ligon, K.L., *et al.*, *Neuron* **53**, 503-517 (2007); Veselska, R., *et al.*, *BMC Cancer* **6**, 32 (2006); Anido, J., *et al.*, *Cancer cell* **18**, 655-668 (2010); Liu, G., *et al.*, *Molecular cancer* **5**, 67 (2006); Son, M.J., *et al.*, *Cell stem cell* **4**, 440-452 (2009); Bao, S., *et al.*, *Cancer research* **68**, 6043-6048 (2008);

Ogden, A.T., *et al.*, *Neurosurgery* **62**, 505-514; discussion 514-505 (2008)) or differentiated cells that express lower level of PUS7.

[0432] Although both patient-derived GSCs and control brain-derived normal NSCs share the self-renewal ability, only GSCs can give rise to tumors. While intensive studies have investigated the tumor-initiating/propagating properties of GSCs, what distinguishes GSCs and NSCs remains a topic of interest in order to develop drugs that specifically targets GSCs. It was found that the protein expression level of PUS7 was substantially higher in GSCs than that in NSCs and human astrocytes (FIGS. 1E and 1G). The expression of PUS7 in established GBM cells varied among different lines (FIG. 1E). One possible reason is that these established GBM cell lines have different extent enrichment of cancer stem-like cells (Qiang, L., *et al.*, *Cancer Lett* **279**, 13-21 (2009). Taken together, the elevated expression of PUS7 in GBM tissues and GSCs suggests that PUS7 plays a role in GBM tumorigenesis.

Example 2. PUS7 regulates GSC growth and self-renewal

[0433] To study the role of PUS7 in GSC growth and self-renewal, PUS7 was knocked down in multiple lines of GSCs derived from different GBM subtypes (Cui, Q., *et al.*, *supra*), including classical, mesenchymal, and proneural. Knockdown (KD) of PUS7 was confirmed by RT-PCR (FIG. 10A) and Western blot (FIG. 10B). The growth of all six GSC lines was dramatically suppressed after KD of PUS7 (FIGS. 2A and 10C). KD of PUS7 also inhibited the self-renewal of GSCs as revealed by reduced sphere formation rate (FIGS. 2B and 10D) and decreased stem cell frequency (FIG. 2C) in PUS7 KD GSCs. To corroborate the effect of shRNA-mediated KD, PUS7 was knocked out in PBT003 GSCs by CRISPR/Cas9 editing using two independent sgRNAs. Western blot revealed substantially reduced PUS7 protein level by both sgRNAs in PUS7 knockout (KO) PBT003 GSCs (Figure 10E). The growth and self-renewal of GSCs were inhibited by PUS7 sgRNAs, compared to control sgRNA (FIGS. 10F and 10G). Consistently, PUS7 KO led to increased cell cycle arrest in G0/G1 phase (FIG. 10I). No statistically significant increase in cell apoptosis was detected in PUS7 KO PBT003 GSCs as revealed by active caspase 3 staining (FIG. 10H). Taken together, these data indicate that PUS7 plays an important role in GSC growth and self-renewal.

[0434] After demonstrating that PUS7 is necessary for GSC growth and self-renewal by KD/KO, we next tested whether PUS7 is sufficient to promote GSC growth and self-renewal by overexpressing PUS7 in GSCs. A mutant PUS7 (D256A) with abolished enzymatic activity was included as a control (Behm-Ansmant, I., *et al.*, *RNA (New York, N.Y)* **9**, 1371-1382 (2003). Overexpression of the wild type (WT) PUS7 and the catalytically inactive D256A mutant was confirmed by Western blot (FIG. 10J). The growth of GSCs with overexpression of the WT PUS7 was increased, compared to control GSCs transduced with an empty vector (FIG. 2D). In contrast, overexpression of the catalytically inactive PUS7 D256A mutant failed to promote GSC growth. Moreover, overexpression of the WT, but not the D256A mutant PUS7, rescued the growth defects induced by PUS7 KD in GSCs (FIG. 11). The self-renewal capacity of GSCs, as revealed by sphere formation rate (FIG. 2E) and stem cell frequency (FIG. 2F), was also increased in GSCs with overexpression of the WT but not the mutant PUS7, compared to control cells. These results together indicate that PUS7 promotes the growth and self-renewal of GSCs in an enzymatic activity-dependent manner.

Example 3. Reduced PUS7 expression in GSCs suppresses tumor progression

[0435] To study whether KD of PUS7 affects GSC tumorigenicity *in vivo*, GSCs with or without KD of PUS7 were transplanted into immunodeficient NSG mice. Tumor growth was monitored by bioluminescent imaging (FIGS. 3A and 3D). Tumor progression was dramatically inhibited in NSG mice transplanted with PUS7 KD GSCs, compared to control mice (FIGS. 3B, 3C, 3E, and 3F). Moreover, NSG mice transplanted with PUS7 KD GSCs survived substantially longer, compared to control mice (FIGS. 3G and 3H).

[0436] To corroborate the effect of shRNA-mediated KD of PUS7 on GSC tumorigenicity, GSCs with sgRNA-mediated PUS7 KO were transplanted into NSG mice. Similar to shRNA-mediated KD, sgRNA-mediated PUS7 KO also inhibited GSC-derived tumor growth dramatically (FIGS. 12A and 12B). Accordingly, NSG mice transplanted with PUS7 KO GSCs survived much longer than the control mice (FIG. 12C). Moreover, the inhibitory effect on tumor progression by PUS7 KO could be rescued by overexpression of the WT, but not the catalytically mutant PUS7 in GSCs (FIGS. 3I and 3J). This result indicates that PUS7 regulates GSC tumorigenicity in an activity-dependent manner. Taken together, these results demonstrate that

reduced PUS7 expression suppresses GSC tumorigenicity and prolongs the life span of GSC-derived tumor-bearing mice.

Example 4. PUS7 inhibitors suppress GSC growth

[0437] Small molecule inhibitors of PUS7 were identified in order to modulate PUS7 in a pharmacologically relevant manner. 270,000 NCI-DTP compounds and 4,086 FDA-approved drugs were screened in a virtual screening to identify small molecules that are predicted to alter PUS7 enzymatic activity. To identify “hits” from the virtual screen candidates, an *in vitro* enzymatic assay was established as secondary screen using recombinant PUS7 and a synthetic RNA substrate for pseudouridine modification. Pseudouridine level in the RNA substrate was increased by PUS7 protein (positive control, PC), compared to the negative control (NC) that has no PUS7 protein. Treatment with compounds from the initial screen led to altered pseudouridine level catalyzed by PUS7 recombinant protein, as revealed by a change in the Ψ to U ratio. Among compounds that reduced PUS7 activity, compounds 4 (C4) and 17 (C17) exhibited the strongest inhibitory effect (FIG. 4A). To determine the cellular effect of these compounds, PBT003 GSCs were treated with C4 and C17 at doses from 0.4 μ M to 50 μ M. Compound C4 exhibited dose-dependent inhibition of PBT003 growth, but mildly (FIG. 13A), compound C17 strongly suppressed the growth of PBT003 at the concentrations tested (FIG. 4B).

[0438] The effect of C17 was tested at nM concentrations and observed dose-dependent inhibition of PBT003 growth by C17 from 4 nM to 400 nM. The IC_{50} of C17 was 92.15 nM in PBT003 cells (FIGS. 4C, 13B, and 13C). The same dose-dependent growth-inhibitory effect by C17 was observed in other GSC lines, including PBT707, PBT726 and PBT111 cells (FIGS. 4C and 13C). In contrast, there is no inhibitory effect on control NSCs by C17 at 100 nM or lower concentrations (0-40 nM), and much less effect (compared to GSCs) at 400 nM of C17 (FIGS. 4C, 4D, and 13B). These results indicate that compound C17 inhibits the growth of GSCs in a dose-dependent manner and that it preferentially targets GSCs compared to NSCs.

[0439] We tested if the cellular effect of C17 is dependent on PUS7. It was shown that C17 was able to reduce the growth of the WT but not PUS7 KO PBT707 GSCs (FIG. 4E), suggesting that this compound could act through PUS7. Moreover, it was found that overexpression of the WT but not the catalytically mutant PUS7 was able to rescue the growth-inhibitory effect of C17

in PBT707 GSCs (FIG. 4F). Taken together, these results indicate that C17 regulates GSC growth in a PUS7-dependent manner.

[0440] A structural analog of C17 was identified and was shown to also inhibit GSC growth in a dose-dependent manner (FIGS. 4G and 13D). Consistent with inhibition of PUS7-dependent pseudouridine modification by C17 *in vitro*, a substantial decrease in pseudouridine level in GSCs treated with C17 or its analog (FIGS. 4H and 4I) was observed. Taken together, these data demonstrate that compound C17 and its structural analog could inhibit pseudouridine modification by PUS7 and suppress GSC growth.

Example 5. The PUS7 inhibitor C17 suppresses tumor progression *in vivo*

[0441] GSC-derived tumor-bearing NSG mice were treated with the C17 compound to test the effect of inhibition of pseudouridine modification in a preclinical model. Specifically, PBT003 GSCs expressing a luciferase reporter were transplanted into NSG mice to establish tumors, followed by compound treatment at 5 μ l of 400 nM C17 (FIG. 5A), corresponding to 25.9 ng/Kg C17 for a 25 g mouse, which could allow achievement of a dose close to the IC₅₀ dose of 92.15 nM, based on our preliminary pharmacodynamics study that detected an average of about 1/5 of the initial dose 3 h after C17 injection. The growth of GSC-derived tumors was significantly inhibited by the treatment of C17, compared to the treatment with vehicle control (FIGS. 5B and 5D). Accordingly, decreased pseudouridine level was detected in tumor tissues treated by C17 (FIG. 5C), confirming the inhibition of PUS activity by C17 *in vivo*. Moreover, the survival of NSG mice treated with C17 was dramatically prolonged, compared to vehicle treated mice (FIG. 5E). A similar tumor-inhibitory effect by C17 was detected in PBT707 GSC-transplanted NSG mice (FIGS. 5F-5I). Taken together, these results indicate that inhibition of PUS7 activity could suppress GSC-derived tumor progression and prolong the lifespan of tumor-bearing mice.

Example 6. PUS7 regulates tRNA pseudouridylation and translation in GSC

[0442] Having uncovered an important role for PUS7 in regulating GSC growth and tumorigenicity, the next was determined how PUS7 exerts this function. PUS7-regulated pseudouridine modification in GSCs was detected through mass spectrometry and DM- Ψ -seq, a

recently developed pseudouridine sequencing method for small RNA (Song, J., *et al.*, *supra*). RNAs were prepared from control and PUS7 KO PBT003 GSCs, fractionated into small RNA (<200 nt) and >200 nt RNAs, and subjected to mass spectrometry analysis. A significant decrease in pseudouridine level was detected in the small RNA population in PUS7 KO GSCs, compared to that in control cells (FIG. 6A), whereas no considerable change was observed in >200 nt RNAs of the PUS7 KO GSCs (FIG. 6A).

[0443] Control and PUS7 KO PBT003 GSCs were subjected to small RNA DM-Ψ-seq to identify the pseudouridine modification profile in small RNAs. 824 pseudouridine sites were detected in tRNA (FIG. 6B) and 6 sites in snRNA. By comparing the Ψ profiles between control and PUS7 KO PBT003 GSCs, 13 PUS7-dependent pseudouridine sites were identified in 8 tRNA types (Supplemental table 4), and no PUS7-dependent pseudouridine sites in snRNAs. In addition to PUS7-regulated pseudouridine sites at positions 13 and 35 of tRNA as reported in previous studies (Brennan, C.W., *et al.*, *supra*), pseudouridine sites were identified at the 50th position of several tRNA isoforms. For instance, tRNA-Arg-CCG-2-1 at position 50 exhibited a dramatic decrease in pseudouridine modification upon PUS7 KO in GSCs (FIGS. 6C, 6D, and 14A). The DM-Ψ-seq data were verified using primer extension (FIG. 14B). The DM-Ψ-seq and primer extension data together indicate that position 50 in tRNA-Arg-CCG-2-1 is a true Ψ modification site and this modification is PUS7-dependent. In addition, a decrease of pseudouridylation level was detected by C17 treatment in tRNAs with PUS7-dependent Ψ sites, such as tRNA-Val-AAC-3-1 and tRNA-Glu-TTC-4-1 (FIG. 14C). In contrast, the Ψ sites in rRNA were unperturbed by C17 treatment (Supplemental table 8).

[0444] In addition to GSCs, small RNA DM-Ψ-seq were performed in NSCs to compare the pseudouridine modification profiles in GSCs vs NSCs. Although most Ψ sites were shared by GSCs and NSCs (FIG. 6E), a list of GSC-specific Ψ sites was identified. In GSC-specific pseudouridine sites, tRNA-Arg-CCG-2-1, which was identified as a tRNA with PUS7-dependent pseudouridine site at position 50, was shown a clear increase in pseudouridylation level at position 50 in GSCs compared to NSCs (FIG. 6F). This result suggests that PUS7 could induce cell type-specific tRNA pseudouridylation in GSCs vs NSCs to regulate GBM tumorigenesis.

[0445] To test whether loss of PUS7-mediated modification affects the stability of target tRNAs, tRNA levels in control and PUS7 KO GSCs were analyzed using input samples in small RNA DM-Ψ-seq. The global tRNA level was not changed in PUS7 KO cells, compared to control cells (FIG. 14D). Northern blot confirmed that KO of PUS7 did not affect the level of tRNAs, such as tRNA-Arg-CCG, that contains PUS7-dependent Ψ sites (FIG. 14E). In addition, tRNA-derived fragment (tRF) analysis was performed and detected no significant change in the level of tRFs derived from tRNAs that have PUS7-dependent Ψ sites in PUS7 KO PBT003 GSCs (FIG. 14F).

[0446] As previous study showed that PUS7 can globally repress translation in human embryonic stem cells and hematopoietic stem cells (Guzzi, N., *et al.*, *supra*), we tested if PUS7 could similarly regulate global translation in GSCs. Puromycin incorporation analysis using OPP (O-propargyl-puromycin, an alkyne analog of puromycin) was performed to test global translation in GSC. The OP-puro incorporation analysis revealed no obvious change in global translation in PUS7 KO PBT003 GSCs (FIG. 14G). Similarly, nascent protein synthesis analysis revealed no obvious change in global translation in PUS7 KO HEK293T cells (FIG. 14H).

[0447] The ability of PUS7 to regulate translation was tested in a more specific manner via its target tRNAs in GSCs. A dual luciferase reporter system was used to test the translation of tRNAs by fusing 6 x codons with the firefly luciferase. While the global translation efficiency revealed by the control reporter was not changed upon KO of PUS7 in PBT003 (FIG. 6G), the translation efficiency of a PUS7-regulated tRNA-Arg-CCG, but not a control tRNA-Arg-TCG, was significantly increased in PUS7 KO GSCs (FIGS. 6G and 14I). The increased translation efficiency of PUS7-regulated tRNA-Arg-CCG in PUS7 KO GSCs was reversed by overexpression of the WT but not the catalytically inactive mutant PUS7 (FIG. 6H). These results indicate that PUS7-mediated pseudouridylation in tRNA inhibits codon-specific translation in GSCs.

[0448] In addition to small RNAs, transcriptome-wide Ψ sequencing in mRNAs and rRNAs was performed. In rRNA, 89 previously reported (Taoka, M., *et al.*, *Nucleic acids research* **46**, 9289-9298 (2018)). Ψ sites were identified in both control and PUS7 KO PBT003 GSCs with similar extent of modification (Supplemental table 8), suggesting that these sites are likely not

PUS7-dependent. In mRNAs, 155 Ψ sites were identified in PBT003 GSCs, 13 of which were PUS7-dependent (Supplemental table 9), it is worth noting that some Ψ sites may be missed due to the stringent cutoff criteria or redundancy). It was reported that the consensus Ψ motif for PUS7 was UG Ψ AR (R=A/G) (Guzzi, N., *et al.*, *supra*). Consistently, the motif UG Ψ AG for PUS7-dependent sites was identified in mRNAs of PBT003 GSCs (FIG. 7A). These sites are located on both coding and non-coding RNAs (FIG. 7B and Supplemental table 9).

Example 7. PUS7 regulates GSC growth through TYK2-mediated IFN pathway

[0449] To investigate PUS7-regulated pathways, RNAs were prepared from control or PUS7 KO PBT003 GSCs and subjected to RNA-seq. Whole transcriptome analysis revealed 205 up-regulated and 46 down-regulated genes in PUS7 KO GSCs compared to control GSCs.

[0450] Among the differentially expressed genes (>1.5-fold), the interferon (IFN) pathway is the top GO-term that is regulated by PUS7 KO. 80 out of 205 up-regulated genes were IFN-stimulated genes (ISGs), including CXCL10, IFIT1, ISG15, XAF1, MX1, and OAS1 (FIGS. 7C, 7D and Supplemental table 9). Up-regulation of ISGs can be reversed by overexpressing the WT but not the mutant PUS7 in PUS7 KO GSCs (FIG. 7E). In addition, an inverse correlation was found between PUS7 expression and ISG expression in GBM patients in the TCGA dataset (FIGS. 7F, 15A and Supplemental table 9), supporting the regulation of ISG expression by PUS7. IFN treatment also reduced GSC growth (FIG. 15B), consistent with the growth inhibitory effect of PUS7 KD (FIGS. 2A and 10A). In addition, up-regulation of ISG expression by C17 was observed in PBT003 GSCs *in vitro* (FIG. 15C) and PBT003-derived tumors *in vivo* (FIG. 15D), indicating that C17 inhibition could affect this pathway.

[0451] Pseudouridine modification sites were not detected in ISG mRNAs or obvious mRNA level change was not observed in mRNAs with PUS7-dependent Ψ sites in PUS7 KO PBT003 GSCs either (Supplemental table 9). We hypothesized that PUS7 may control protein expression to regulate the IFN pathway. Quantitative proteomics was performed using the tandem mass tag (TMT) system in control and PUS7 KO PBT003 GSCs. A significant change in the expression of 189 genes was detected at the protein level (Supplemental table 10). Consistent with reduced growth and self-renewal of PUS7 KO GSCs, decreased protein expression of a list of oncogenes and increased protein expression of tumor suppressors was observed in GSCs upon PUS7 KO.

Among the list, tyrosine kinase 2 (TYK2), an important regulator of the IFN pathway, was upregulated at the protein level (FIGS. 8A and 8B) but not mRNA level (FIG. 8C) in PUS7 KO GSCs, suggesting that PUS7 may regulate TYK2 protein synthesis. The upregulation of TYK2 protein expression in PUS7 KO GSCs was confirmed by Western blot (FIG. 8D). Consistent with increased TYK2 expression, the phosphorylated STAT1, a downstream effector of TYK2, was increased in PUS7 KO GSCs, while the total STAT1 level was not changed (FIG. 8E).

[0452] Codon usage analysis revealed that codon usage of the PUS7-regulated tRNA-Arg-CCG is 2.6% in TYK2, higher than 90% of genes (FIG. 8F), whereas tRNA-Arg-CGA, which is not a PUS7 target in GSCs, is much less used in TYK2 (0.67%) (FIG. 8F). Among the 189 differentially expressed proteins identified by the TMT analysis, 17 of 94 up-regulated proteins had high usage of codons for tRNA-Arg-CCG (codon usage frequency >2%, rank >80%) (Supplemental table 10). This ratio is significantly (one-sample t-test, two-tailed p-value = 1.292×10^{-8}) higher than a background level (Supplemental table 10). In addition, codon bias analysis for TYK2 was expanded to other tRNA substrates of PUS7 and it was found that 5 of 8 PUS7-dependent tRNAs in GSCs are frequently used in TYK2, including tRNA-Arg-CCG, tRNA-Gln-CTG, tRNA-Asp-GTC, tRNA-Glu-CTC and tRNA-Tyr-GTA (Supplemental table 10). These results suggest that PUS7 may play a role in modulating TYK2 translation through PUS7-modified tRNAs. Accordingly, polysome profiling analysis revealed that the occupancy of polysomes on TYK2 mRNA was substantially elevated in PUS7 KO GSCs (FIG. 8G), supporting a role for PUS7 in regulating TYK2 translation. To further support this idea, the CGG codon was mutated of Arg to the CGA codon of Arg in a Flag-tagged TYK2 fragment. The CGG codon corresponds to the PUS7-regulated tRNA-Arg-CCG, whereas the CGA codon corresponds to the PUS7-independent tRNA-Arg-TCG. PUS7 KO in GSCs led to increased protein expression of the WT Flag-TYK2, but not that of the mutant TYK2, in which the CGG codons were mutated to the CGA codons (FIGS. 8H, 16A, 16B, and 16C). These data indicate that PUS7 regulates the expression of TYK2 at the translation level via tRNA pseudouridylation.

[0453] It was further investigated whether PUS7 regulates GSC growth by modulating the TYK2 pathway. TYK2 KO increased the growth of GSCs (FIGS. 8I and 16D), consistent with increased GSC growth upon STAT1 KO (FIGS. 8I and 16E). More importantly, KO of either TYK2 or STAT1 rescued reduced GSC growth induced by KO of PUS7 (FIGS. 8J and 16F).

Treatment of GSCs by a STAT1 inhibitor fludarabine also rescued the growth inhibition by PUS7 KO in GSCs (FIG. 16G). Taken together, these data indicate that PUS7 could regulate GSC growth by modulating the TYK2-STAT1 pathway.

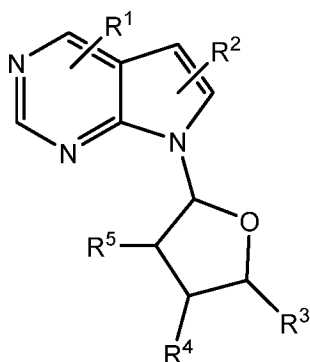
[0454] The inventors have uncovered a direct role of PUS7 in GBM tumorigenesis. It was demonstrated that PUS7 regulates the growth and tumorigenesis of GSCs through modulating TYK2 translation via PUS7-dependent tRNA pseudouridylation, providing a direct evidence for PUS7 in modulating tumorigenesis. It was also shown that PUS7-mediated pseudouridine in tRNA affects its translation efficiency, in turn regulating downstream gene expression and GBM tumorigenesis.

[0455] The clinical significance of this invention is the discovery of chemical inhibitors of PUS7 in suppression of GBM tumorigenesis. Although an association between pseudouridine modification and cancer has been made, inhibitors for pseudouridine synthases are lacking, preventing pseudouridine-targeting therapeutic development. In this study, a structure-based virtual screening coupled with *in vitro* enzymatic activity screening was used for inhibitor discovery for PUS7. The identified inhibitors were able to reduce pseudouridine levels and inhibit GSC growth and tumorigenesis. These inhibitors could be exploited as potential therapeutic candidates for targeting PUS7 in GBM and other cancers. Moreover, the screening strategies used in this invention may be applicable to other epitranscriptomic machineries for discovery of chemical therapeutics.

[0456] 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 of formula (I):



(I), or a pharmaceutically acceptable salt thereof,

wherein:

R¹ is halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -N₃, -SO_{n1}R^{1A}, -SO_{v1}NR^{1B}R^{1C}, -NHN^{1B}R^{1C}, -ONR^{1B}R^{1C}, -NHC(O)NHN^{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}SO₂R^{1A}, -NR^{1B}C(O)R^{1D}, -NR^{1B}C(O)OR^{1D}, -NR^{1B}OR^{1D}, -OCX¹₃, -OCHX¹₂, -OCH₂X¹, 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;

R² is halogen, -CX²₃, -CHX²₂, -CH₂X², -CN, -N₃, -SO_{n2}R^{2A}, -SO_{v2}NR^{2B}R^{2C}, -NHN^{2B}R^{2C}, -ONR^{2B}R^{2C}, -NHC(O)NHN^{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}SO₂R^{2A}, -NR^{2B}C(O)R^{2D}, -NR^{2B}R^{2C}CNOR^{2D}, -NR^{2B}C(O)OR^{2D}, -NR^{2B}OR^{2D}, -OCX²₃, -OCHX²₂, -OCH₂X², 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;

R³ is hydrogen, halogen, -CX³₃, -CHX³₂, -CH₂X³, -CN, -N₃, -SO_{n3}R^{3A}, -SO_{v3}NR^{3B}R^{3C}, -NHN^{3B}R^{3C}, -ONR^{3B}R^{3C}, -NHC(O)NHN^{3B}R^{3C}, -NHC(O)NR^{3B}R^{3C}, -N(O)_{m3}, -NH₂, -C(O)R^{3D}, -C(O)OR^{3D}, -C(O)NH₂, -OR^{3A}, -NR^{3B}SO₂R^{3A}, -NR^{3B}C(O)OR^{3D},

$-\text{NR}^{3\text{B}}\text{OR}^{3\text{D}}$, $-\text{OCX}^3$, $-\text{OCHX}^3$, $-\text{OCH}_2\text{X}^3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^4 is hydrogen, halogen, $-\text{CX}^4$, $-\text{CHX}^4$, $-\text{CH}_2\text{X}^4$, $-\text{CN}$, $-\text{N}_3$, $-\text{SO}_{\text{m}4}\text{R}^{4\text{A}}$, $-\text{SO}_{\text{v}4}\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{NHN}\text{R}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{ONR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{NHC}(\text{O})\text{NHN}\text{R}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{NHC}(\text{O})\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{N}(\text{O})_{\text{m}4}$, $-\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{C}(\text{O})\text{R}^{4\text{D}}$, $-\text{C}(\text{O})\text{OR}^{4\text{D}}$, $-\text{C}(\text{O})\text{NR}^{4\text{B}}\text{R}^{4\text{C}}$, $-\text{OR}^{4\text{A}}$, $-\text{NR}^{4\text{B}}\text{SO}_2\text{R}^{4\text{A}}$, $-\text{NR}^{4\text{B}}\text{C}(\text{O})\text{R}^{4\text{D}}$, $-\text{NR}^{4\text{B}}\text{C}(\text{O})\text{OR}^{4\text{D}}$, $-\text{NR}^{4\text{B}}\text{OR}^{4\text{D}}$, $-\text{OCX}^4$, $-\text{OCHX}^4$, $-\text{OCH}_2\text{X}^4$, 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, $-\text{CX}^5$, $-\text{CHX}^5$, $-\text{CH}_2\text{X}^5$, $-\text{CN}$, $-\text{N}_3$, $-\text{SO}_{\text{n}5}\text{R}^{5\text{A}}$, $-\text{SO}_{\text{v}5}\text{NR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{NHN}\text{R}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{ONR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{NHC}(\text{O})\text{NHN}\text{R}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{NHC}(\text{O})\text{NR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{N}(\text{O})_{\text{m}5}$, $-\text{NR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{C}(\text{O})\text{R}^{5\text{D}}$, $-\text{C}(\text{O})\text{OR}^{5\text{D}}$, $-\text{C}(\text{O})\text{NR}^{5\text{B}}\text{R}^{5\text{C}}$, $-\text{OR}^{5\text{A}}$, $-\text{NR}^{5\text{B}}\text{SO}_2\text{R}^{5\text{A}}$, $-\text{NR}^{5\text{B}}\text{C}(\text{O})\text{R}^{5\text{D}}$, $-\text{NR}^{5\text{B}}\text{C}(\text{O})\text{OR}^{5\text{D}}$, $-\text{NR}^{5\text{B}}\text{OR}^{5\text{D}}$, $-\text{OCX}^5$, $-\text{OCHX}^5$, $-\text{OCH}_2\text{X}^5$, 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;

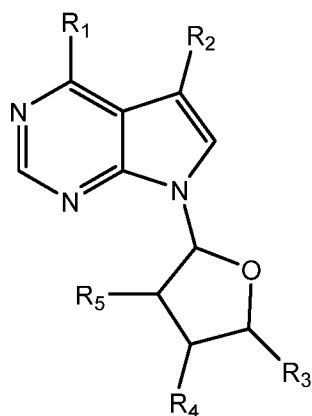
$\text{R}^{1\text{A}}$, $\text{R}^{1\text{B}}$, $\text{R}^{1\text{C}}$, $\text{R}^{1\text{D}}$, $\text{R}^{2\text{A}}$, $\text{R}^{2\text{B}}$, $\text{R}^{2\text{C}}$, $\text{R}^{2\text{D}}$, $\text{R}^{3\text{A}}$, $\text{R}^{3\text{B}}$, $\text{R}^{3\text{C}}$, $\text{R}^{3\text{D}}$, $\text{R}^{4\text{A}}$, $\text{R}^{4\text{B}}$, $\text{R}^{4\text{C}}$, $\text{R}^{4\text{D}}$, $\text{R}^{5\text{A}}$, $\text{R}^{5\text{B}}$, $\text{R}^{5\text{C}}$, and $\text{R}^{5\text{D}}$ 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 $\text{R}^{4\text{C}}$, and $\text{R}^{5\text{B}}$ and $\text{R}^{5\text{C}}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

X^1 , X^2 , X^3 , X^4 , and X^5 are independently halogen;

$\text{n}1$, $\text{n}2$, $\text{n}3$, $\text{n}4$, and $\text{n}5$ are independently an integer from 0 to 4; and

$\text{m}1$, $\text{m}2$, $\text{m}3$, $\text{m}4$, $\text{m}5$, $\text{v}1$, $\text{v}2$, $\text{v}3$, $\text{v}4$, and $\text{v}5$ are independently 1 or 2.

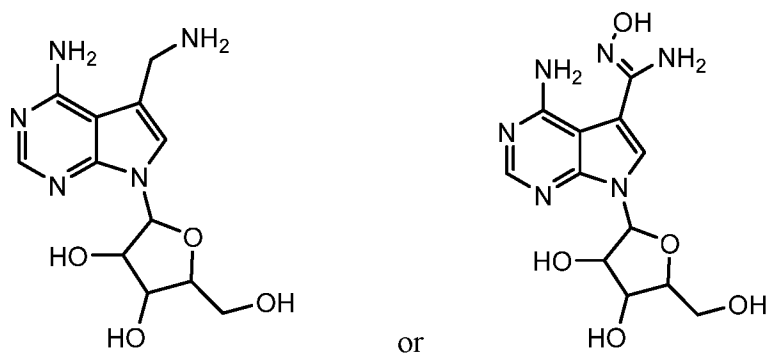
2. The compound of claim 1 having the formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein R^1 is $-\text{COOH}$, $-\text{NH}_2$, substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.
4. The compound of claim 1, wherein R^1 is $-\text{COOH}$, or $-\text{NH}_2$.
5. The compound of claim 1, wherein R^1 is $-\text{NH}_2$.
6. The compound of claim 1, wherein R^2 is $-\text{COOH}$, $-\text{NH}_2$, substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.
7. The compound of claim 1, wherein R^2 is substituted or unsubstituted 2 to 4 membered heteroalkyl.
8. The compound of claim 1, wherein R^2 is $-\text{CH}_2\text{NH}_2$.
9. The compound of claim 1, wherein R^2 is $-\text{C}(\text{NOH})\text{NH}_2$.
10. The compound of claim 1, wherein R^3 is unsubstituted $\text{C}_1\text{-C}_3$ alkyl or unsubstituted 2 to 4 membered heteroalkyl.
11. The compound of claim 1, wherein R^3 is unsubstituted 2 membered heteroalkyl.
12. The compound of claim 1, wherein R^3 is $-\text{CH}_2\text{OH}$.

13. The compound of claim 1, wherein R^4 is $-\text{COOH}$, $-\text{OH}$, substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.
14. The compound of claim 1, wherein R^4 is $-\text{OH}$, substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.
15. The compound of claim 1, wherein R^4 is $-\text{OH}$.
16. The compound of claim 1, wherein R^5 is $-\text{COOH}$, $-\text{OH}$, substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.
17. The compound of claim 1, wherein R^5 is $-\text{OH}$, substituted or unsubstituted $\text{C}_1\text{-C}_3$ alkyl or substituted or unsubstituted 2 to 4 membered heteroalkyl.
18. The compound of claim 1, wherein R^5 is $-\text{OH}$.
19. The compound of claim 1, wherein the compound is:



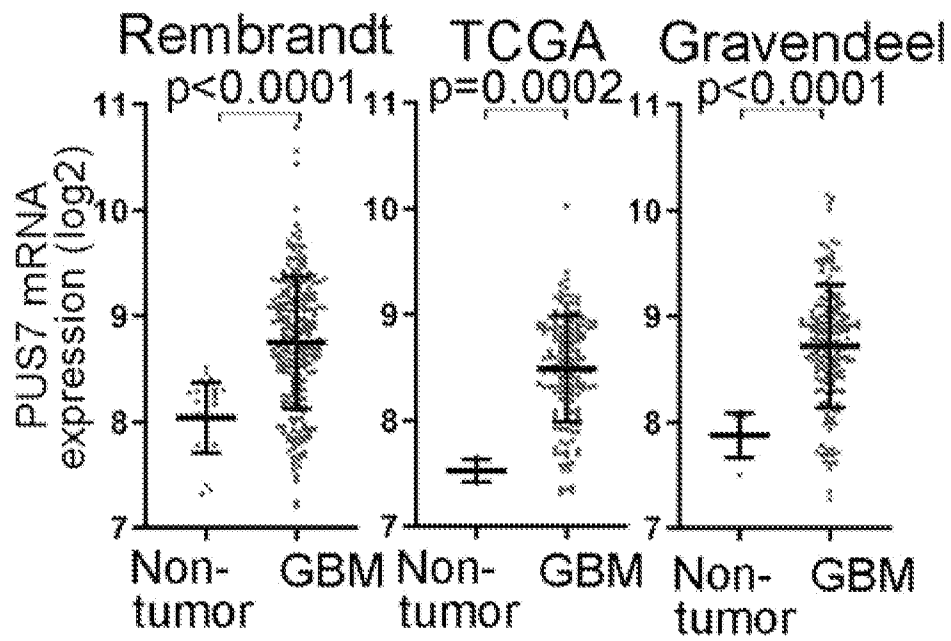
20. A pharmaceutical composition comprising a compound of any one of claims 1 to 19 and a pharmaceutically acceptable excipient.
21. A method of inhibiting pseudouridine synthase 7 (PUS7) activity, said method comprising contacting the PUS7 with the compound of any one of claims 1 to 19.
22. A method 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 claims 1 to 19.

23. The method of claim 22, wherein said cancer is associated with increased PUS7 gene expression or increased PUS7 activity.

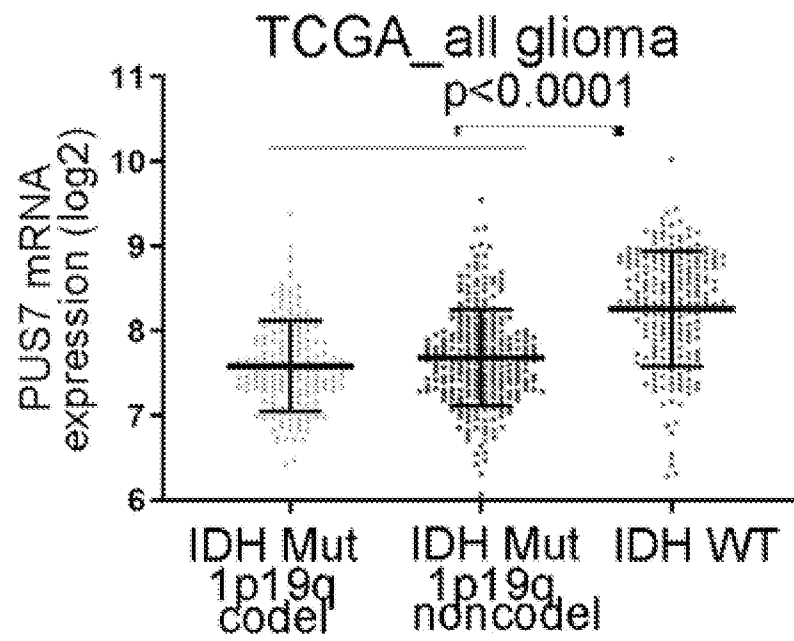
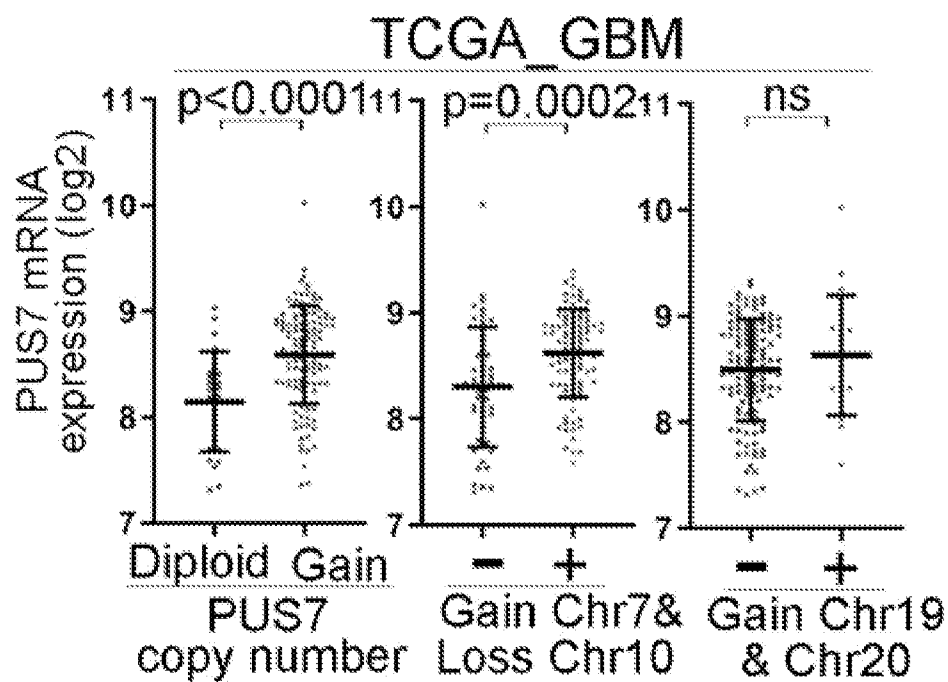
24. The method of claim 22, wherein said cancer is prostate cancer, glioblastoma, glioma, myelodysplastic syndrome, leukemia, stomach cancer, colorectal cancer, endometrial cancer, breast cancer, pancreatic cancer, kidney cancer, mesothelioma, or sarcoma.

25. The method of claim 22, further comprising administering to said subject an anti-cancer agent.

26. The method of claim 25, wherein the anti-cancer agent is a mitotic inhibitor or a histone deacetylase (HDAC) inhibitor.

**Fig. 1A**

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**Fig. 1B****Fig. 1C**

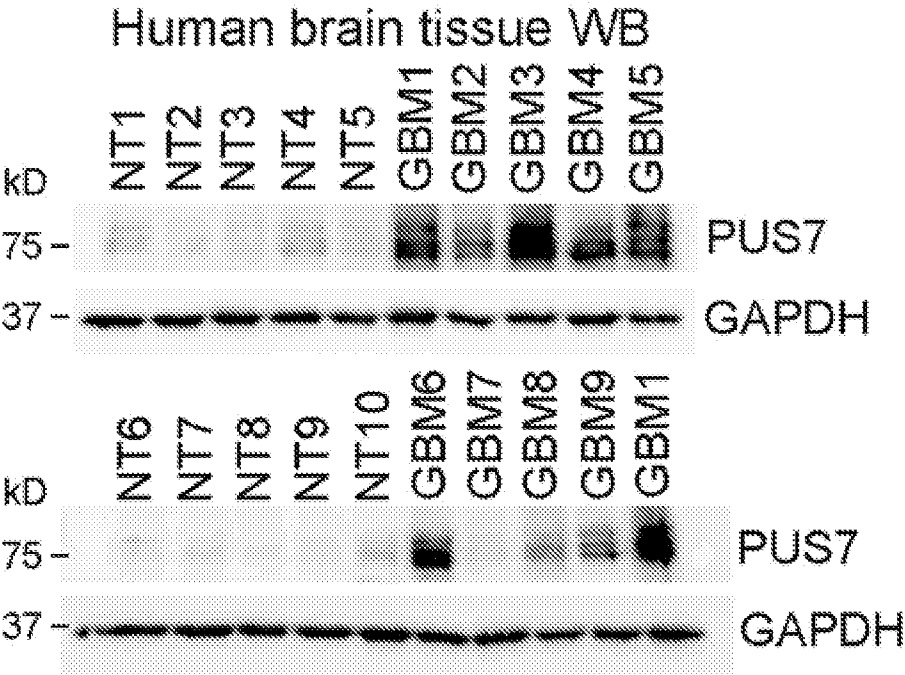


Fig. 1D

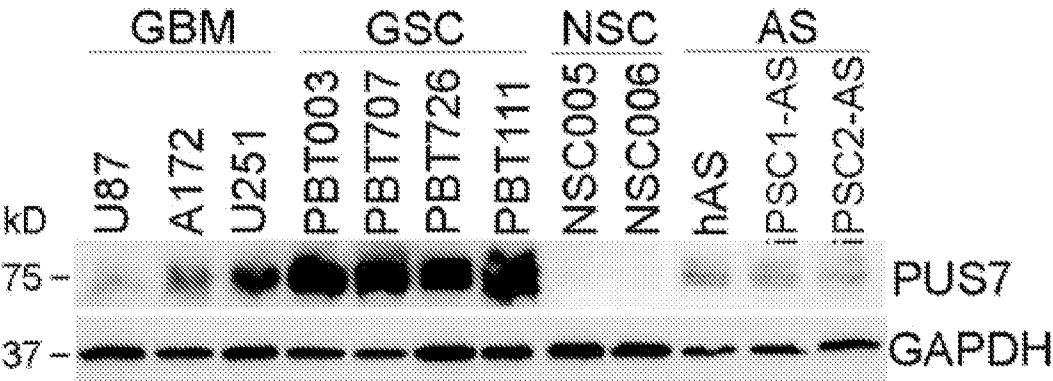


Fig. 1E

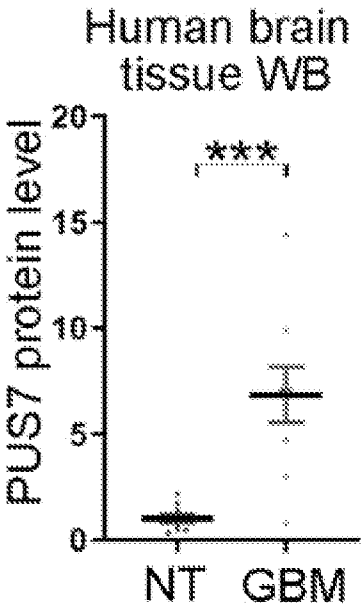


Fig. 1F

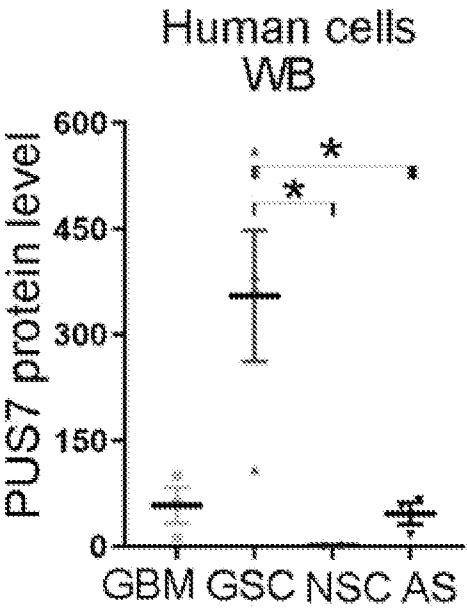


Fig. 1G

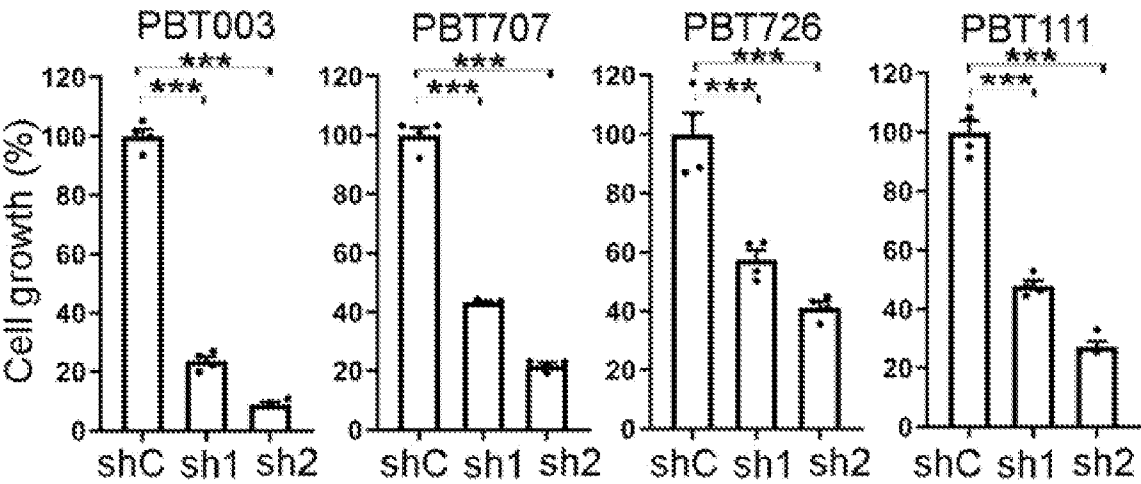


Fig. 2A

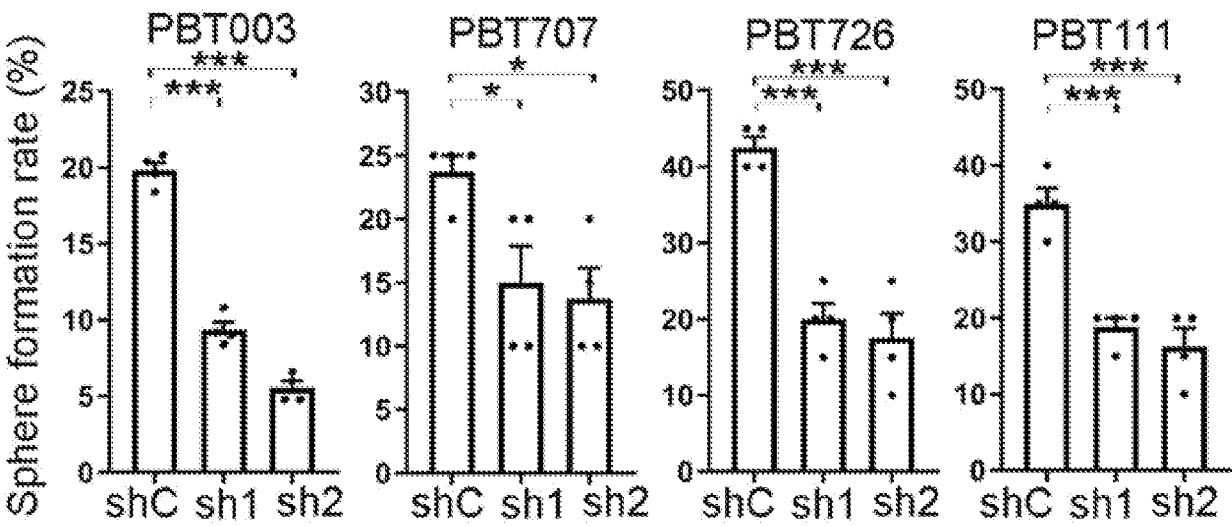
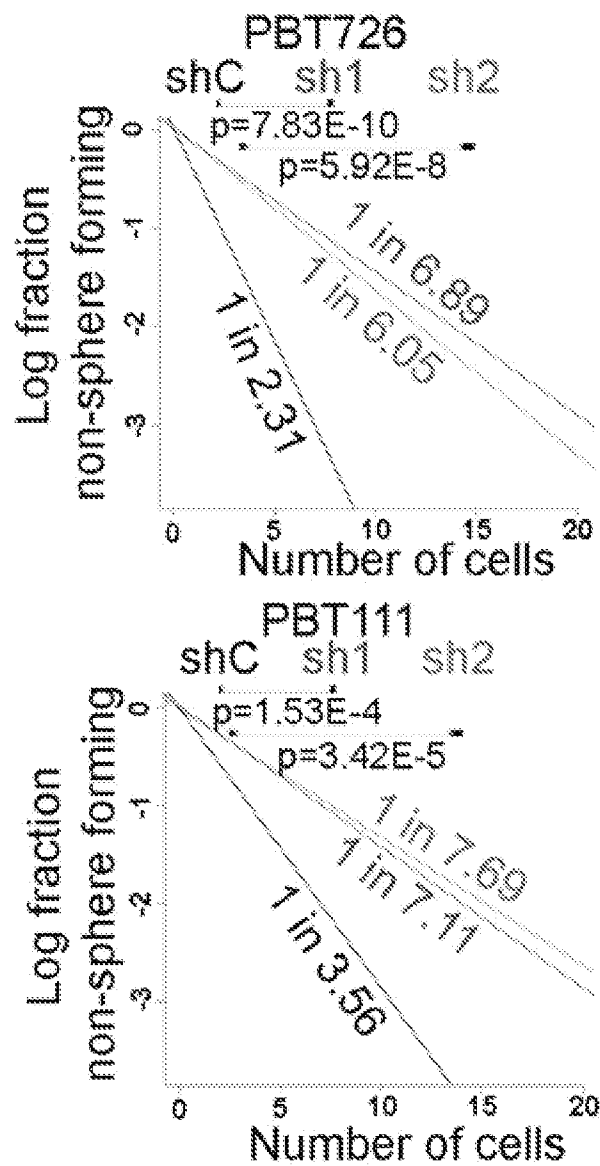


FIG. 2B

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**FIG. 2C**

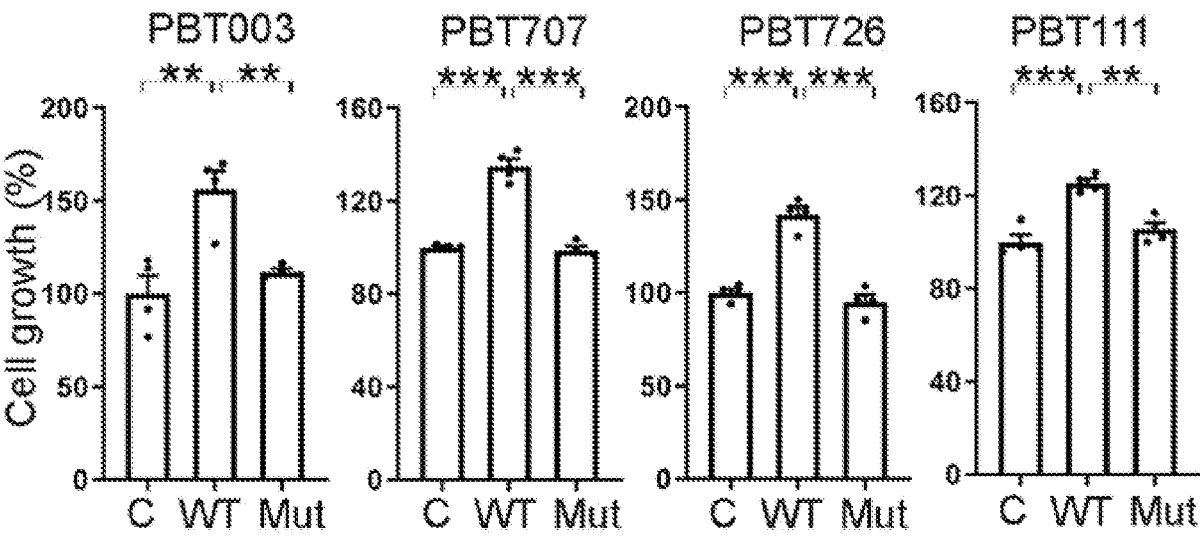


FIG. 2D

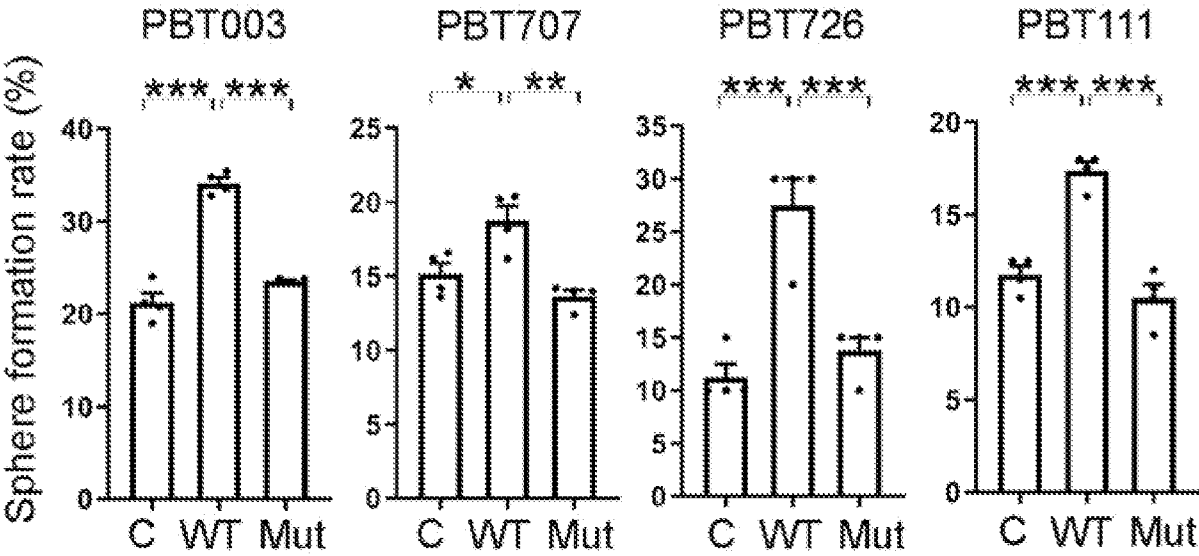


FIG. 2E

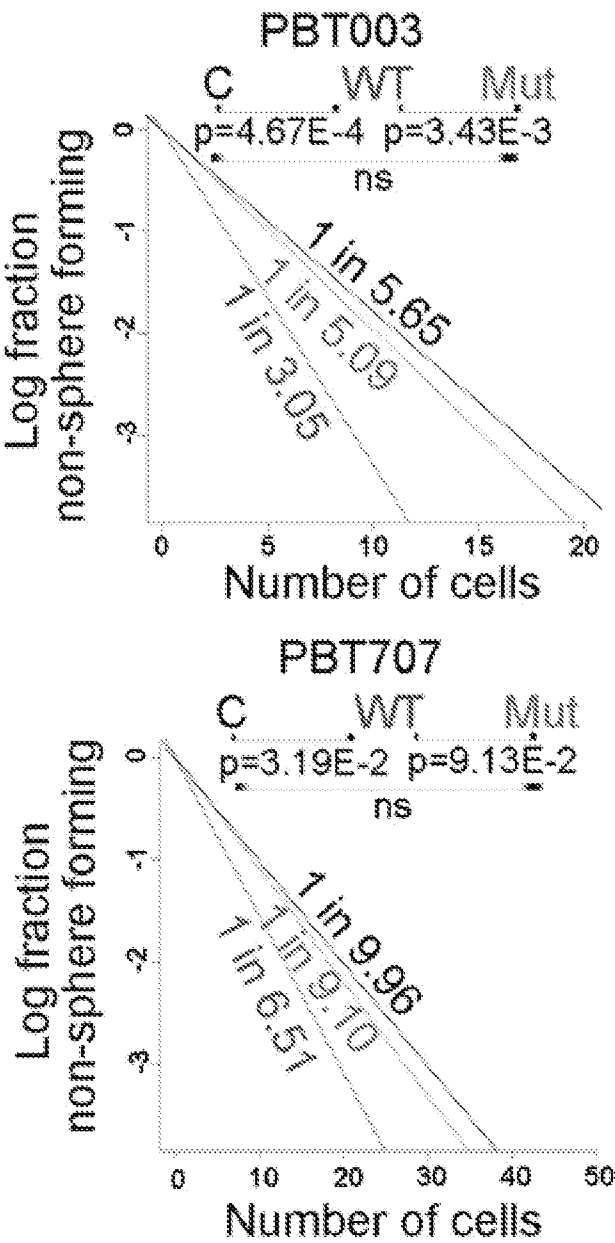


FIG. 2F

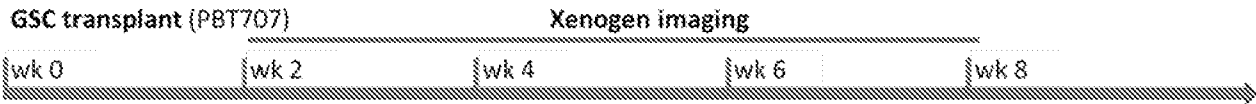


FIG. 3A

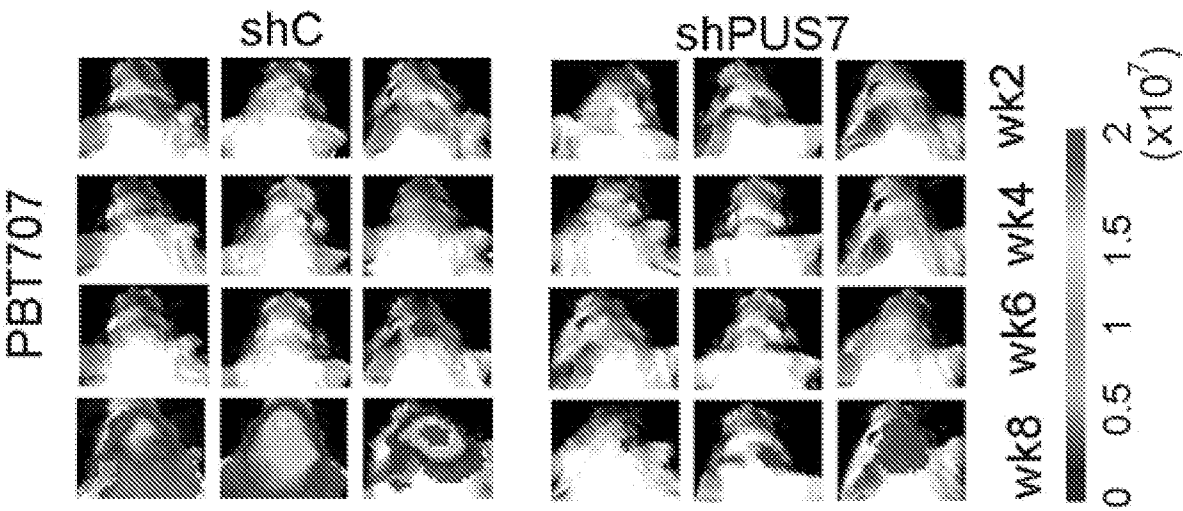


FIG. 3B

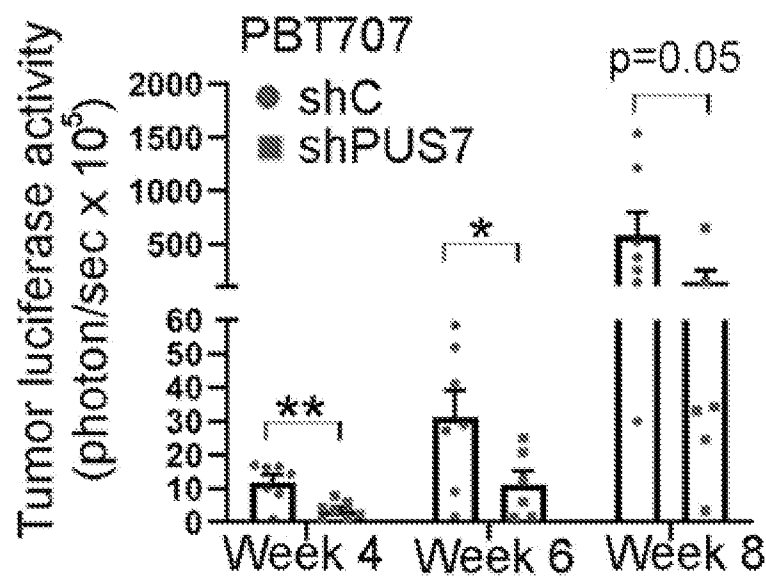


FIG. 3C

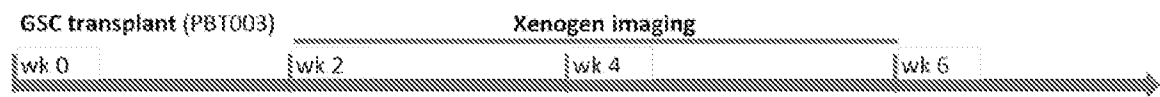


FIG. 3D

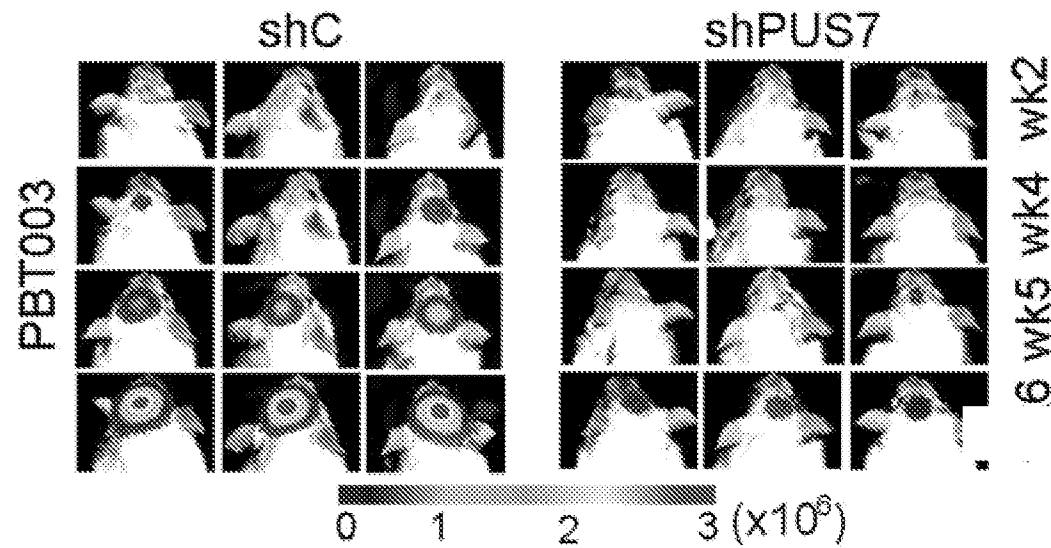


FIG. 3E

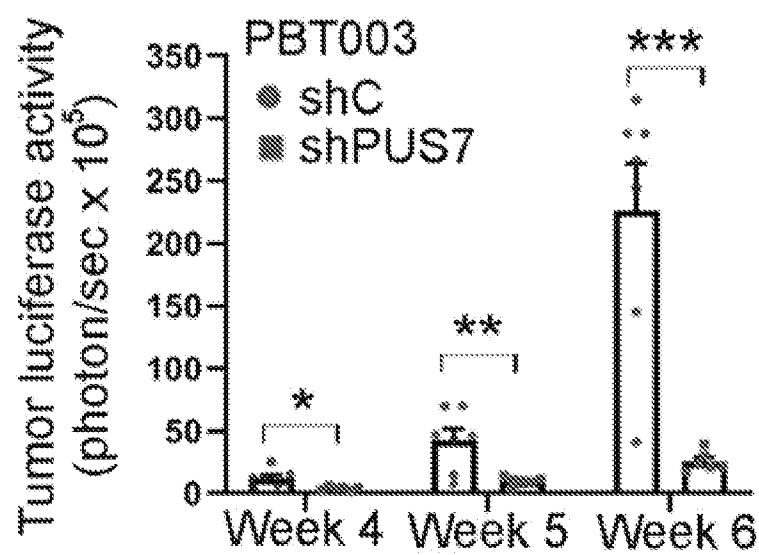


FIG. 3F

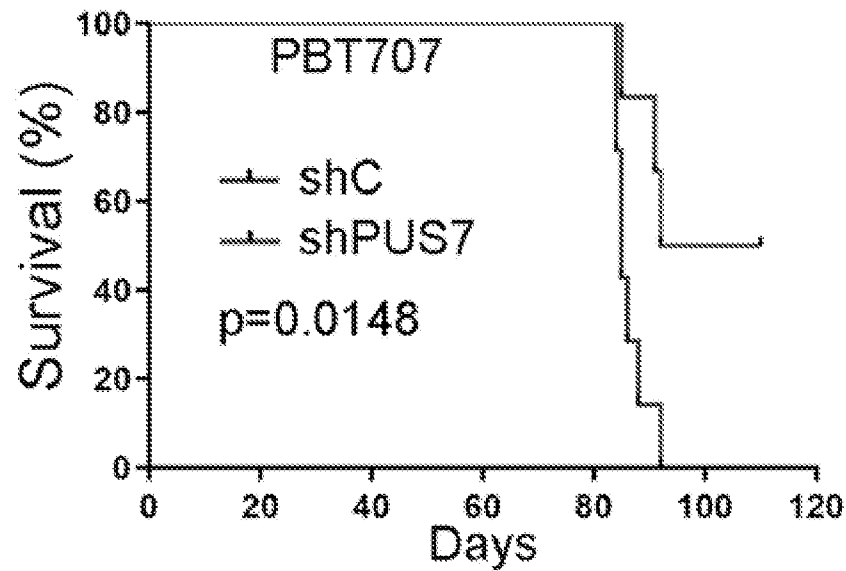


FIG. 3G

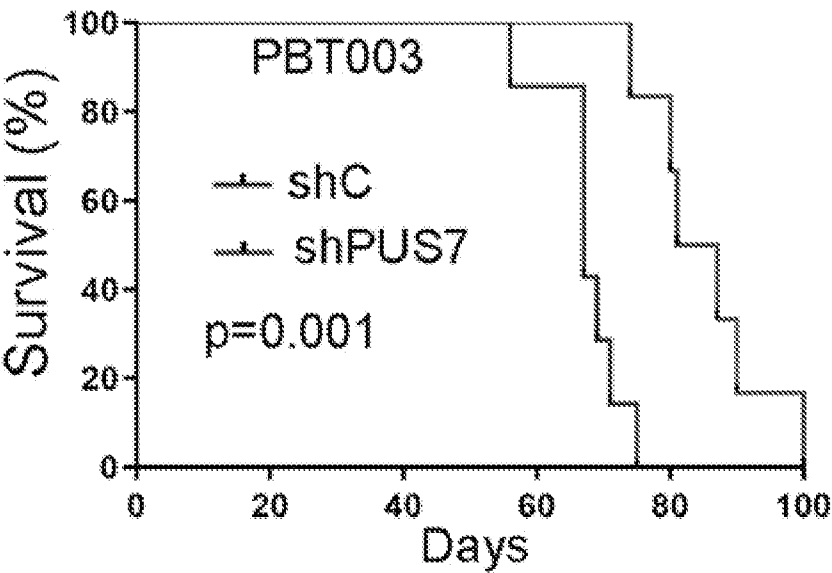


FIG. 3H

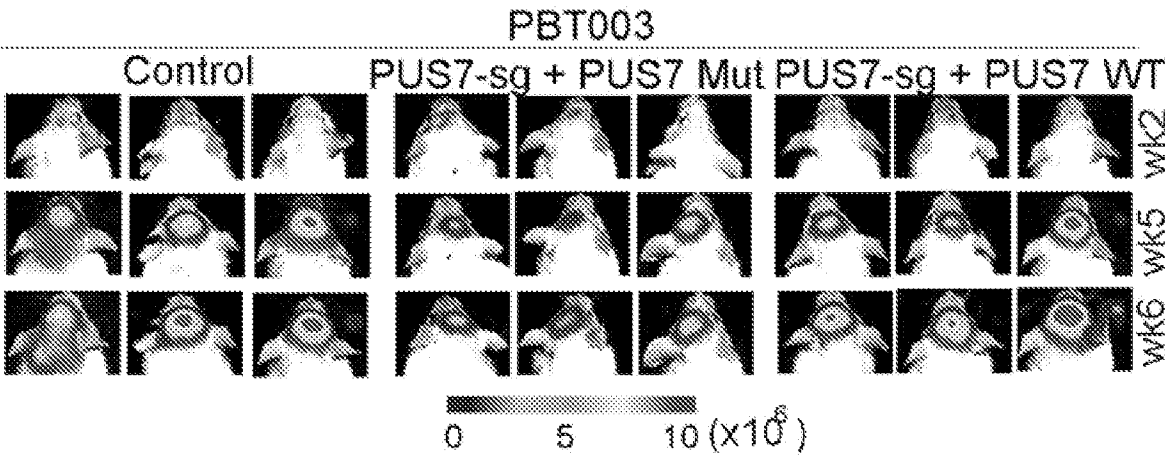


FIG. 3I

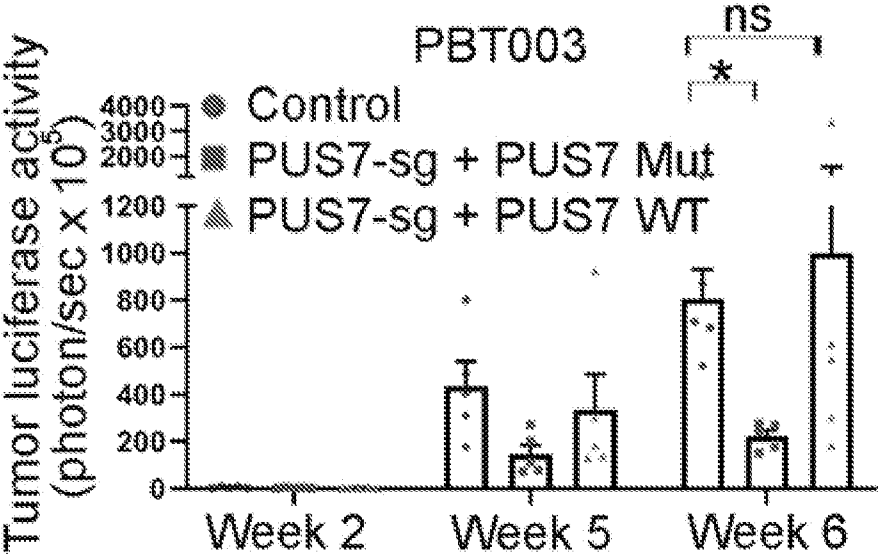


FIG. 3J

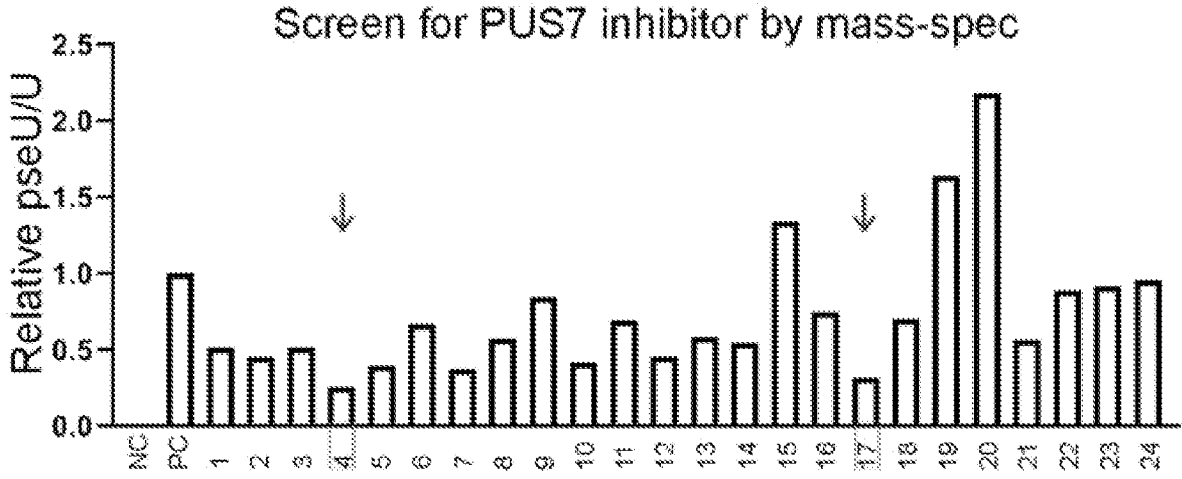


FIG. 4A

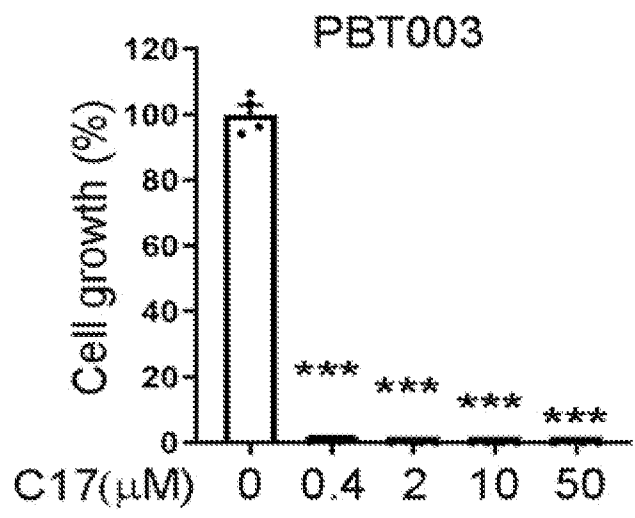


FIG. 4B

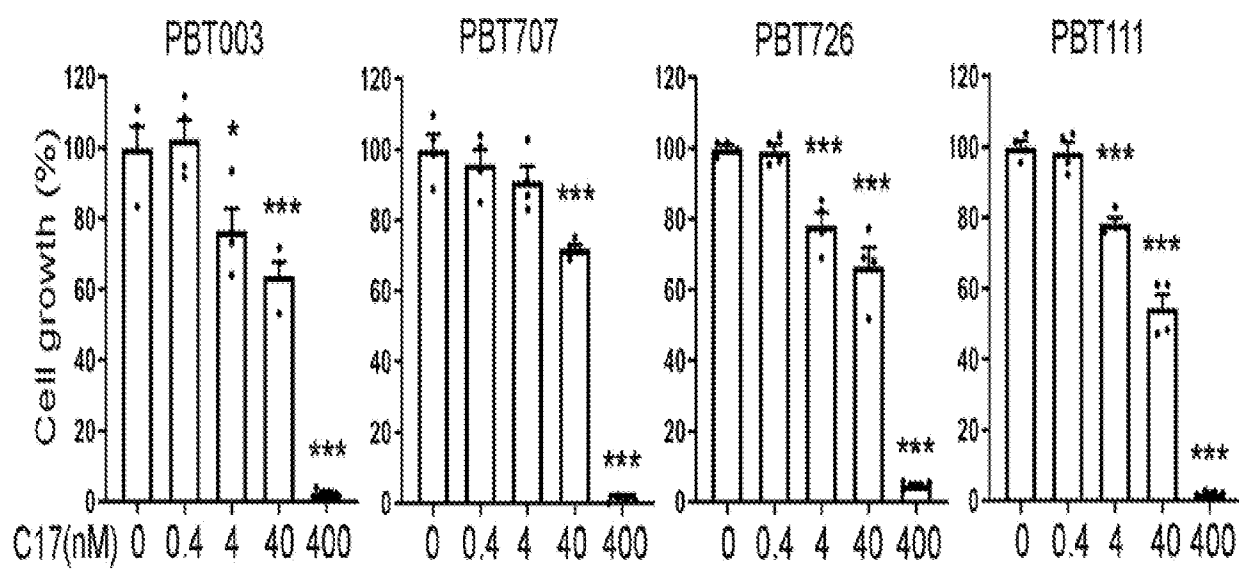


FIG. 4C

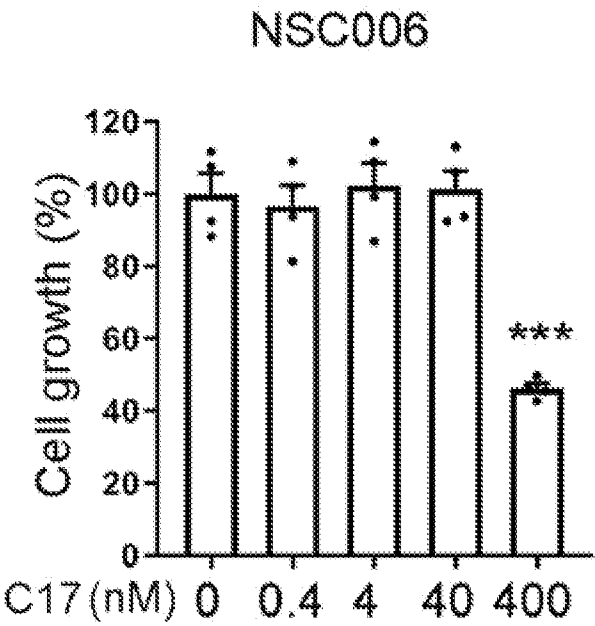


FIG. 4D

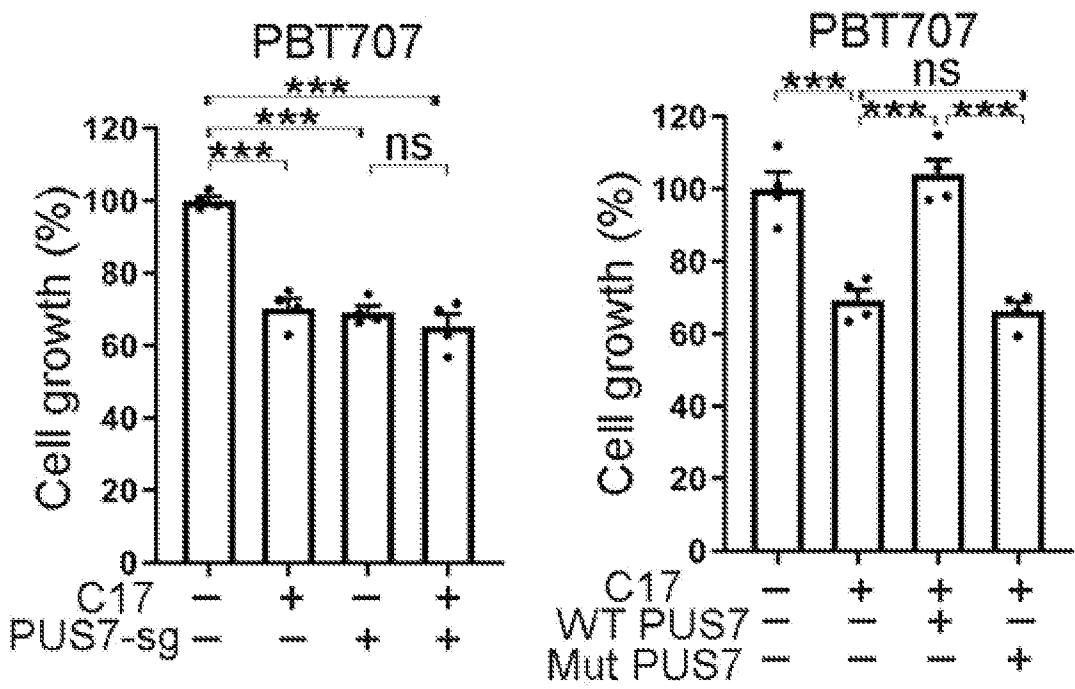


FIG. 4E

FIG. 4F

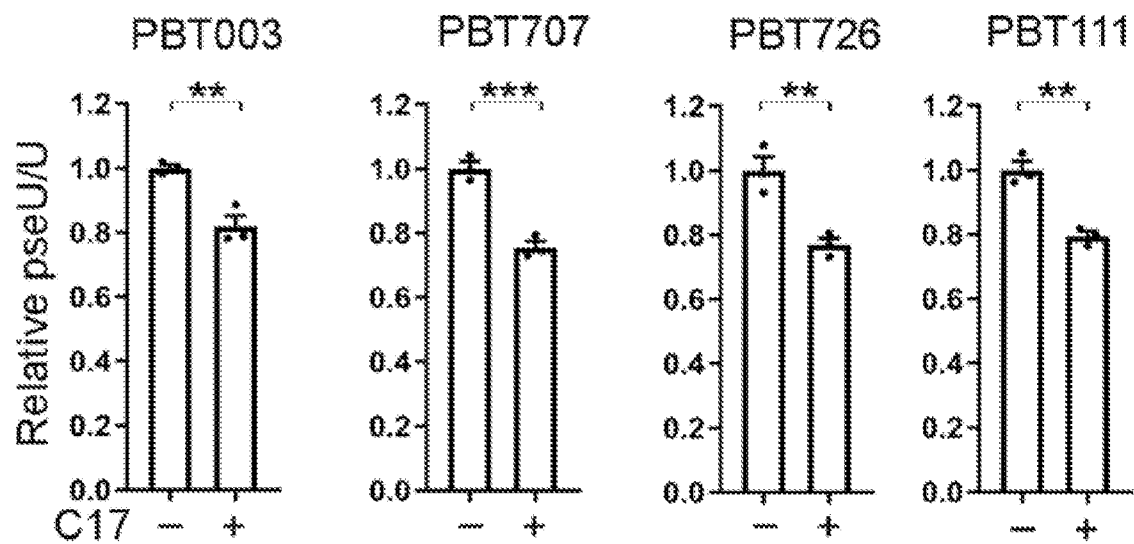


FIG. 4H

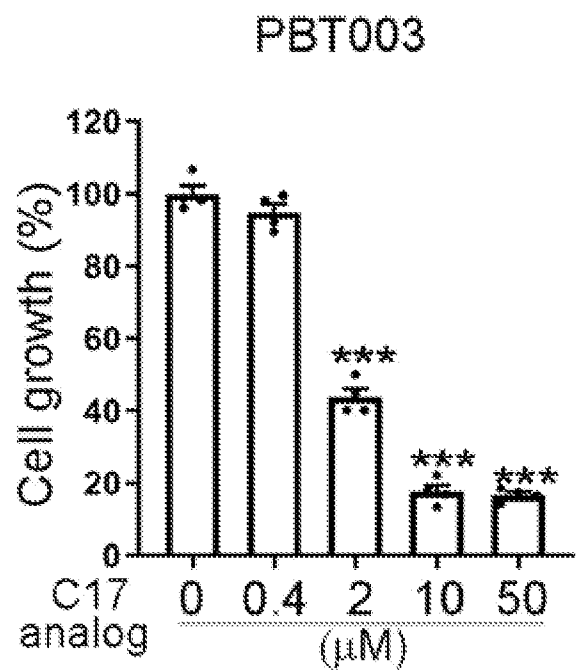


FIG. 4G

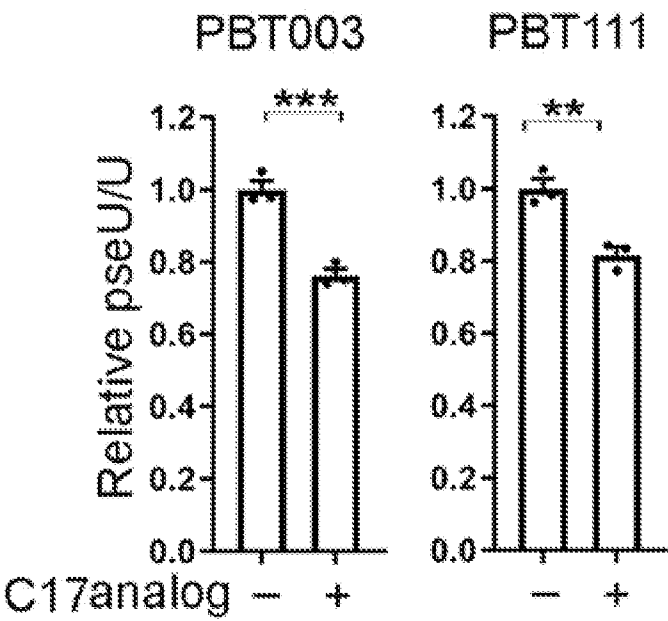


FIG. 4I

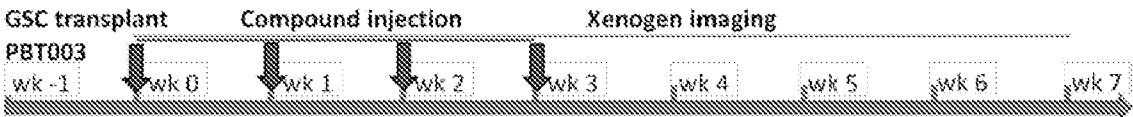


FIG. 5A

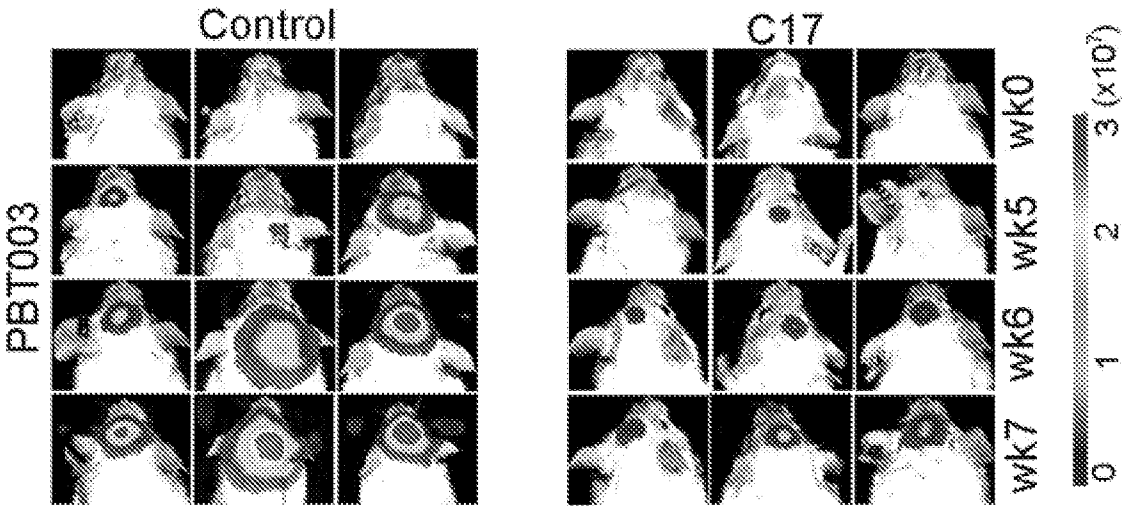


FIG. 5B

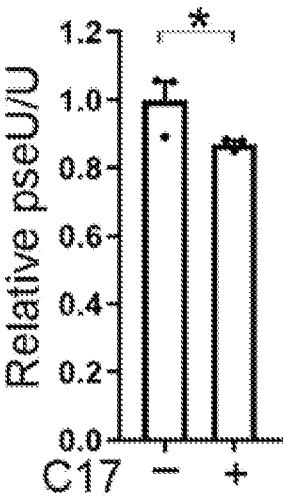


FIG. 5C

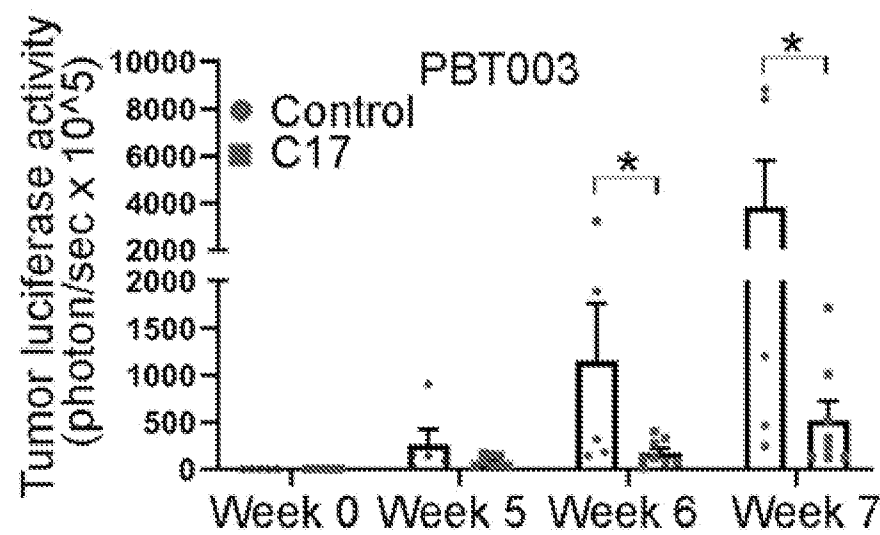


FIG. 5D

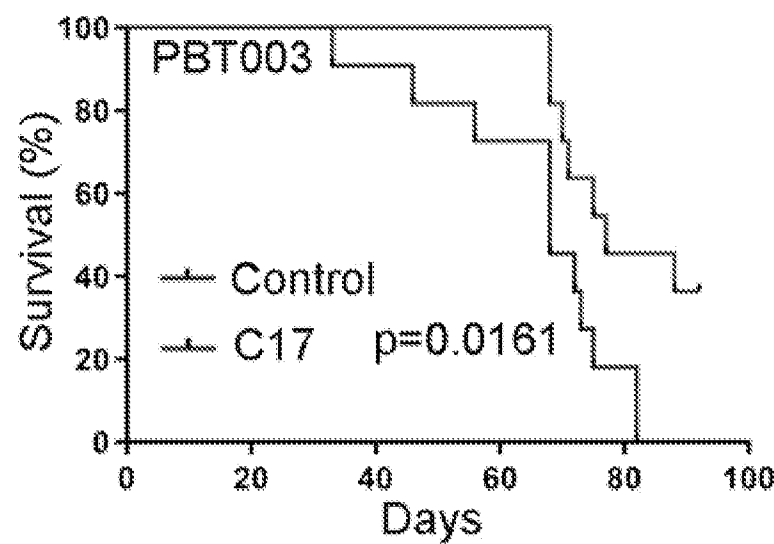


FIG. 5E

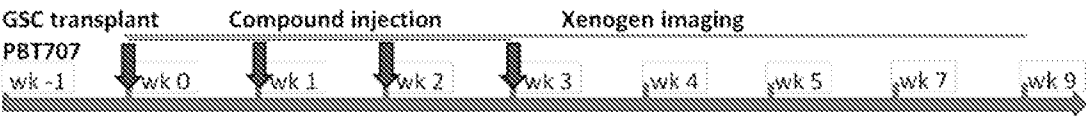


FIG. 5F

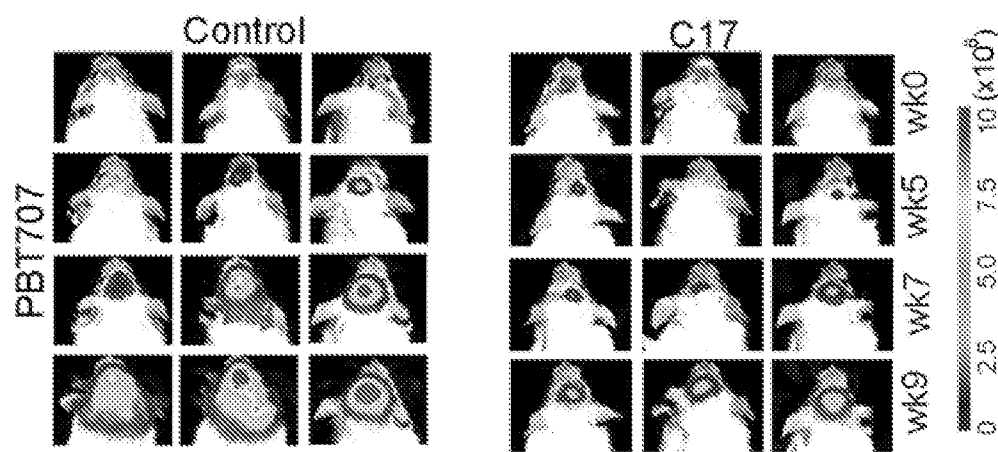


FIG. 5G

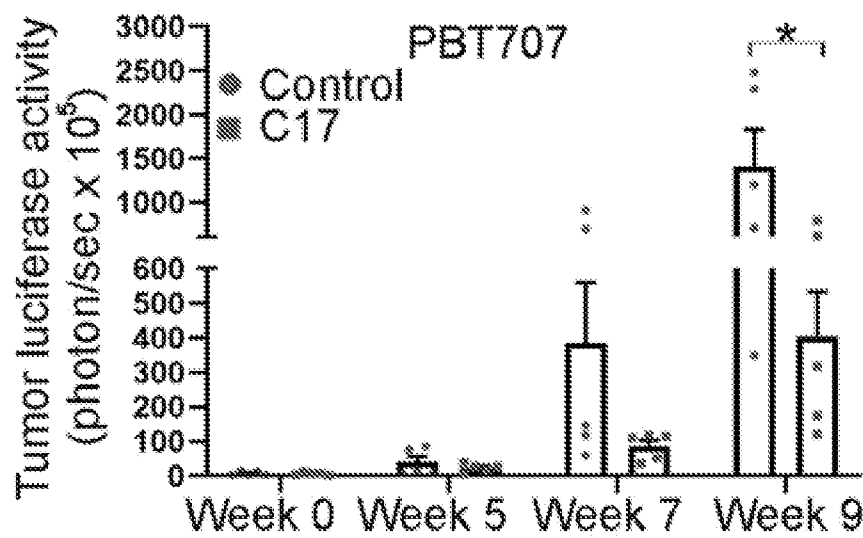


FIG. 5H

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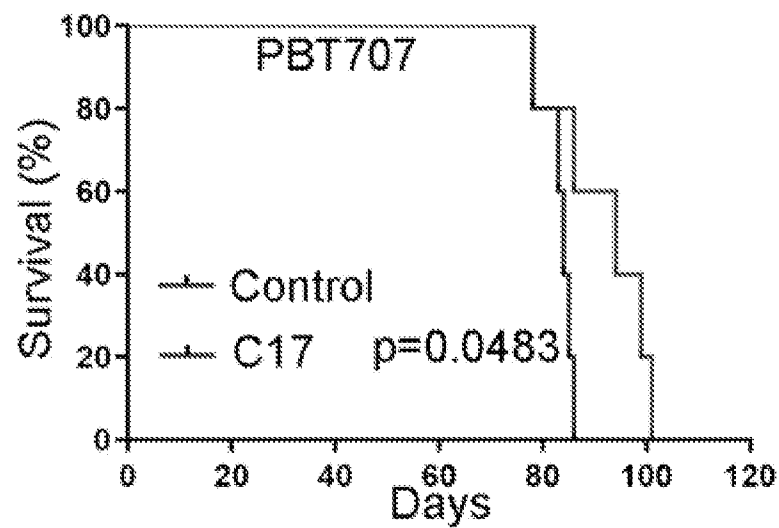


FIG. 5I

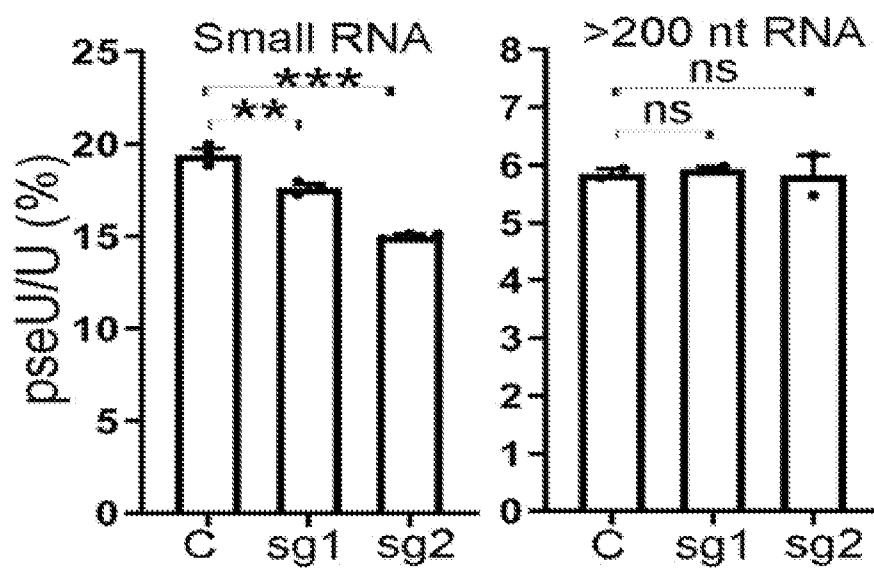


FIG. 6A

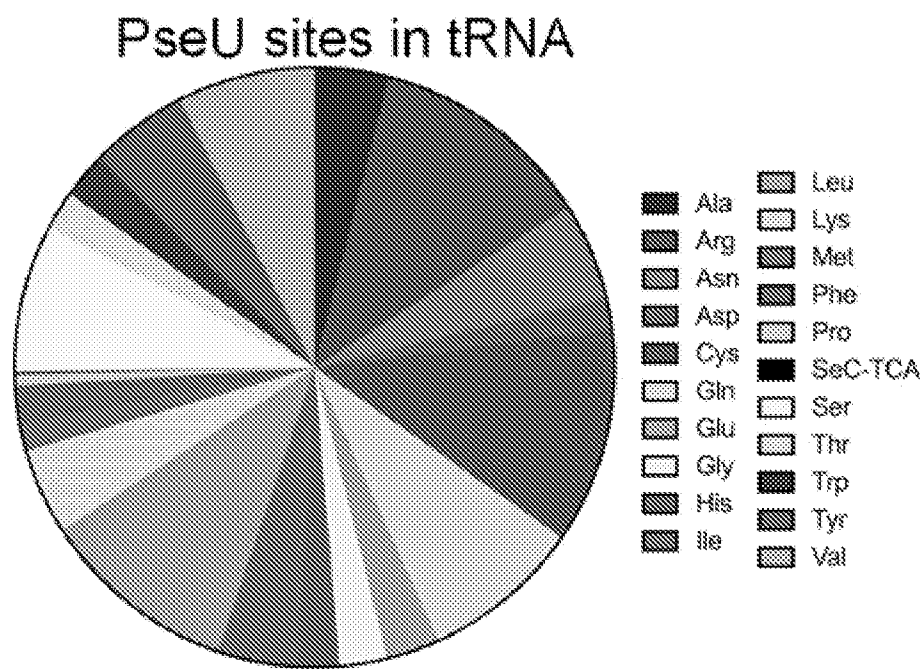
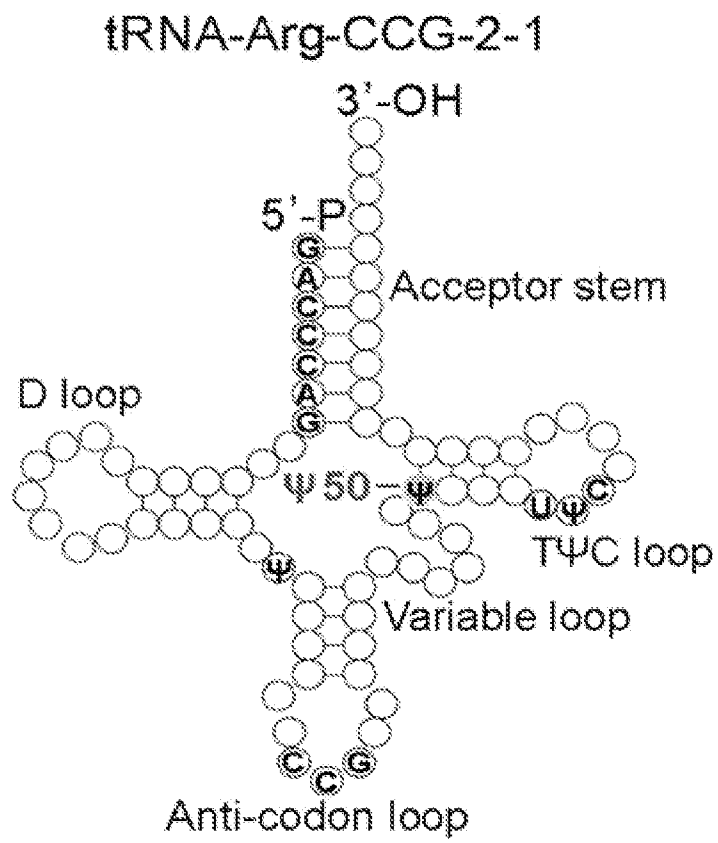


FIG. 6B

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**FIG. 6C**

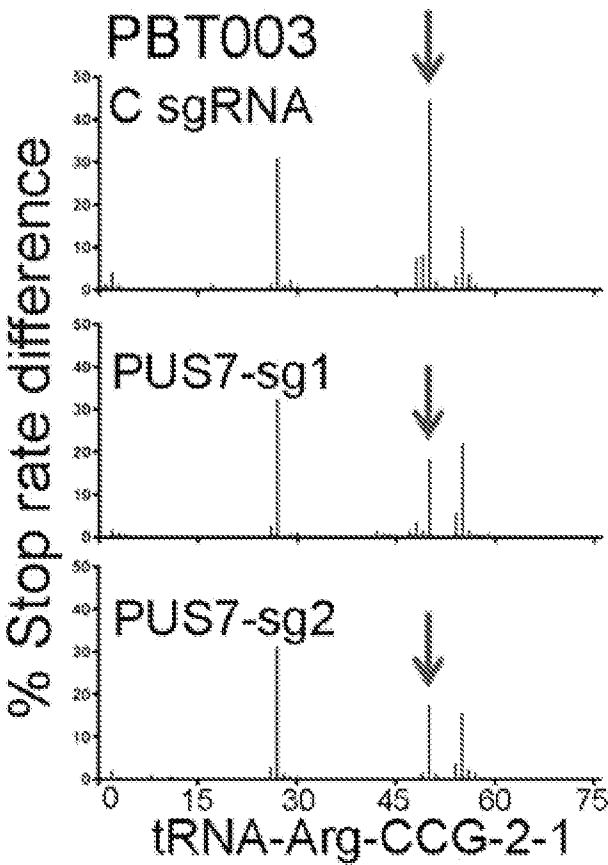


FIG. 6D

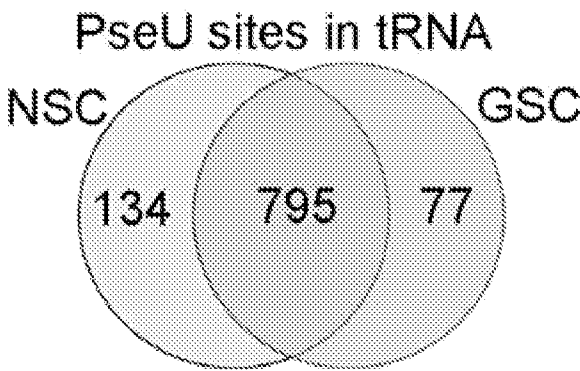


FIG. 6E

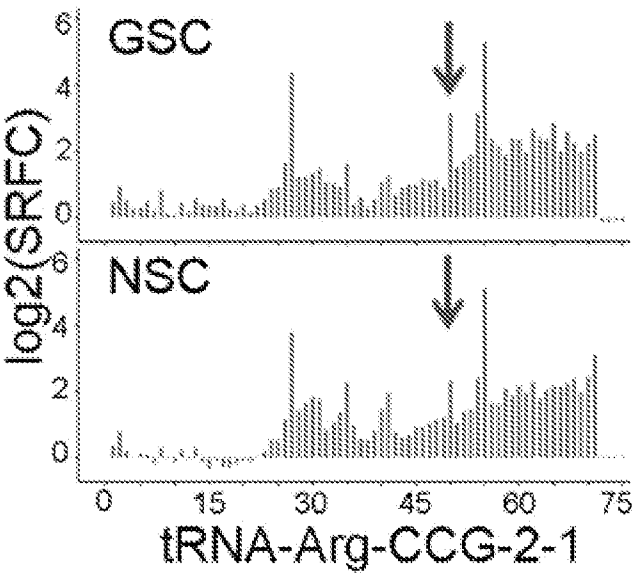


FIG. 6F

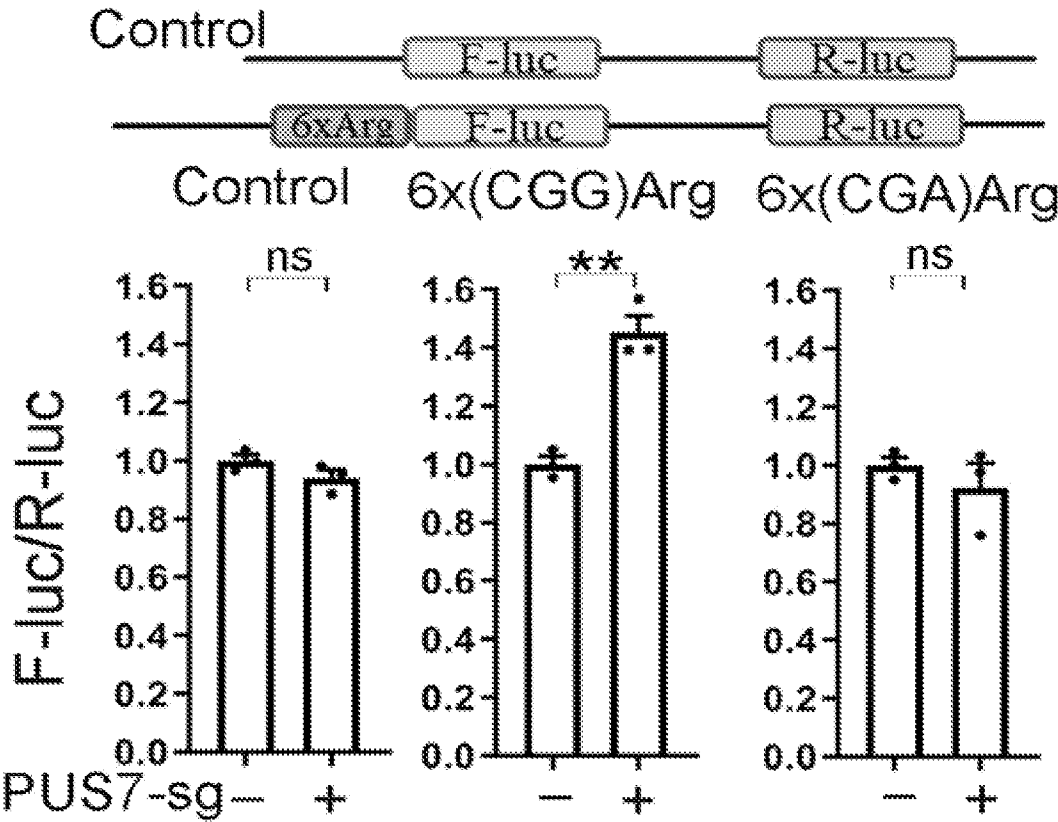


FIG. 6G

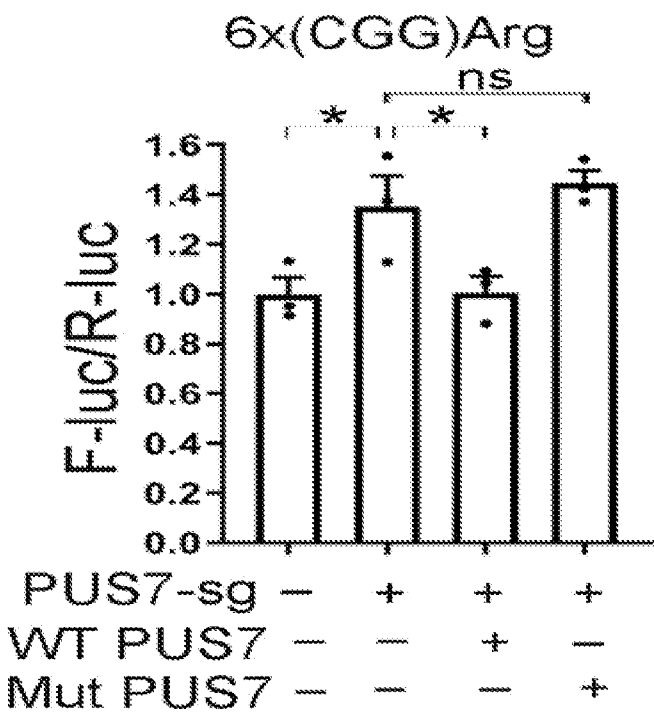


FIG. 6H

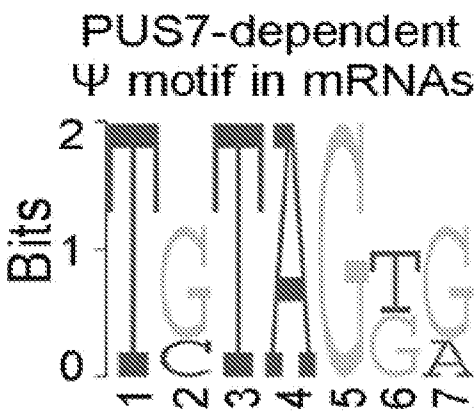


FIG. 7A

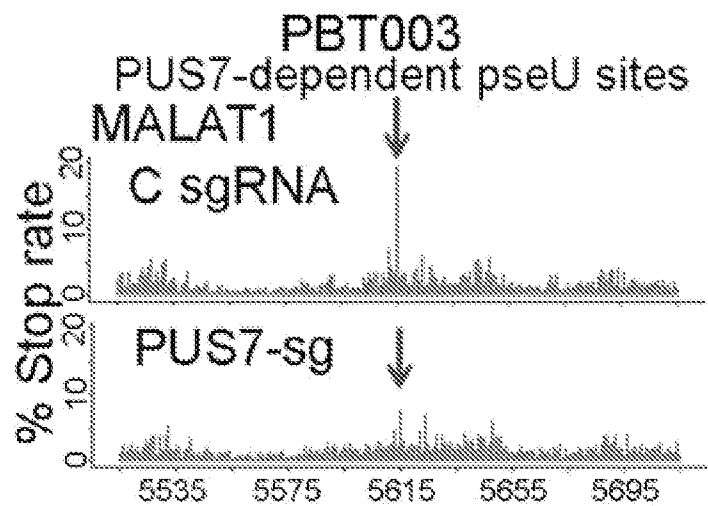


FIG. 7B

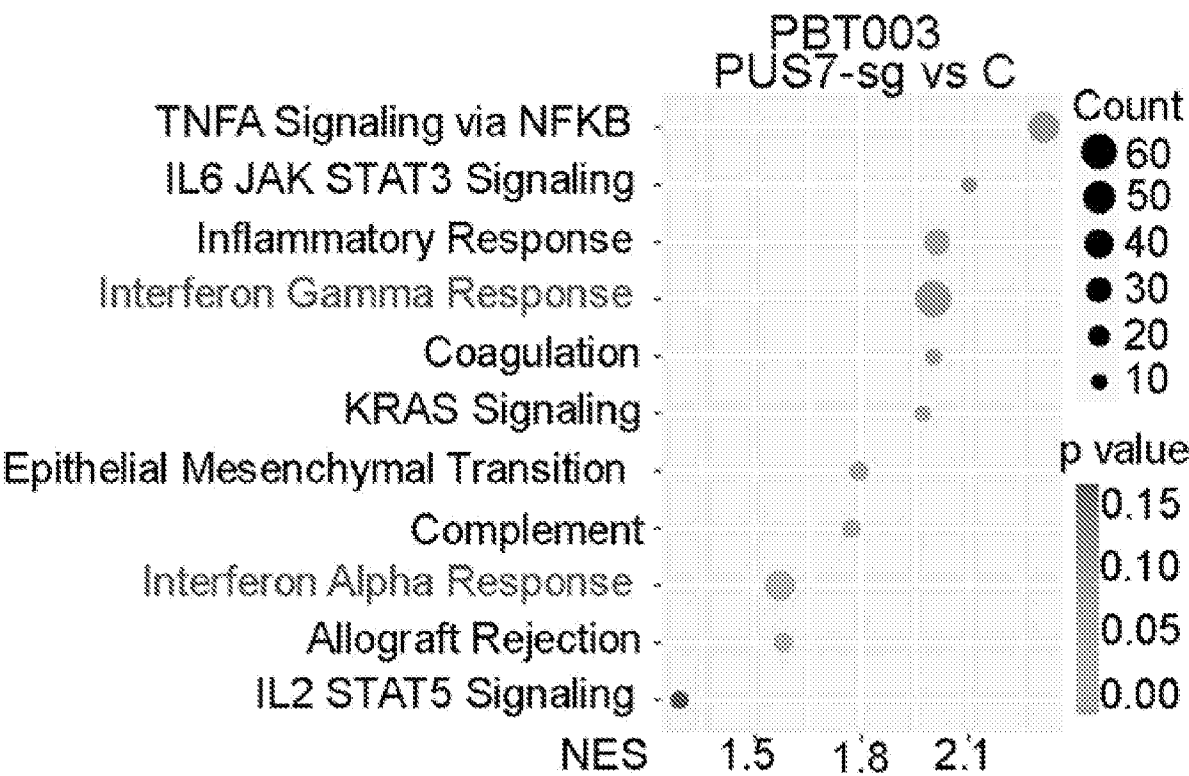


FIG. 7C

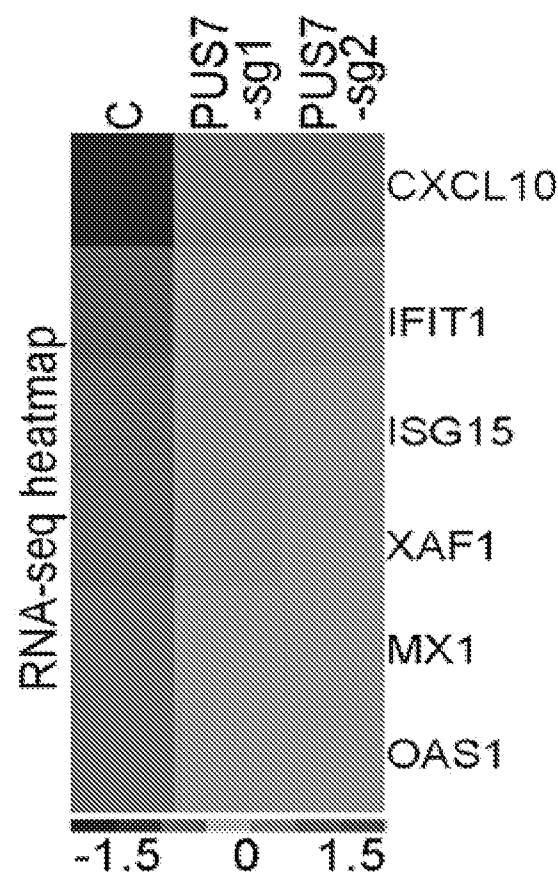


FIG. 7D

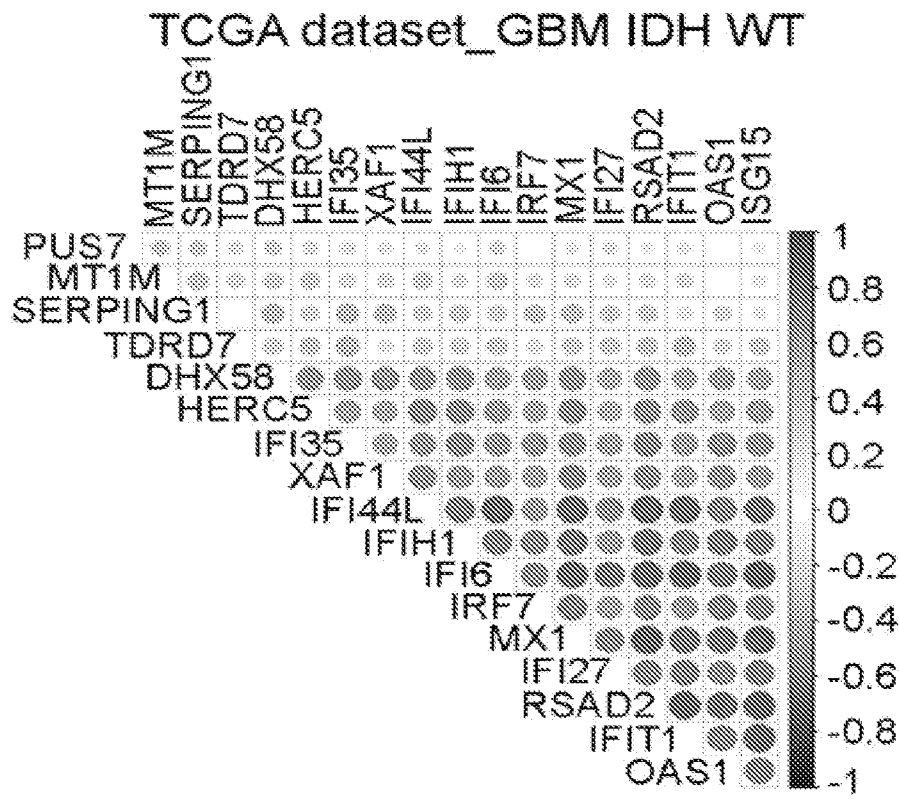


FIG. 7F

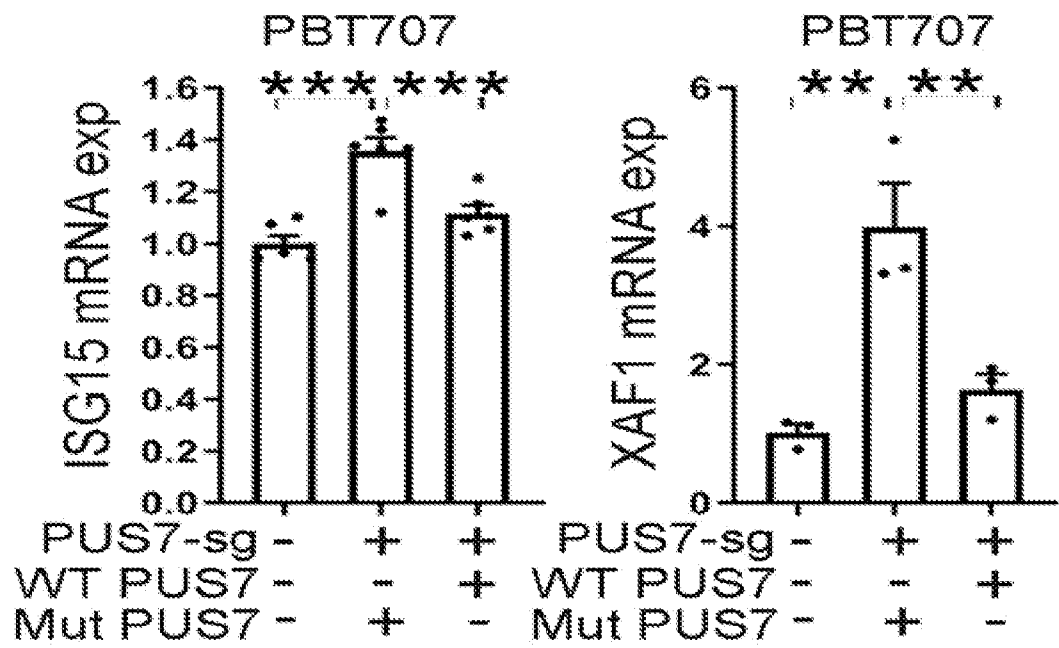


FIG. 7E

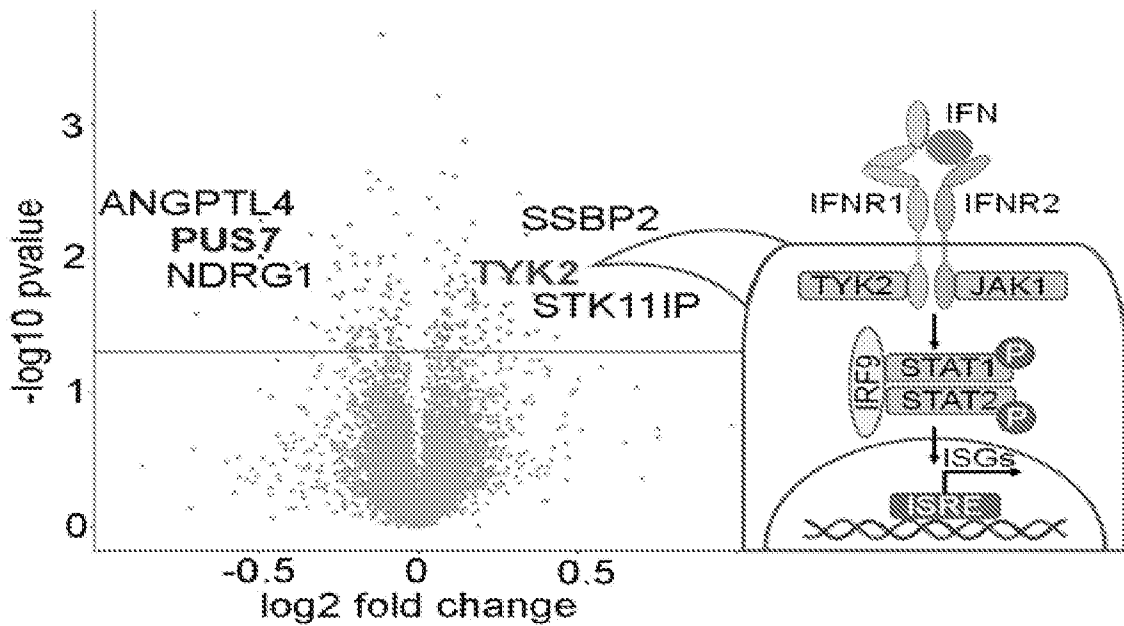


FIG. 8A

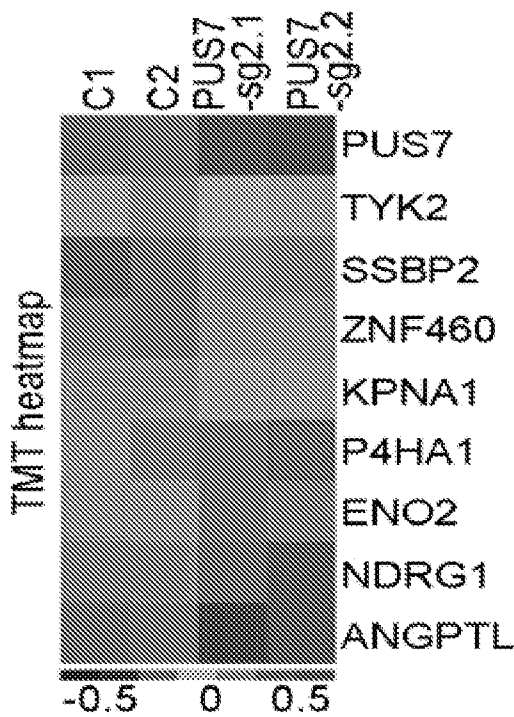


FIG. 8B

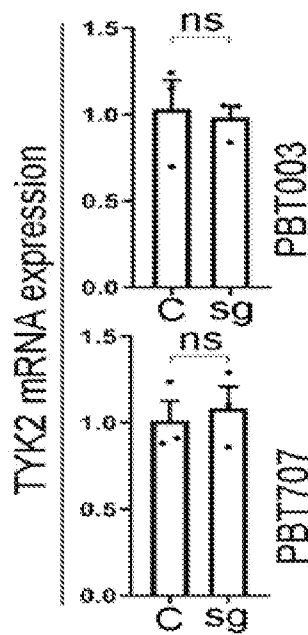


FIG. 8C



FIG. 8D

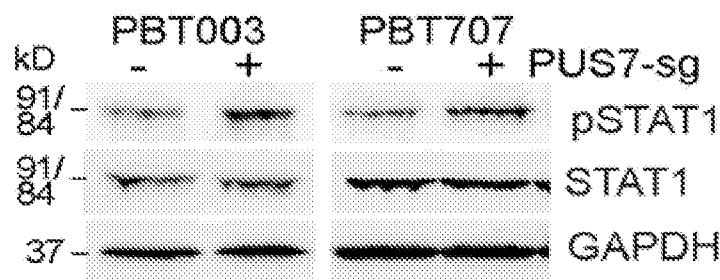


FIG. 8E

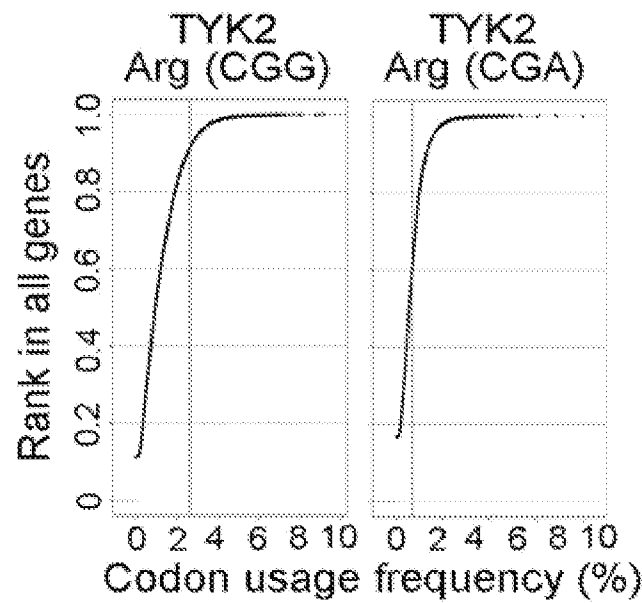


FIG. 8F

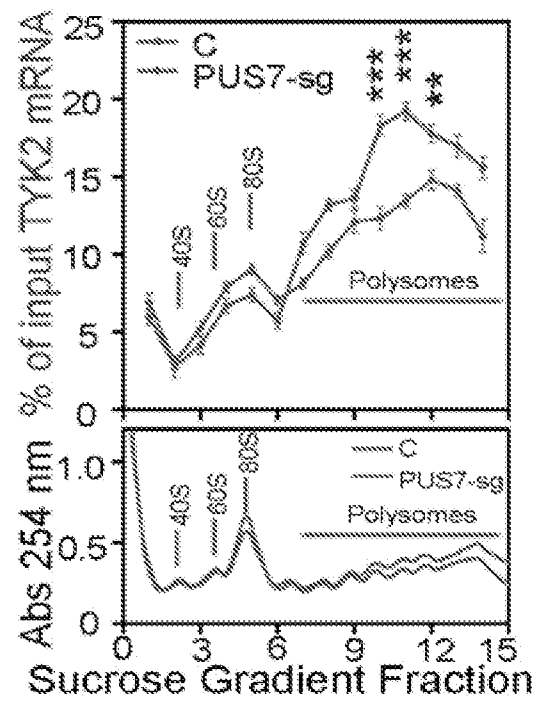


FIG. 8G

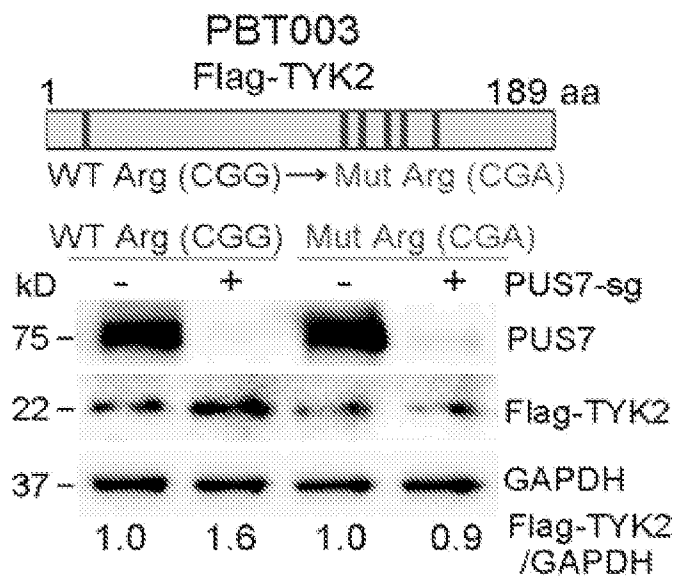


FIG. 8H

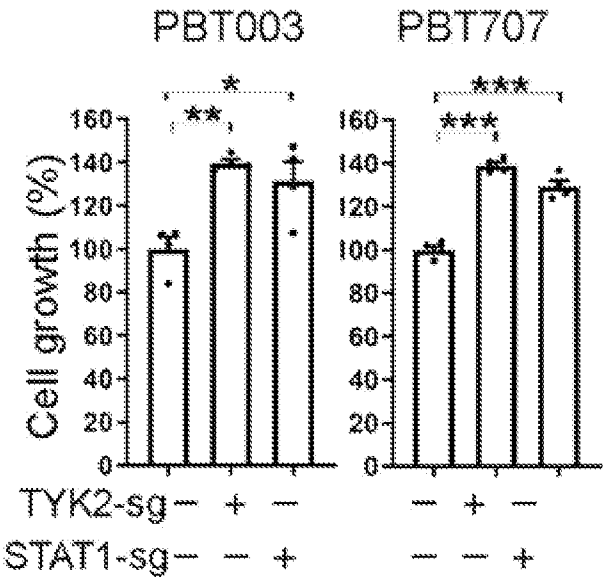


FIG. 8I

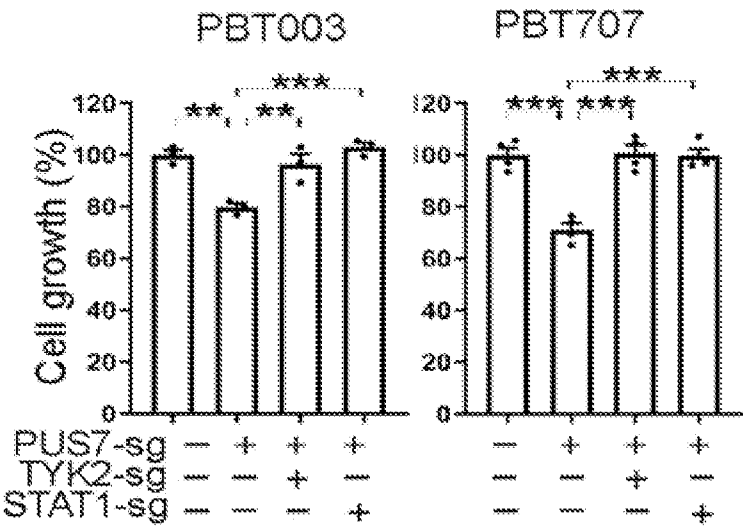


FIG. 8J

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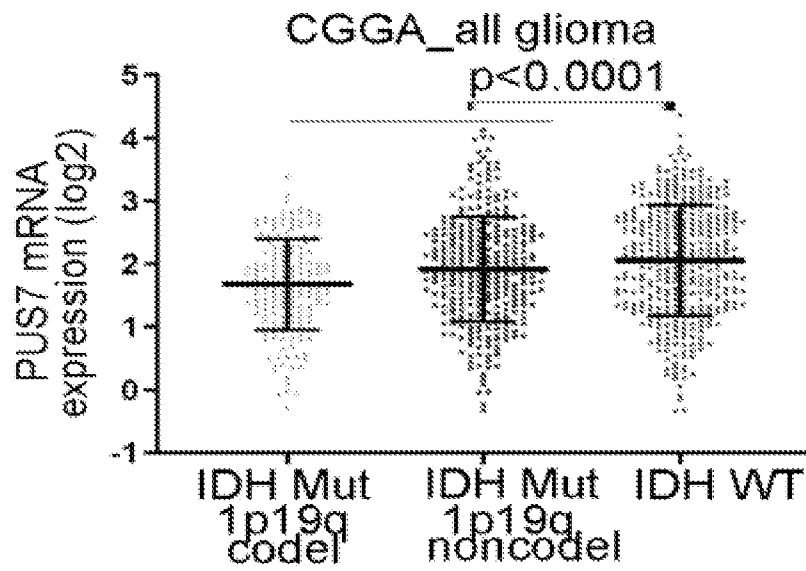


FIG. 9A

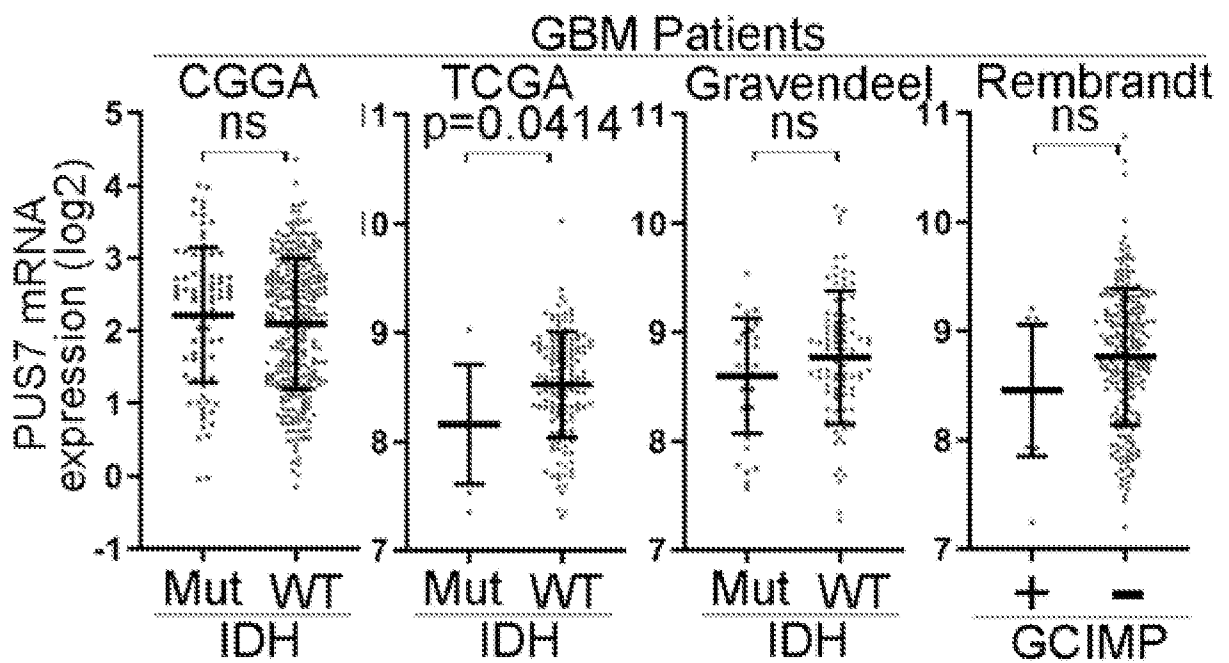
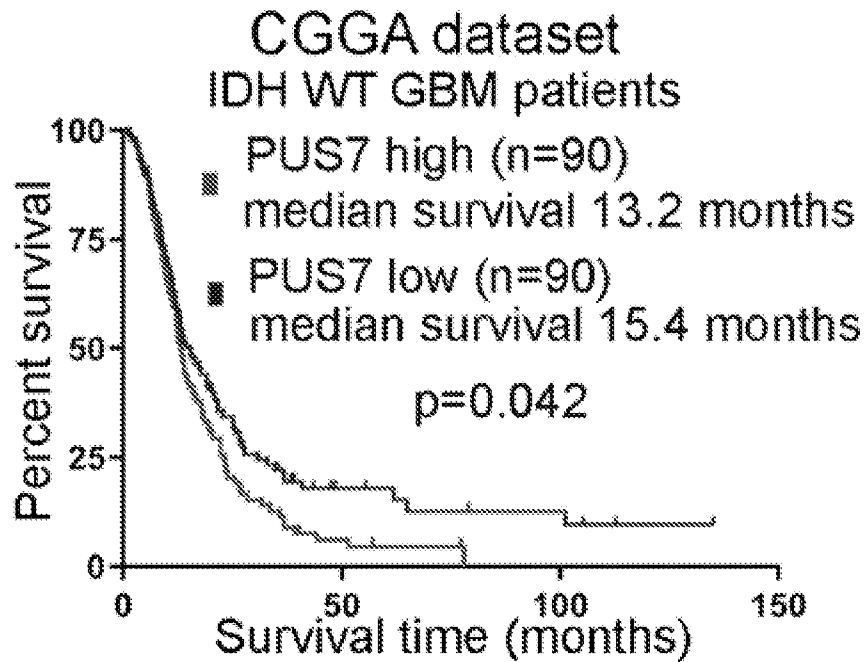
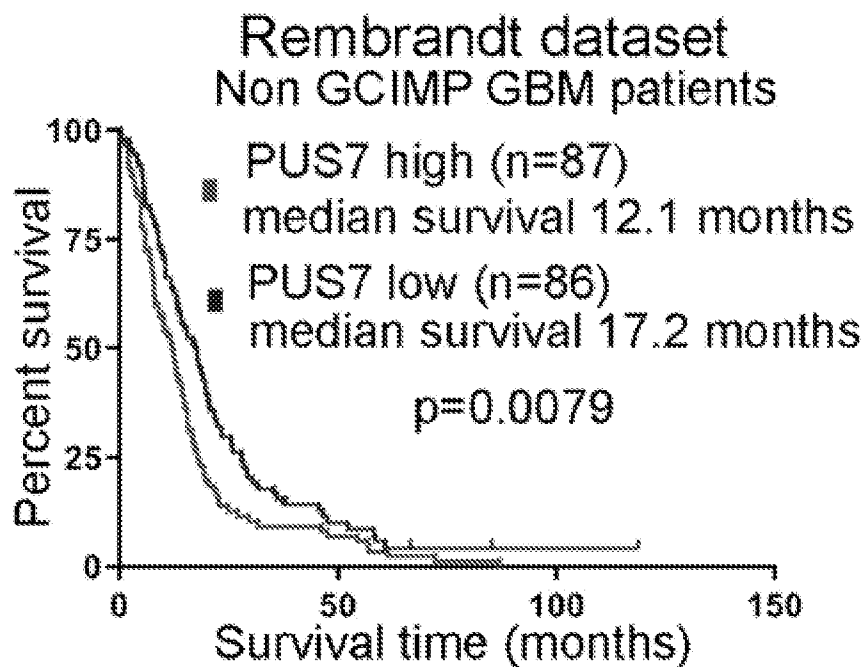


FIG. 9B

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**FIG. 9C****FIG. 9D**

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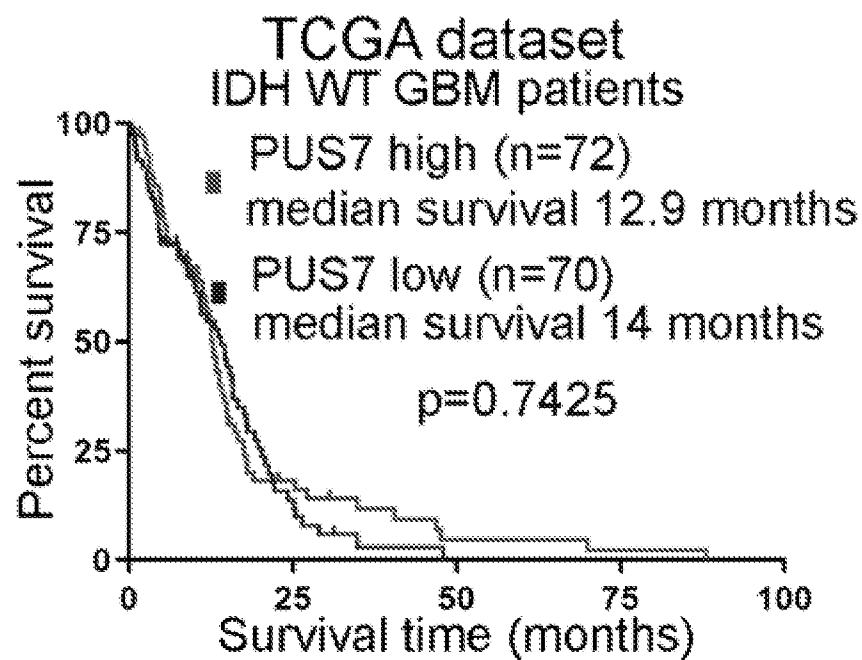
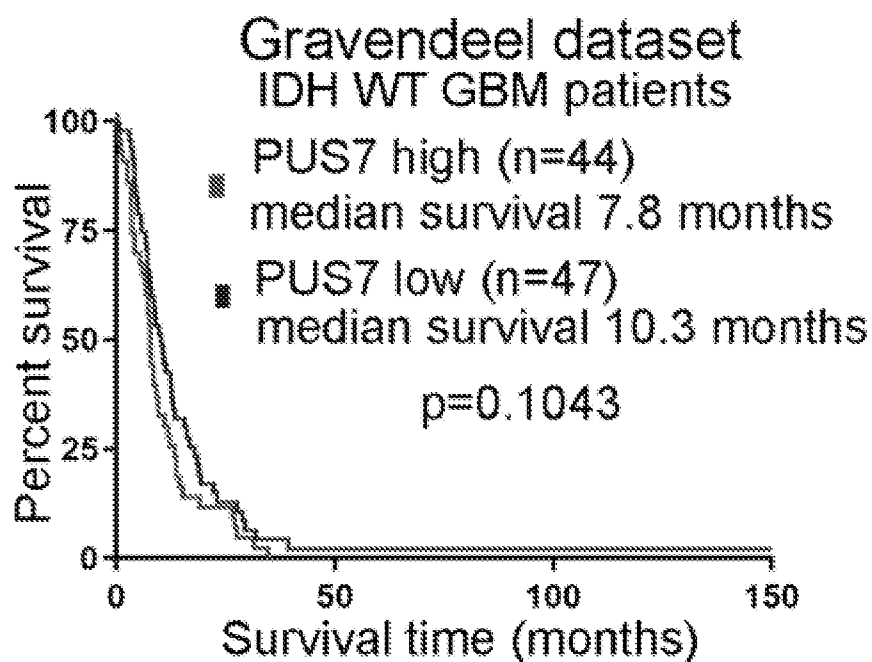
**FIG. 9E****FIG. 9F**



FIG. 9G

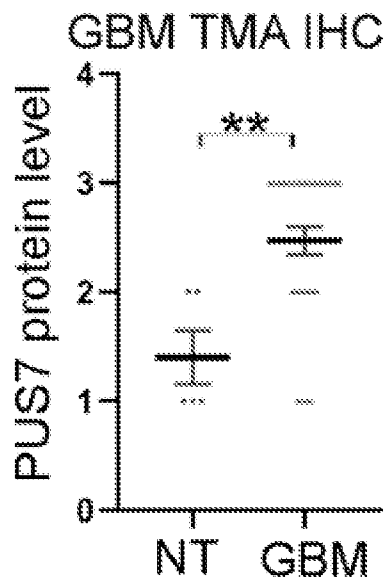


FIG. 9H

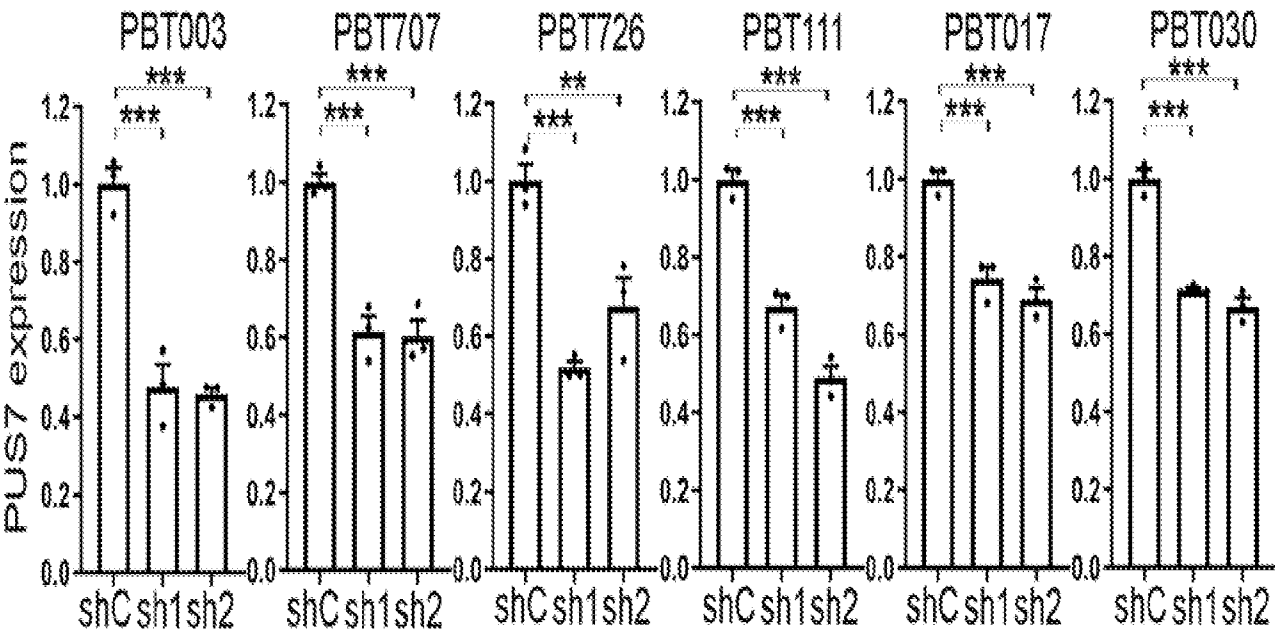


FIG. 10A

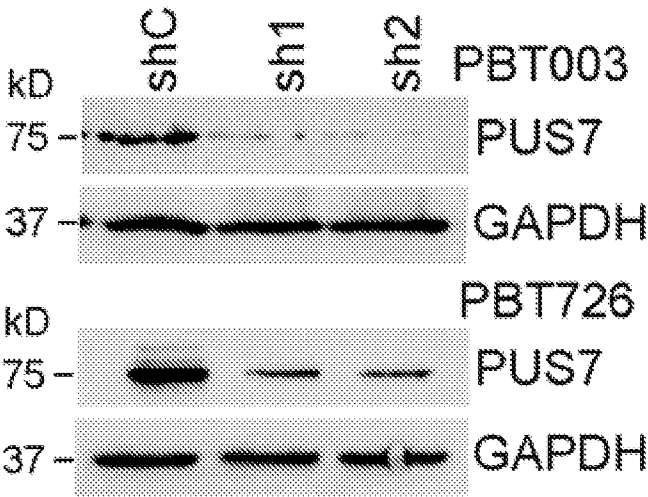


FIG. 10B

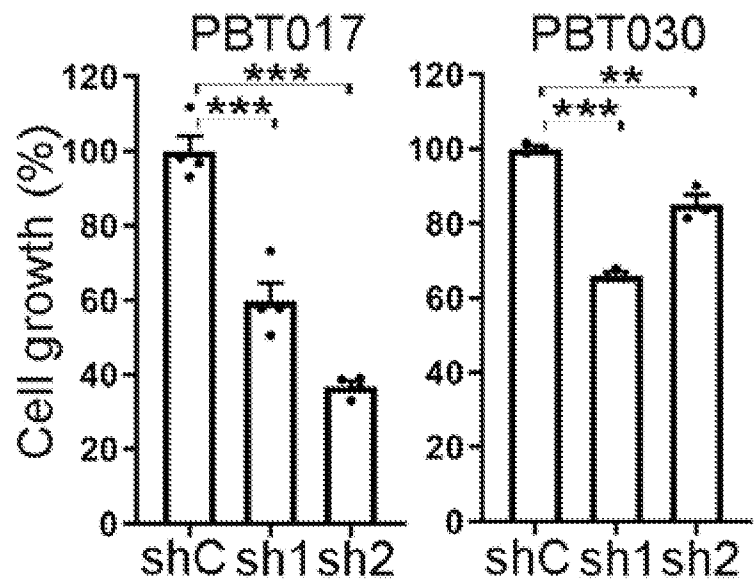


FIG. 10C

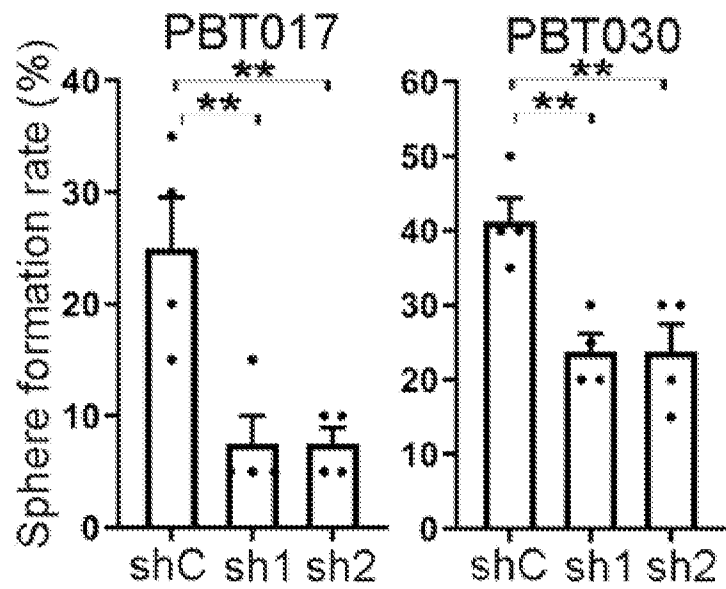


FIG. 10D



FIG. 10E

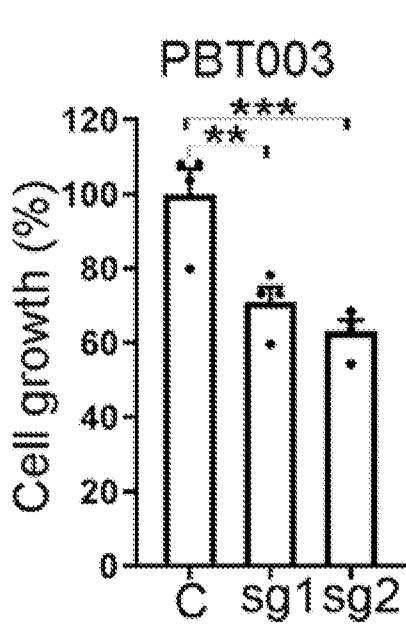


FIG. 10F

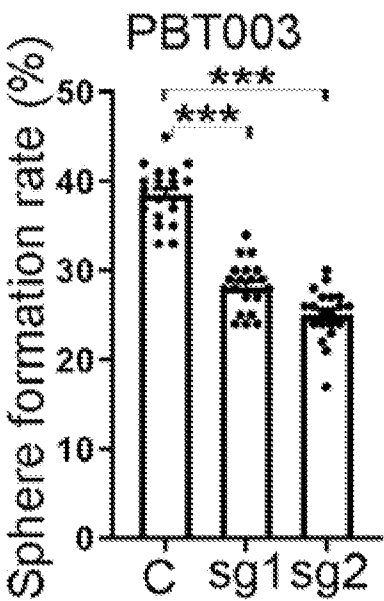


FIG. 10G

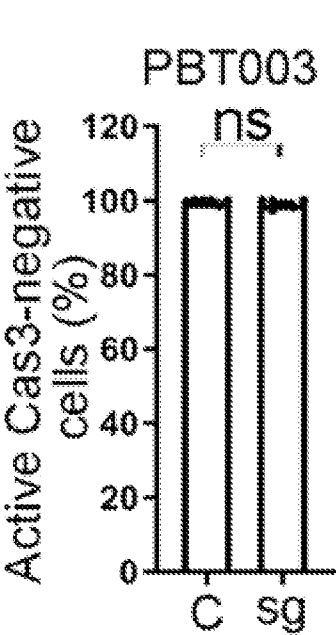


FIG. 10H

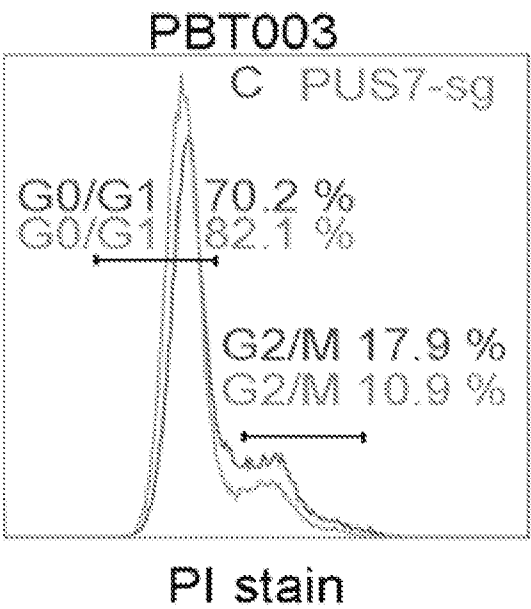


FIG. 10I



FIG. 10J

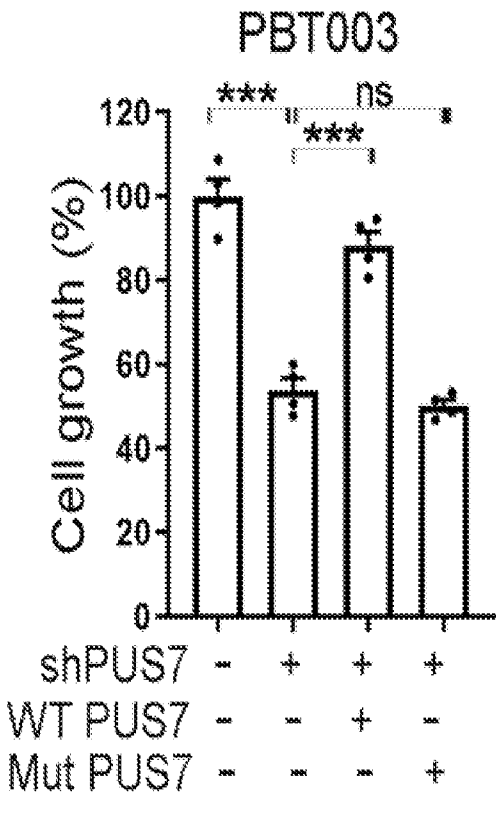


FIG. 11A

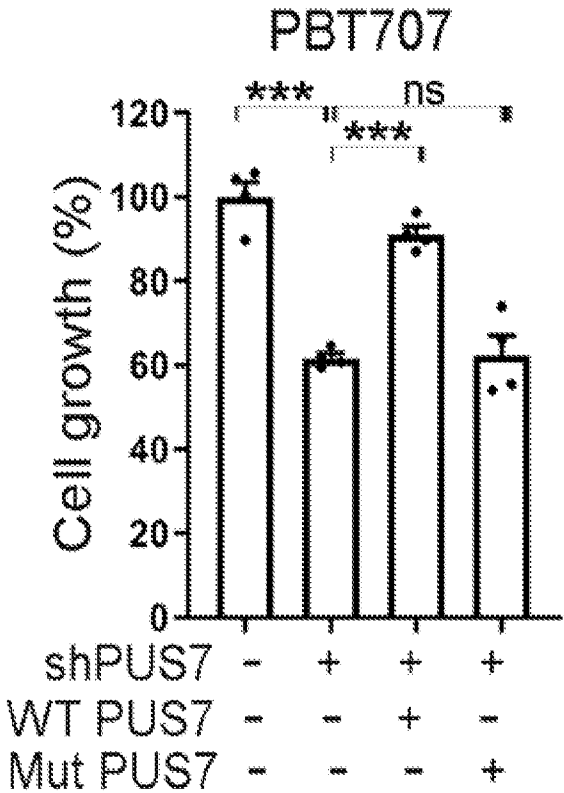


FIG. 11B

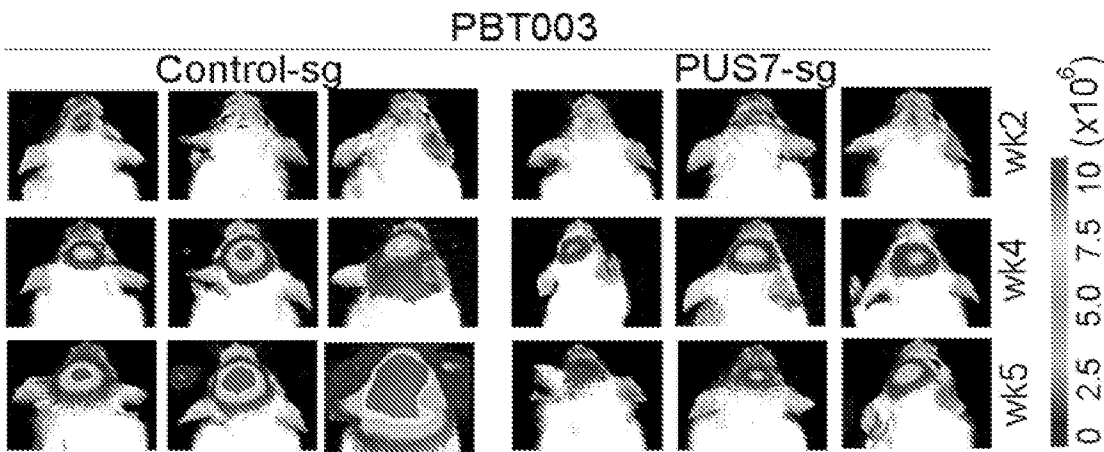


FIG. 12A

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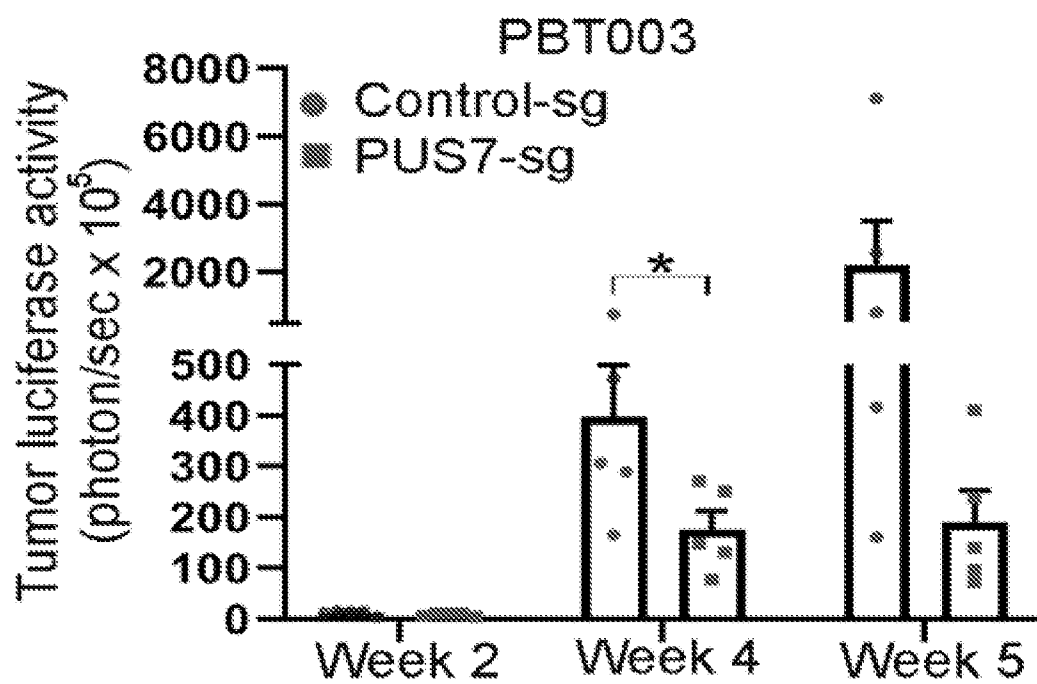


FIG. 12B

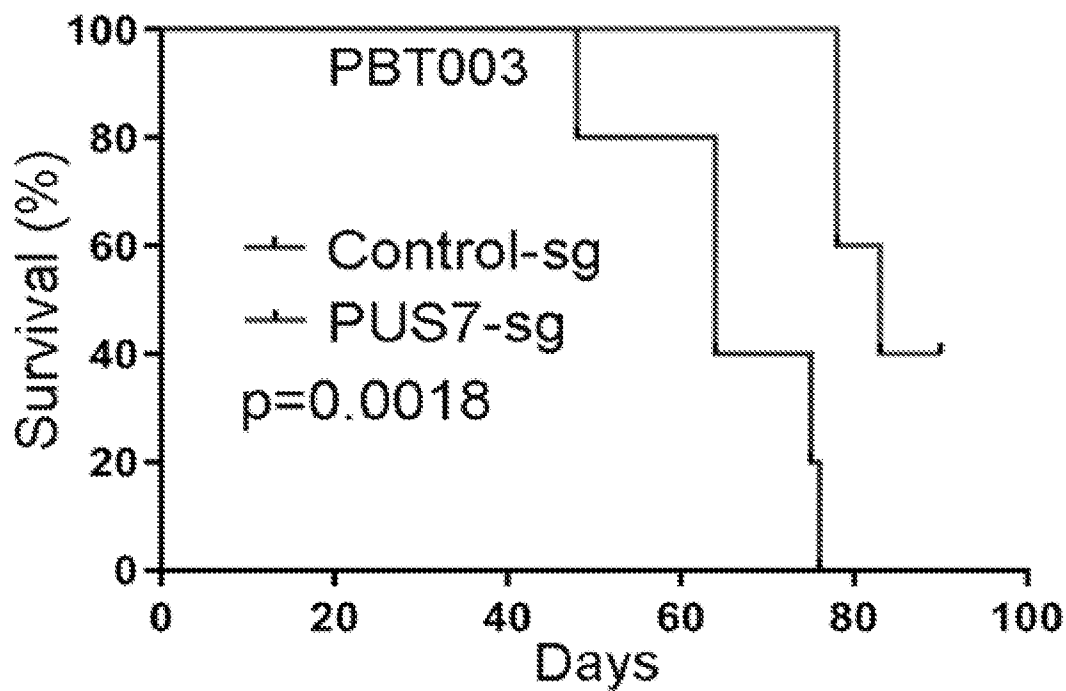


FIG. 12C

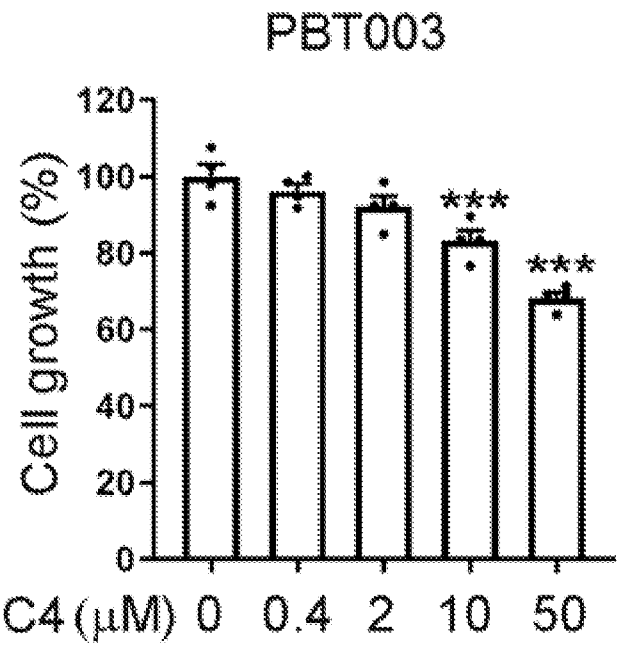


FIG. 13A

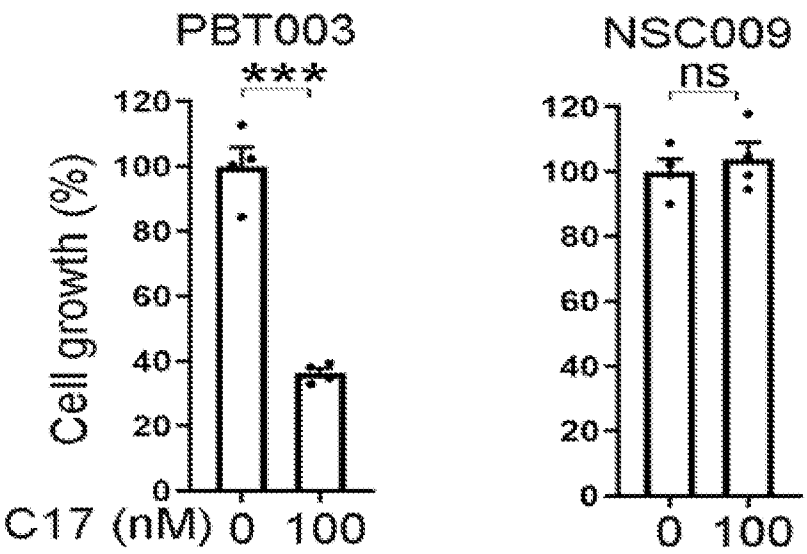


FIG. 13B

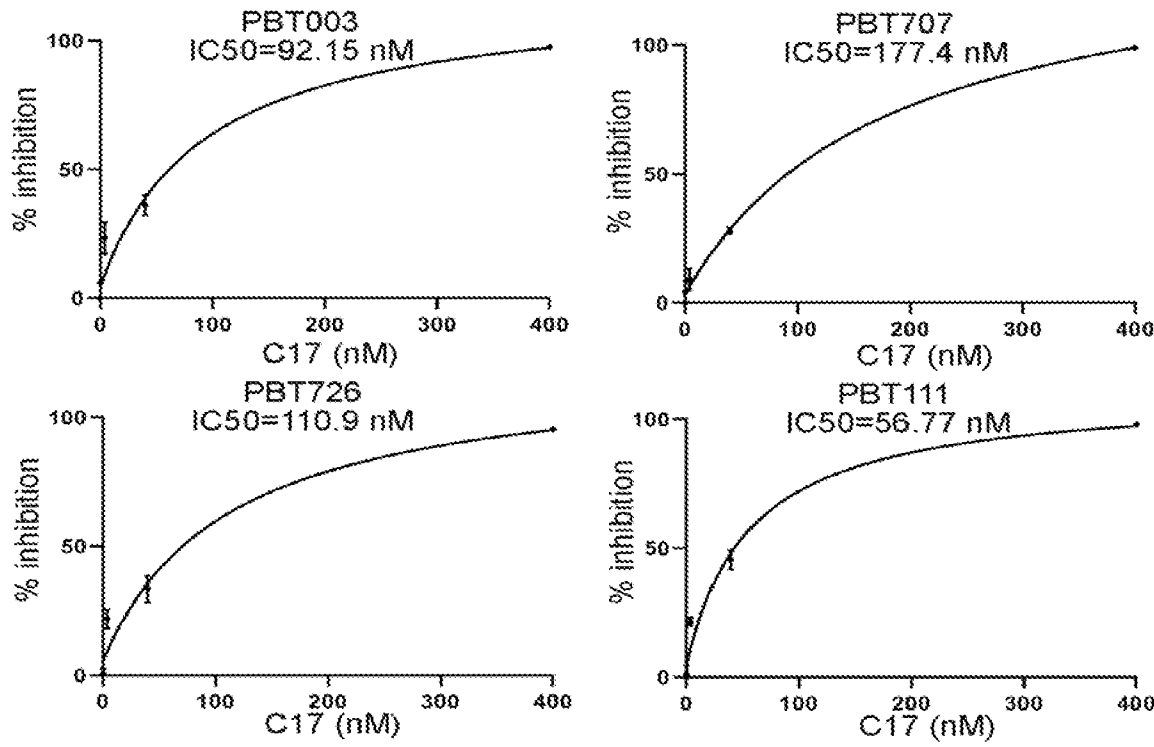


FIG. 13C

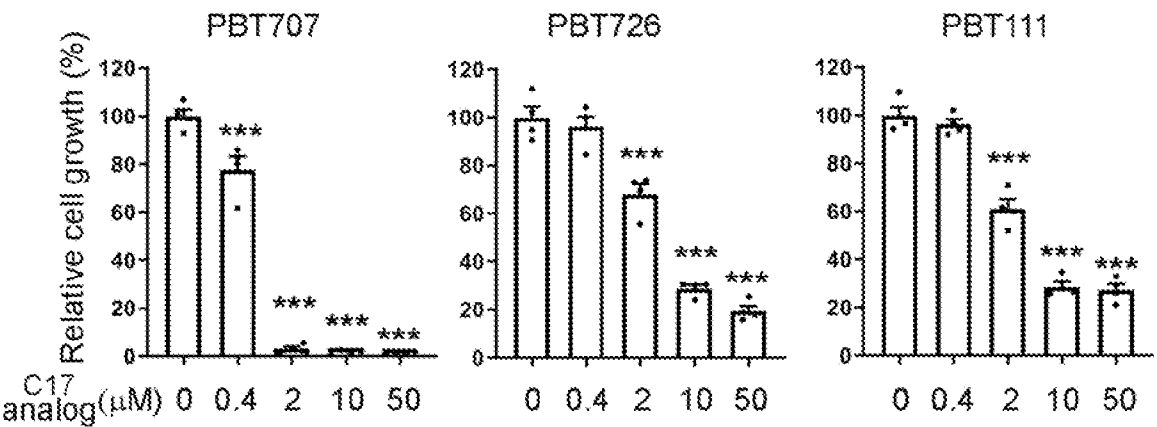


FIG. 13D

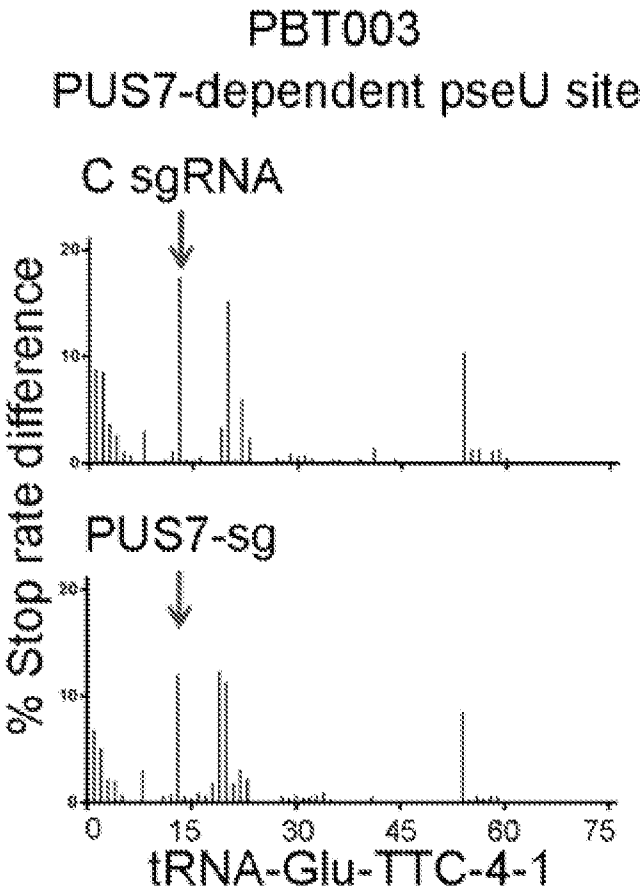


FIG. 14A

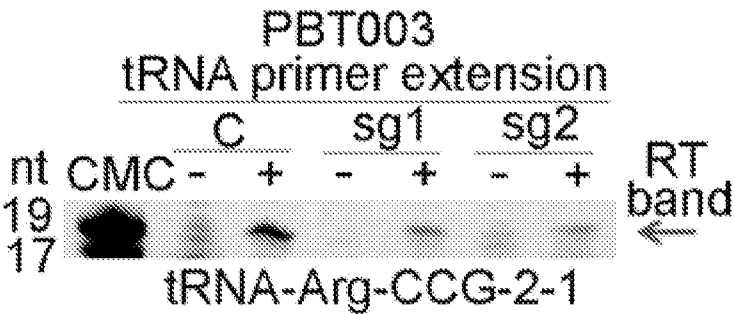


FIG. 14B

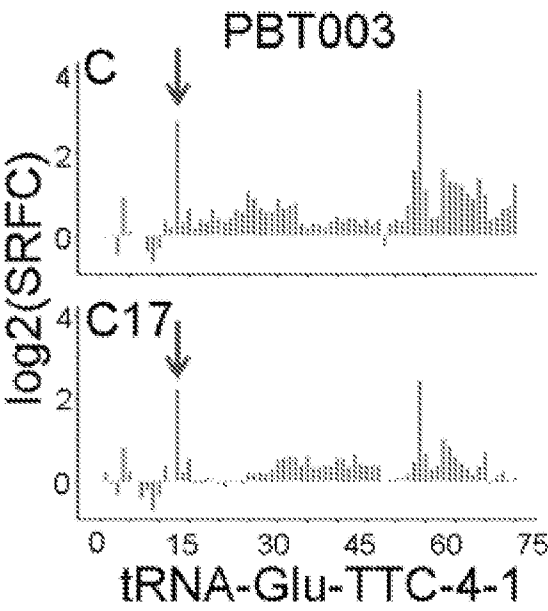


FIG. 14C

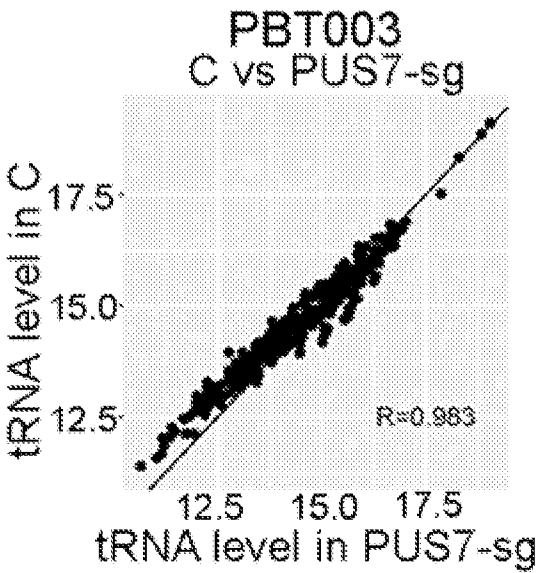


FIG. 14D

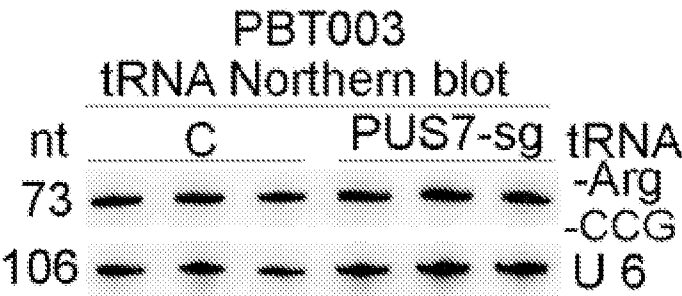


FIG. 14E

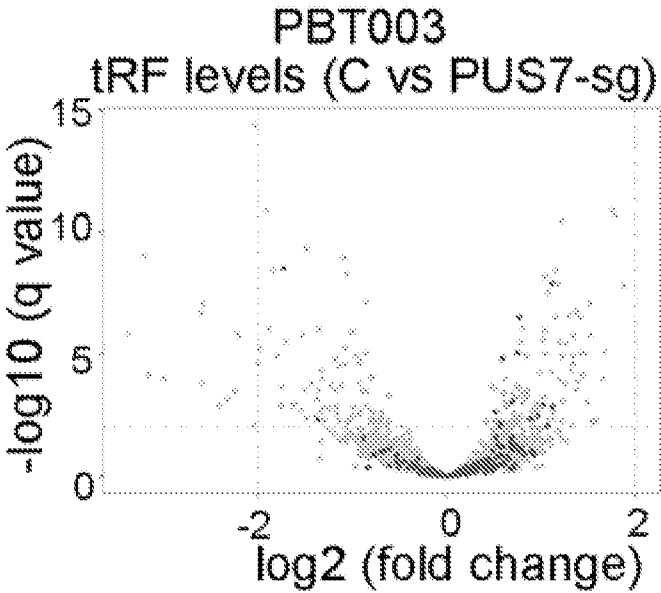


FIG. 14F

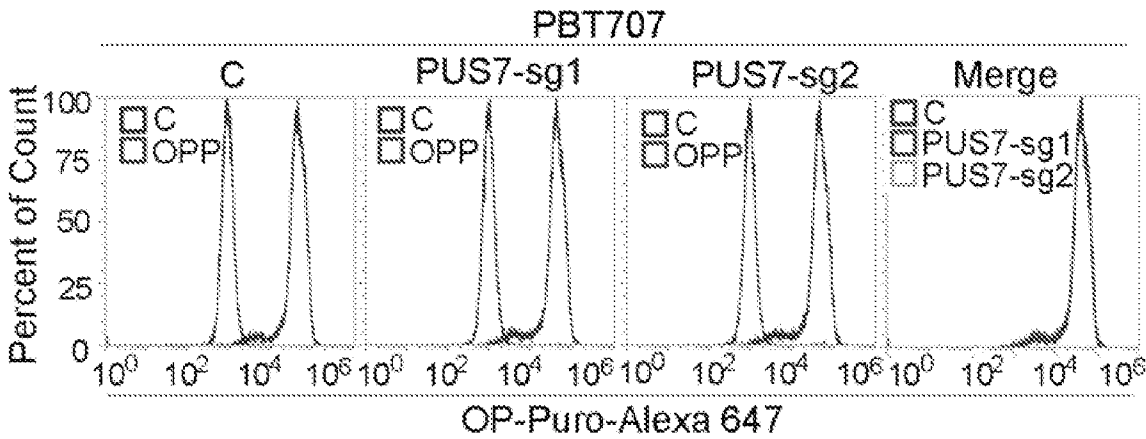


FIG. 14G

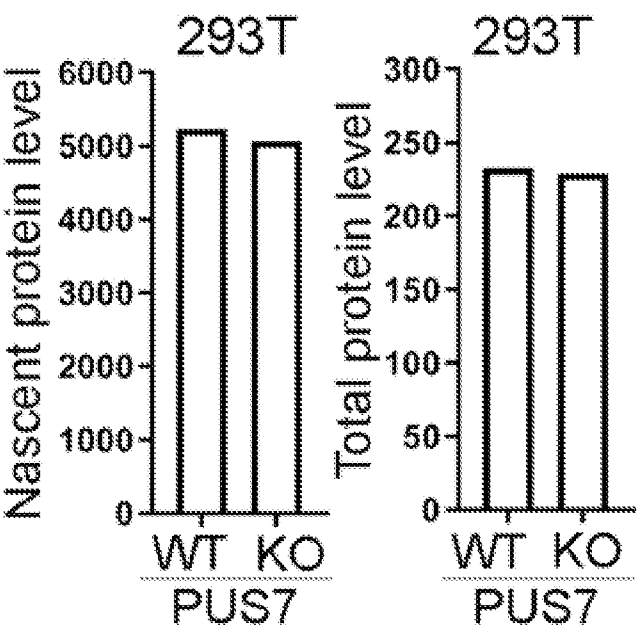


FIG. 14H

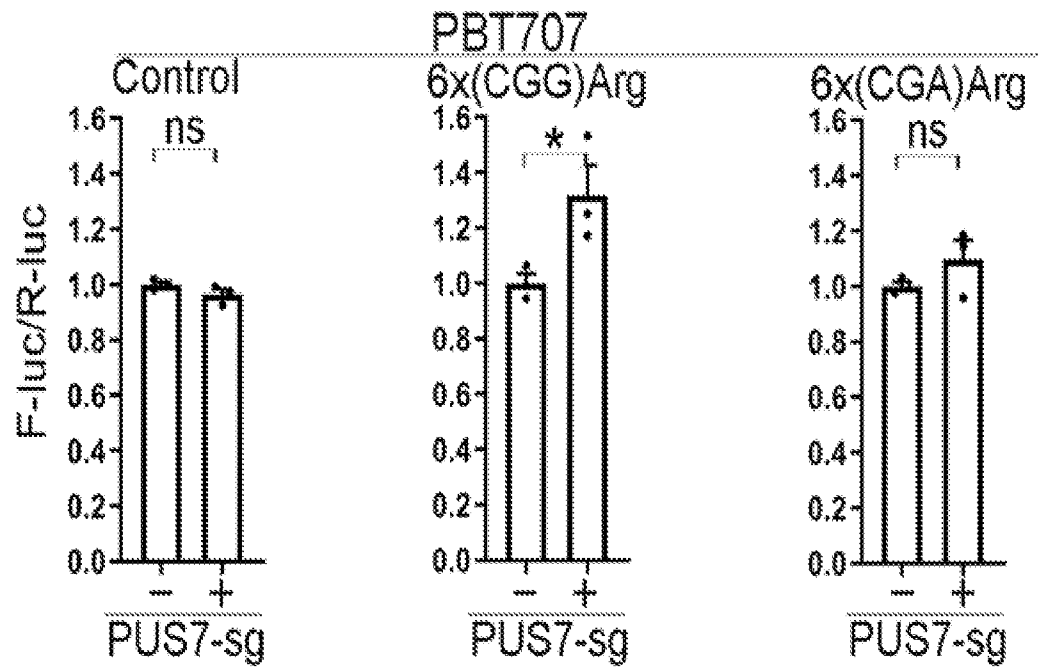
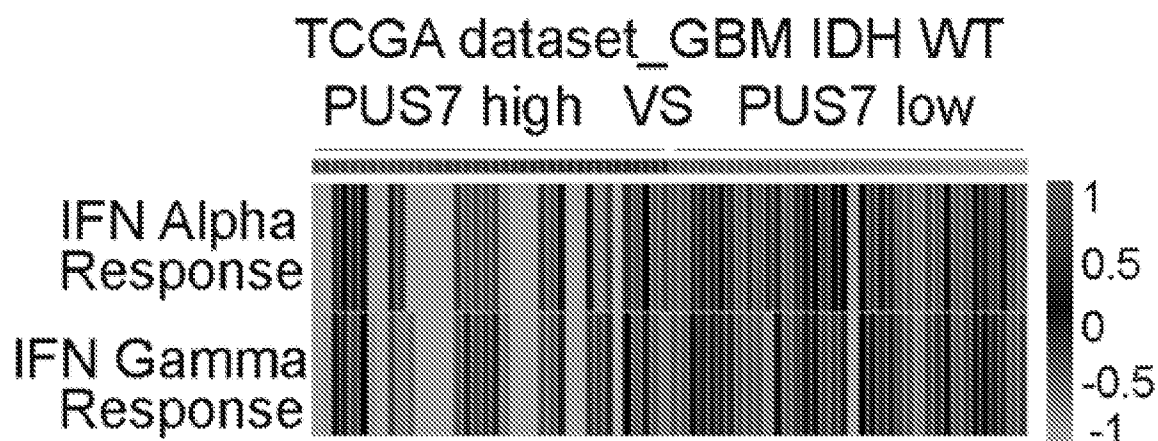
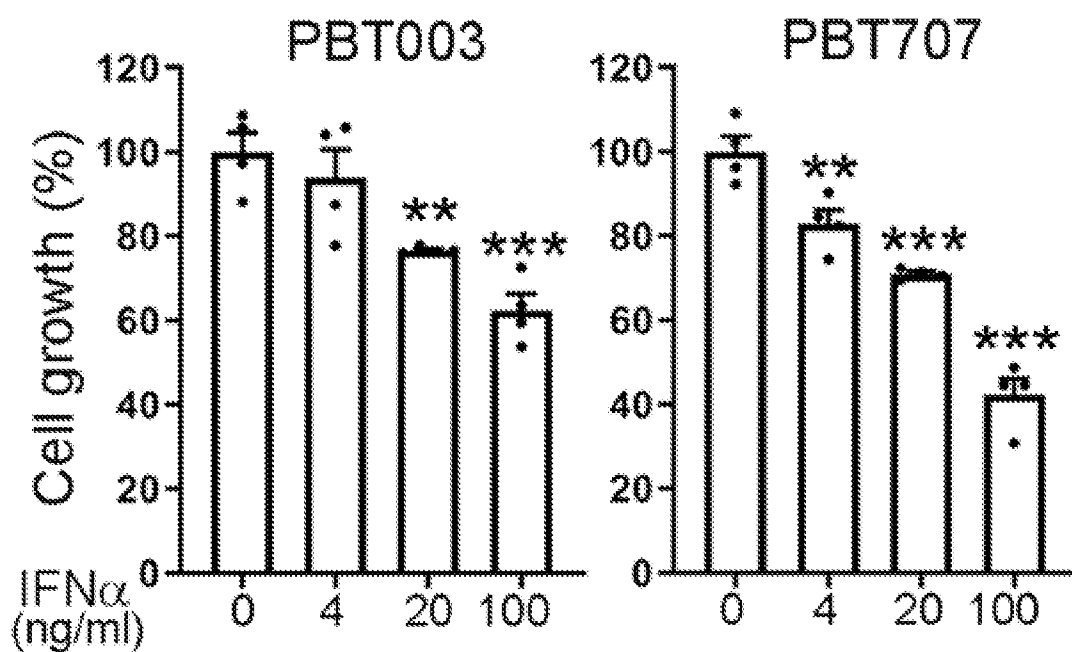


FIG. 14I

**FIG. 15A****FIG. 15B**

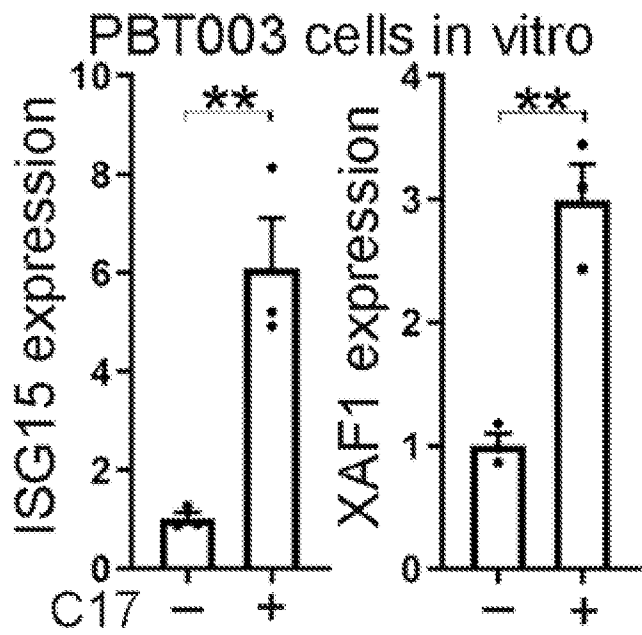


FIG. 15C

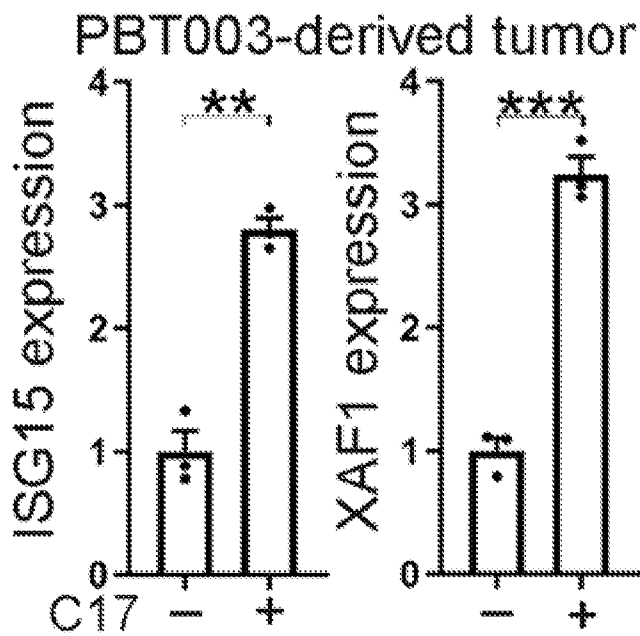


FIG. 15D

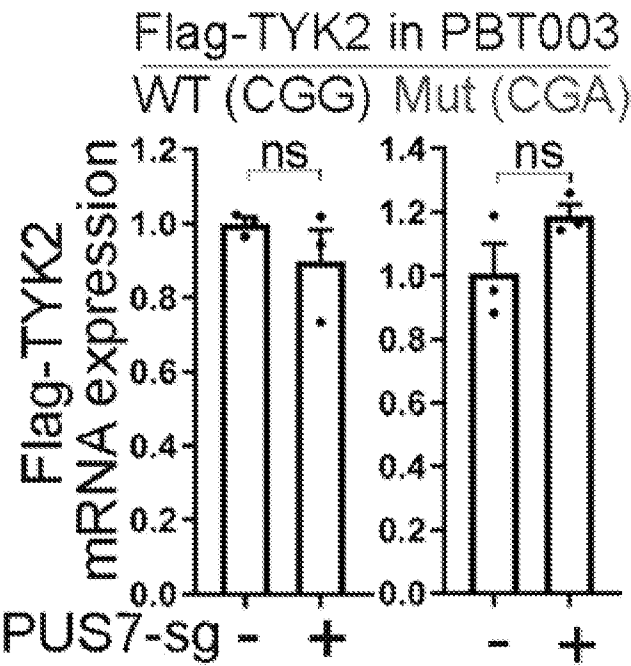


FIG. 16A

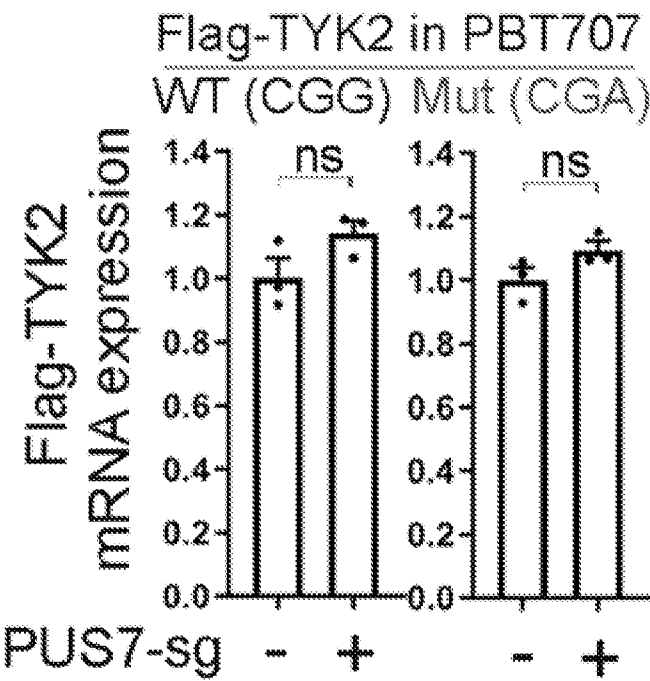


FIG. 16B

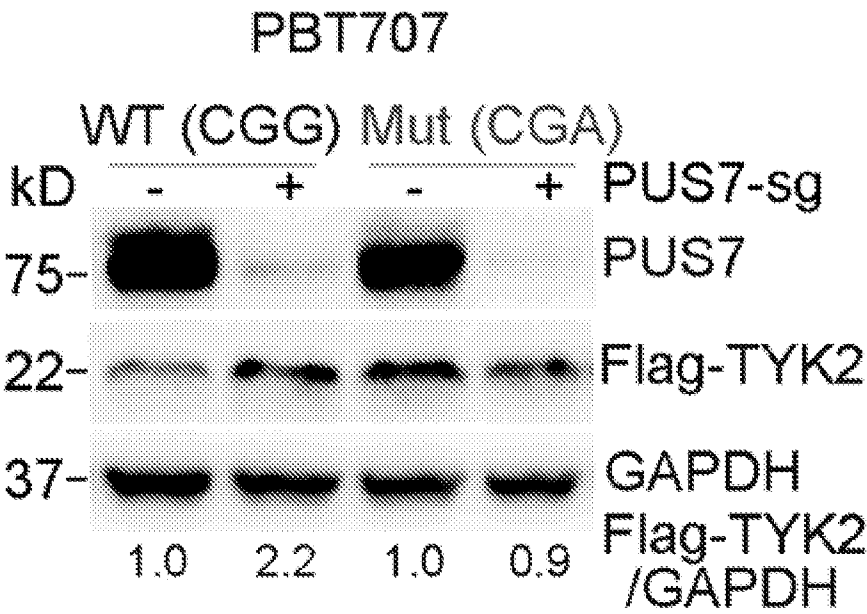


FIG. 16C

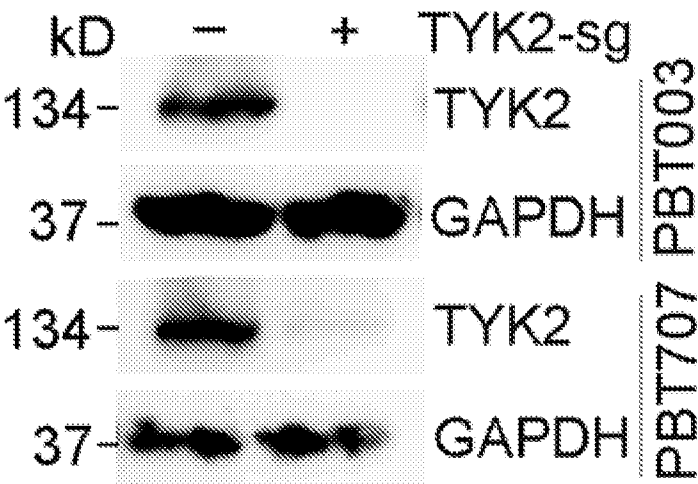


FIG. 16D

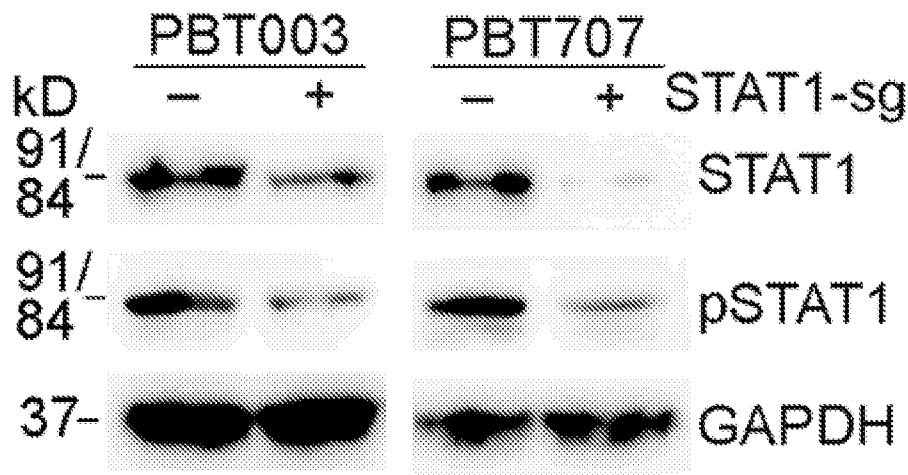


FIG. 16E

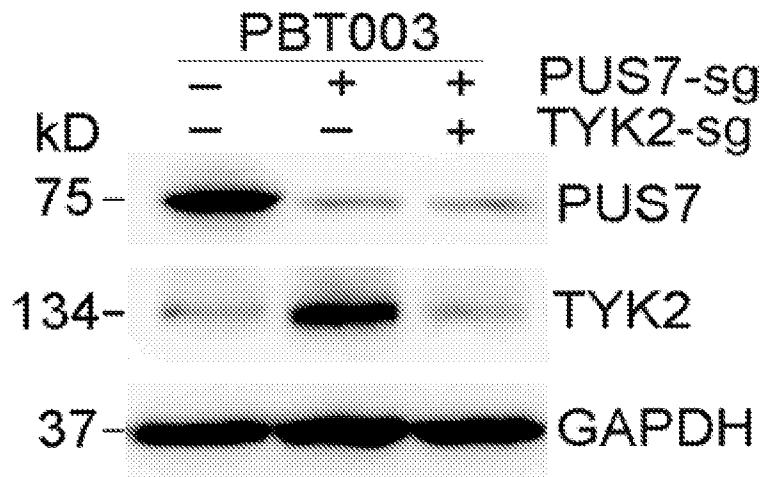
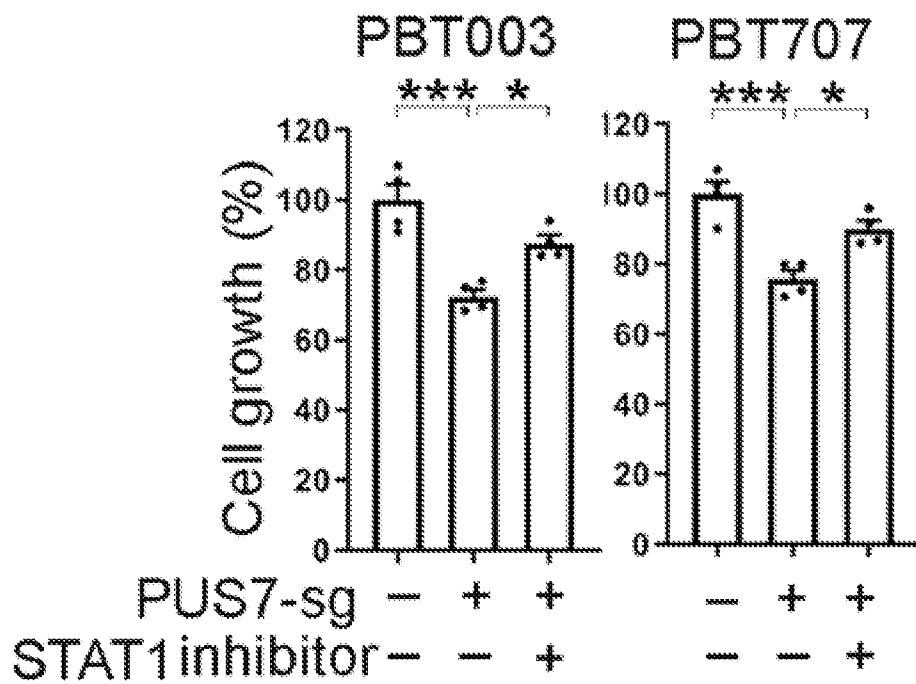
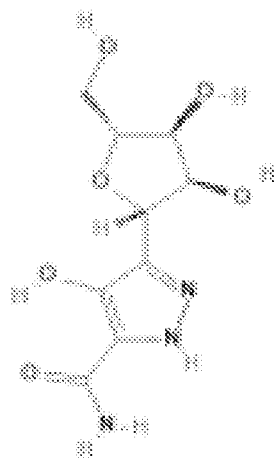


FIG. 16F

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**FIG. 16G****Pyrazofurin****FIG. 17A**

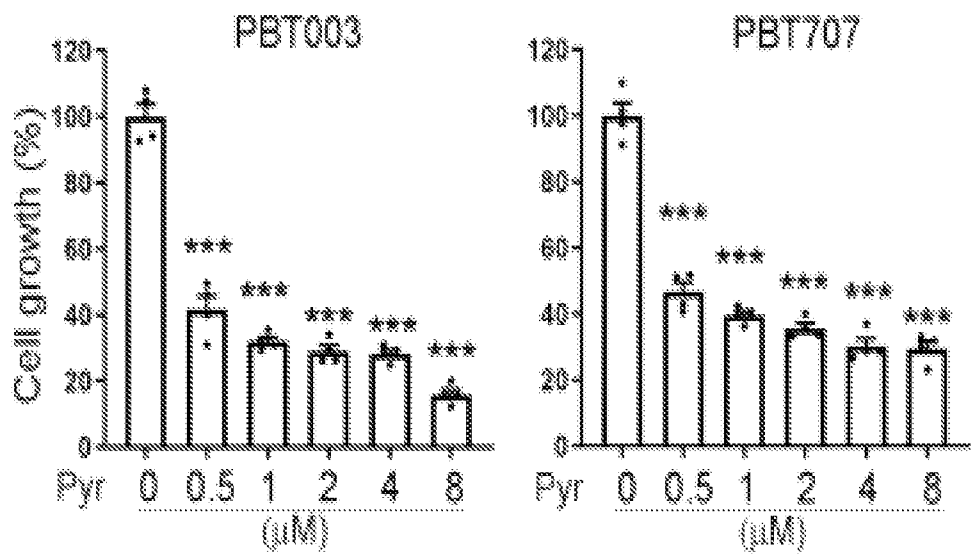


FIG. 17B

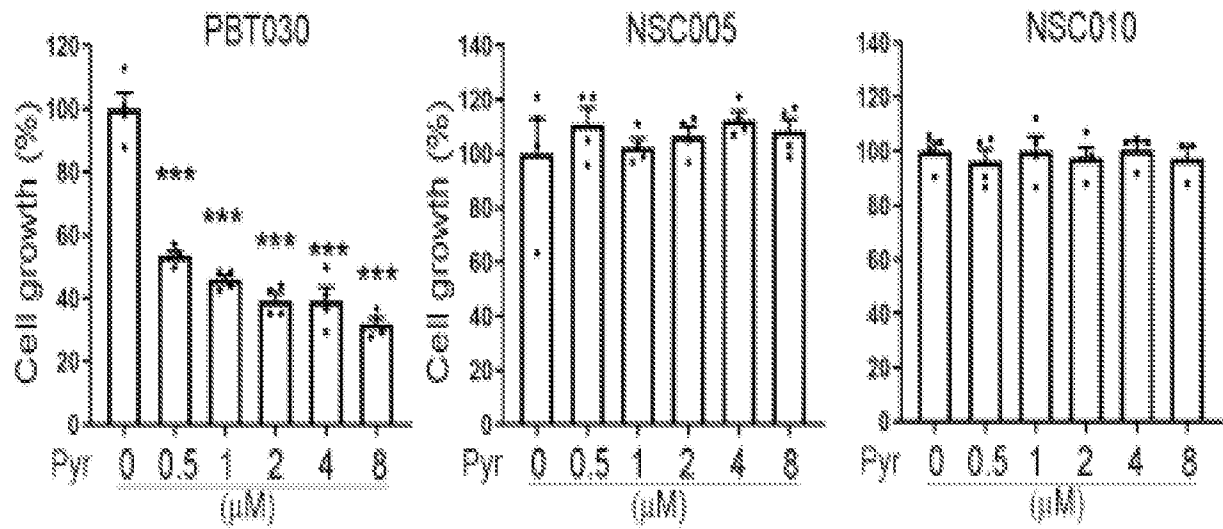


FIG. 17C

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/40244

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/33, A61K 31/429, A61K 31/4355, A61K 31/505 (2022.01)

ADD. A61K 8/18, A61K 31/4745 (2022.01)

CPC - INV. A61K 31/33, A61K 31/429, A61K 31/4355, A61K 31/505

ADD. A61K 8/18, A61K 31/4745

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 — A	PubChem-SID-331819615, Modify Date: 10 April 2017 (10.04.2017), pg 2, figure, this is a purchasable chemical.	1-2 20-26
A	MCCARTY et al. "Biosynthesis of pyrrolopyrimidines", Bioorg Chem. 2012. 43: pp 15-25, especially: pg 11, para 2; pg 21, Figure 1, formula 2.	21-26
A	STOCKERT et al. "Predictive value of pseudouridine in prostate cancer", Am J Clin Exp Urol. 2019. 7(4): pp 262-272, especially: pg 263, col 1, para 2; pg 270, col 1, para 1.	21-26
A	PARK et al. "METABOLISM OF FLUORINE-CONTAINING DRUGS", Annu. Rev. Pharmacol. Toxicol. 2001. 41: pp 443-470, especially: pg 443, para 2; pg 444, para 1; pg 450, para 6.	1-2, 20-26
A	PubChem-CID-135413551, Create Date: 15 January 2019 (15.01.2019), pg 2, figure.	1-2, 20-26
A	PubChem-SID-104577903, Modify Date: 22 February 2011 (22.02.2011), pg 2, figure, this is a purchasable chemical.	1-2, 20-26

☐ 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

23 November 2022 (23.11.2022)

Date of mailing of the international search report

JAN 05 2023

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Kari Rodriguez

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 22/40244

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)

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.:
1-2, 20-26

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.

-Box III - Lack of Unity-

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

Group I+: Claims 1-26, directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof. The compound of formula (I) will be searched to the extent that it encompasses the first species of claim 1, wherein R1 is halogen; R2 is halogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen. It is believed that claims 1-2 and 20-26 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of formula (I), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein R1 is -C(X1)3, X1 is halogen; R2 is halogen; R3 is hydrogen; R4 is hydrogen; R5 is hydrogen (i.e. claims 1-2 and 20-26).

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

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula (I), which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound having the structure of formula (I).

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by the document entitled PubChem-SID-104577903 (hereinafter 'PubChem-903').

PubChem-903 teaches a compound of formula (I): wherein R1 is -NR1BR1C, R1B and R1C are hydrogen; R2 is unsubstituted heteroalkyl; R3 is unsubstituted heteroalkyl; R4 is -OR4A, R4A is hydrogen; R5 is -OR5A, R5A is hydrogen (pg 2, figure, this is a purchasable chemical; see also instant specification para [0031] 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)).

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.