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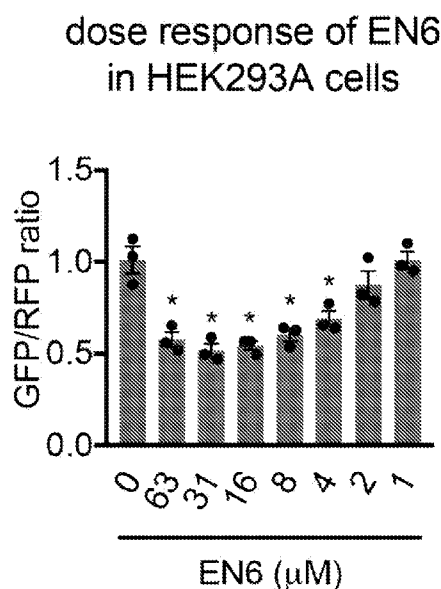
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(54) Title: mTORC1 INHIBITORS FOR ACTIVATING AUTOPHAGY

FIG. 1D



(57) Abstract: Described herein, *inter alia*, are compounds and methods useful for increasing autophagy.

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

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mTORC1 INHIBITORS FOR ACTIVATING AUTOPHAGY**CROSS-REFERENCES TO RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. Provisional Application No. 62/791,655, filed January 11, 2019, which is incorporated herein by reference in their entirety and for all purposes.

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

[0002] The Sequence Listing written in file 052103-519001WO_Sequence_Listing_ST25.txt, created January 6, 2020, 44,632 bytes, machine format IBM-PC, MS Windows operating system, is hereby incorporated by reference.

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

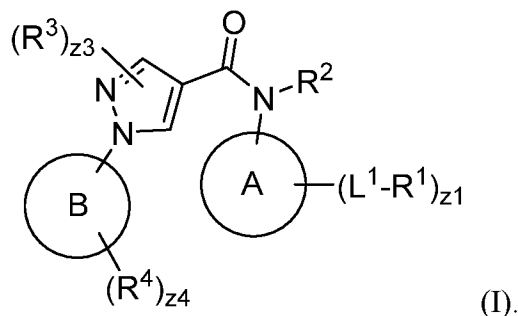
[0003] This invention was made with government support under grant no. CA195761 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

[0004] Autophagy is central to the maintenance of organismal homeostasis in both physiological and pathological situations. It is an essential, conserved lysosomal degradation pathway that controls the quality of the cytoplasm by eliminating aggregated proteins and damaged organelles. Accordingly, alterations in autophagy have been linked to a wide range of diseases and conditions, including aging, cancer, metabolic disorders, and neurodegenerative diseases (1-3). Throughout the past decade, autophagy has attracted considerable attention as a target for the development of novel therapeutics. Disclosed herein, *inter alia*, are solutions to these and other problems in the art.

BRIEF SUMMARY

[0005] In an aspect is provided a compound, or a pharmaceutically acceptable salt thereof, having the formula:



[0006] Ring A is a phenyl or 5 to 6 membered heteroaryl.

[0007] Ring B is a phenyl or 5 to 6 membered heteroaryl.

[0008] L^1 is independently a bond, $-S(O)_2-$, $-N(R^5)-$, $-O-$, $-S-$, $-C(O)-$, $-C(O)N(R^5)-$,

5 $-N(R^5)C(O)-$, $-N(R^5)C(O)NH-$, $-NHC(O)N(R^5)-$, $-C(O)O-$, $-OC(O)-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0009] R^5 is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$,

10 $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHOSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl,

15 unsubstituted aryl, or unsubstituted heteroaryl.

[0010] R^1 is independently halogen, $-CX^{13}$, $-CHX^{12}$, $-CH_2X^1$, $-OCX^{13}$, $-OCH_2X^1$,

$-OCHX^{12}$, $-CN$, $-SO_{n1}R^{1D}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-C(O)R^{1C}$, $-C(O)-OR^{1C}$, $-C(O)NR^{1A}R^{1B}$, $-OR^{1D}$, $-NR^{1A}SO_2R^{1D}$, $-NR^{1A}C(O)R^{1C}$, $-NR^{1A}C(O)OR^{1C}$, $-NR^{1A}OR^{1C}$, $-N_3$, E, substituted or unsubstituted alkyl, substituted or unsubstituted

20 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent $-L^1-R^1$ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

25 **[0011]** E is an electrophilic moiety.

[0012] R² is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0013] R³ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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.

[0014] R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R⁴ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0015] In embodiments, R³ and R⁴ are independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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.

[0016] R^{1A} , R^{1B} , R^{1C} , and R^{1D} are independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$,
 5 $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$,
 $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$,
 $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$,
 $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
 10 substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B}
 substituents bonded to the same nitrogen atom may be joined to form a substituted or
 unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0017] In embodiments, R^{1A} , R^{1B} , R^{1C} , and R^{1D} are independently hydrogen, halogen,
 $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$,
 15 $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$,
 $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$,
 $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$,
 $-OCHF_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
 20 substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0018] X^1 is independently $-F$, $-Cl$, $-Br$, or $-I$.

[0019] $n1$ is independently an integer from 0 to 4.

[0020] $m1$ and $v1$ are independently 1 or 2.

[0021] $z1$ is independently an integer from 0 to 5.

25 **[0022]** $z3$ is independently an integer from 0 to 2.

[0023] $z4$ is independently an integer from 0 to 5.

[0024] In an aspect is provided a pharmaceutical composition including a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0025] In an aspect is provided a method for treating cancer in a subject in need thereof, the method including administering to the subject in need thereof a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0026] In an aspect is provided a method for treating a neurodegenerative disease, the method including administering to a subject in need thereof an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0027] In an aspect is provided a method for treating a metabolic disease, the method including administering to a subject in need thereof an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0028] In an aspect is provided a method for treating aging, the method including administering to a subject in need thereof an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0029] In an aspect is provided a method of reducing the level of activity of mTORC1 in a subject in need thereof, the method including administering to the subject in need thereof an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0030] In an aspect is provided a method of reducing the level of activity of mTORC1 in a cell, the method including contacting a Vacuolar H⁺-ATPase in the cell with a compound as described herein, or a pharmaceutically acceptable salt thereof.

[0031] In an aspect is provided a method of reducing the level of activity of a Vacuolar H⁺-ATPase, the method including contacting the Vacuolar H⁺-ATPase with a compound described herein, or a pharmaceutically acceptable salt thereof.

[0032] In an aspect is provided a method of reducing the level of activity of a Vacuolar H⁺-ATPase protein complex, the method including contacting a ATP6V1A in the Vacuolar H⁺-ATPase protein complex with a compound described herein, or a pharmaceutically acceptable salt thereof.

[0033] In an aspect is provided a method of reducing the level of activity of mTORC1 in a cell, the method including contacting a ATP6V1A in the cell with a compound as described herein, or a pharmaceutically acceptable salt thereof.

[0034] In an aspect is provided a method of reducing the level of activity of an ATP6V1A, the method including contacting the ATP6V1A with a compound described herein, or a pharmaceutically acceptable salt thereof.

[0035] In an aspect is provided a method for increasing autophagy in a subject in need thereof, the method including administering to the subject in need thereof a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0036] In an aspect is provided a Vacuolar H⁺-ATPase protein complex covalently bonded to a compound described herein, or a pharmaceutically acceptable salt thereof, which may be referred to herein as a Vacuolar H⁺-ATPase protein complex-compound complex.

[0037] In an aspect is provided a ATP6V1A protein covalently bonded to a compound described herein, or a pharmaceutically acceptable salt thereof, which may be referred to herein as a ATP6V1A protein-compound complex.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] FIGS. 1A-1F. Covalent ligand screen for autophagy activators. FIG. 1A: A covalent ligand screen in MEF cells. MEF cells expressing a fluorescent probe GFP-LC3-RFP-LC3DG to measure autophagic flux 32, were treated with vehicle DMSO or a covalent ligand (50 mM) for 24 h and GFP/RFP ratios were analyzed. From left to right, the covalent ligand or vehicle is: Torin 1, TRH 1-194, Rapamycin, EN6, KEA 1-37, DKM 3-16, DKM 2-37, DKM 2-98, TRH 1-170, DKM 3-30, TRH 1-168, TRH 1-60, EN2, KEA 1-69, KEA 1-100, TRH 1-57, DKM 3-3, KEA 1-46, TRH 1-179, TRH 1-58, TRH 1-140, TRH 1-152, EN59, EN53, KEA1-31, TRH 1-78, EN84, TRH 1-20, DKM 3-12, KEA 1-98, KEA 1-40, EN51, TRH 1-12, TRH 1-27, DKM 2-47, DKM 3-36, DKM 3-9, EN8, EN71, DKM 3-7, TRH 1-156, TRH 1-65, DKM 2-85, DKM 2-116, DKM 2-43, KEA 1-91, TRH 1-54, DKM 2-71, EN62, TRH 1-59, EN54, KEA 1-95, EN48, TRH 1-189, TRH 1-177, KEA 1-45, DKM 3-29, TRH 1-68, KEA 1-39, DKM 2-94, DKM 2-93, EN37, KEA 1-42, TRH 1-178, KEA 1-97, DKM 3-42, KEA 1-58, TRH 1-53, KEA 1-38, EN58, DKM 3-11, EN10, TRH 1-68, DKM 3-10, TRH 1-32, EN50, TRH 1-19, KEA 1-85, KEA 1-63, KEA 1-94, EN4, TRH 1-70, TRH 1-162, EN20, EN70, DKM 2-117, DKM 2-42, DKM 2-114, DKM 3-43, KEA 1-70, EN65, EN66, KEA 1-93, DKM 2-83, KEA 1-48, DKM 3-31, TRH 1-59, TRH 1-56, DKM 2-108, TRH 1-57, EN60, DKM 2-119, DKM 2-50, DKM 3-32, YP 1-42, KEA 1-77, KEA 1-60, KEA 1-67, DKM 3-5, TRH 1-196, EN52, DKM 2-80, TRH 1-58, TRH 1-134, DKM 2-52,

EN46, EN75, EN61, EN67, EN26, DMSO, KEA 1-59, EN43, DKM 3-42, EN1, KEA 1-23, DKM 2-76, KEA 1-62, DKM 2-40, TRH 1-56, EN69, DKM 2-97, DKM 2-113, KEA 1-43, TRH 1-65, TRH 1-163, KEA 1-71, TRH 1-135, KEA 1-54, DKM 2-100, TRH 1-135, TRH 1-27, EN47, KEA 1-22, KEA 1-30, KEA 1-50, KEA 1-78, DKM 3-4, DKM 2-101, TRH 1-149, 5 DKM 3-41, EN18, TRH 1-176, KEA 1-99, EN29, TRH 1-167, KEA 1-56, TRH 1-54, EN3, DKM 2-107, TRH 1-32, KEA 1-32, KEA 1-55, YP 1-36, KEA 1-49, EN68, EN45, KEA 1-72, DKM 3-8, TRH 1-133, KEA 1-90, DKM 3-15, KEA 1-47, EN57, KEA 1-81, EN40, DKM 2-106, EN64, EN80, DKM 2-49, EN7, DKM 2-60, DKM 2-33, TRH 1-160, DKM 2-58, KEA 1-61, DKM 3-36, DKM 2-110, DKM 2-48, EN12, KEA 1-68, DKM 2-59, EN49, 10 DKM 2-32, DKM 2-31, DKM 3-32, EN5, EN15, TRH 1-55, DKM 2-47, EN16, EN55, EN19, KEA 1-87, KEA 1-64, KEA 1-53, EN9, EN17, KEA 1-57, DKM 2-34, DKM 2-109, DKM 3-43, EN13, KEA 1-73, EN32, TRH 1-13, EN103, EN21, EN25, KEA 1-83, EN36, KEA 1-84, EN86, DKM 2-86, KEA 1-41, DKM 2-111, KEA 1-88, EN33, DKM 2-62, KEA 1-74, EN44, KEA 1-79, TRH 1-155, DKM 2-103, EN38, EN24, DKM 3-13, EN23, DKM 2-120, EN22, DKM 3-70, EN63, EN27, DKM 2-95, EN39, EN14, EN85, DKM 2-102, EN30, 15 DKM 2-87, KEA 1-75, DKM 2-84, KEA 1-80, EN35, and EN28. FIG. 1B: Compounds that showed significantly ($p < 0.05$ compared to vehicle-treated controls) lower GFP/RFP ratios in MEF cells were screened in HEK293A cells expressing the same fluorescent autophagic flux probe. From left to right, the covalent ligand or vehicle is: Torin1, EN6, DKM 3-16, 20 Rapamycin, EN2, DKM 3-30, DKM 3-70, DKM 2-84, KEA 1-46, TRH 1-168, EN14, KEA 1-100, DKM 2-72, KEA 1-80, KEA 1-36, KEA 1-75, TRH 1-170, DKM 2-102, DKM 2-95, EN30, TRH 1-170, TRH 1-60, TRH 1-140, EN28, KEA 1-37, KEA 1-79, TRH 1-194, DMSO, DKM 3-3, DKM 2-89, KEA 1-69, DKM 2-37, TRH 1-50, DKM 2-98, and TRH 1-155. FIG. 1C: Structure of cysteine-reactive covalent ligand hit EN6 that shows autophagy 25 activating in both MEF and HEK293A cells. FIG. 1D: Dose-response of EN6 in HEK293A cells expressing the fluorescent autophagic flux probe. FIG. 1E: LC3B levels in HEK293A cells treated with EN6 (50 mM). FIG. 1F: LC3B puncta in HEK293 cells treated with vehicle DMSO, EN6 (50 mM), or Torin1 (0.25 mM). Data shown in FIG. 1A, FIG. 1B, FIG. 1D, and FIG. 1F are average $\pm$ sem, $n=3-25$ biological replicates/group. Statistical significance was 30 calculated with unpaired two-tailed Student's t-tests. Significance is expressed as $*p < 0.05$ compared to vehicle-treated controls.

[0039] FIGS. 2A-2C. Chemoproteomic profiling to identify targets of EN6. FIG. 2A: Schematic of isoTOP-ABPP in which cells were pre-treated with DMSO or EN6 (50 mM, 4 h

in situ) prior to labeling of proteomes *in vitro* with IA-alkyne (100 mM, 1 h), followed by appendage of isotopically light (for DMSO-treated) or heavy (for EN6-treated) TEV protease cleavable biotin-azide tags by copper-catalyzed azide-alkyne cycloaddition (CuAAC).

Control and treated proteomes were subsequently combined in a 1:1 ratio, probe-labeled proteins were avidin-enriched, digested with trypsin, and probe-modified tryptic peptides were eluted by TEV protease, analyzed by LC-MS/MS, and light to heavy probe-modified peptide ratios were quantified. FIG. 2B: isoTOP-ABPP analysis of EN6 (50 mM) in MEF cells *in situ* analyzed as described in FIG. 2A. FIG. 2C: Gel-based ABPP analysis of EN6 interactions with recombinant ATP6V1A. Vehicle DMSO or EN6 were pre-incubated with recombinant human ATP6V1A (1 h) followed by labeling with a rhodamine-functionalized iodoacetamide probe (IA-rhodamine) (1 μ M, 1 h) after which probe-labeled proteins were read-out by SDS/PAGE and in-gel fluorescence. Data shown in FIG. 2C are average $\pm$ sem from n=3 biological replicates/group.

[0040] FIGS. 3A-3E. EN6 inhibits mTORC1 signaling and lysosomal recruitment. FIG.

3A: mTORC1 signaling with EN6 treatment in HEK293A cells. HEK293A cells, starved or stimulated with amino acids, were treated with vehicle DMSO or EN6 (20 μ M) for 1 h and mTORC1 signaling was assessed by Western blotting. FIG. 3B: AKT signaling in HEK293 cells treated with vehicle DMSO, rapamycin (0.1 μ M), Torin1 (0.25 μ M), or EN6 (25 μ M) for 4 h. AKT signaling was assessed by Western blotting. FIG. 3C: ATP6V1A knockdown by short hairpin (shRNA) assessed by Western blotting. FIG. 3D: LC3B levels and mTORC1 signaling in Hela cells treated with EN6. Endogenous ATP6V1A was knocked down with shRNA and replaced with a Flag-tagged wild-type or C277A mutant ATP6V1A and these cells were treated with EN6 (25 μ M) for 4 h. FIG. 3E: mTORC1 localization in HEK293T cells treated with vehicle DMSO or EN6 (25 μ M) for 1 h under amino acid starvation or stimulation. Shown are representative microscopy images of mTORC1 or the lysosomal marker LAMP2. Gels and microscopy images shown in FIGS. 3A-3E are representative gels of n=2-3 biological replicates/group.

[0041] FIGS. 4A-4E. EN6 effects on v-ATPase and TFEB. FIG. 4A: Co-

immunoprecipitation experiments between stably expressed, FLAG-tagged Regulator subunit p14 and endogenous v-ATPase components in HEK293T cells, in the absence or presence of amino acids treated with vehicle DMSO or EN6 (25 μ M) for 1 h. Blots shown in FIG. 4A are representative gels from n=3 biological replicates/group. FIG. 4B: Localization of TFEB-

GFP in HeLa cells treated with vehicle DMSO or EN6 (25 μ M, 4 h). Cells were stained with Hoechst 33342 and GFP-TFEB were imaged by microscopy. Shown are representative microscopy images and quantification of percentage of nuclear TFEB from n=6-7 biological replicates/group. FIG. 4C: Gene expression of TFEB target genes in HeLa cells treated with EN6 (25 μ M) for 0 or 8 h, assessed by qRT-PCR from n=3 biological replicates/group. FIG. 4D: Lysosomal acidification of HEK293A cells treated with vehicle DMSO, bafilomycin A1 (0.2 μ M), EN6 (50 μ M), or with co-treatment of EN6 and bafilomycin A1 for 4 h, readout by LysoSensor DND-160. Microscopy images shown in FIG. 4D are representative images from n=4 biological replicates/group. FIG. 4E: Quantification of lysosomal acidification from experiment described in FIG. 4D. Statistical significance calculated with unpaired two-tailed Student's t-tests. Significance in FIG. 4B and FIG. 4C expressed as *p<0.05 compared to vehicle-treated controls or 0 h EN6-treated controls, respectively. Significance in FIG. 4E is expressed as *p<0.05 compared to the vehicle-treated group, #p<0.05 compared to EN6-treated group.

[0042] FIGS. 5A-5B. EN6 improves clearance of TDP-43 aggregates in cells. Effect of EN6 and bafilomycin treatment on TDP-43 aggregate clearance. U2OS cells expressing an IPTG-inducible GFP-TDP-43 were co-treated with vehicle DMSO, IPTG (50 μ M), IPTG and EN6 (25 μ M), or IPTG, EN6, and bafilomycin (0.2 μ M) for 7 h. Cells were stained with Hoechst 33342 and GFP-TDP-43 puncta were imaged by microscopy in FIG. 5A.

Microscopy images are representative images from n=26 biological replicates/group. Data was quantified using ImageJ in FIG. 5B and data shown as average $\pm$ sem.

[0043] FIGS. 6A-6C. EN6 inhibits mTORC1 signaling in mice. mTORC1 signaling in mouse heart (FIG. 6A), kidney (FIG. 6B), and skeletal muscle (FIG. 6C). C57BL/6 male mice were treated intraperitoneally with vehicle (18:1:1 saline:ethanol:PEG40), rapamycin (10 mg/kg) or EN6 (50 mg/kg) for 4 h. mTORC1 signaling and LC3B levels were measured by Western blotting and quantified by densitometry. LC3B was normalized to actin loading controls, pS6 was normalized to total S6 levels, p4EBP1 was normalized to total 4EBP1 levels, and pAKT was normalized to total AKT levels. All normalized values were then normalized to vehicle-treated control levels. Data shown in are average $\pm$ sem, n=4 mice/group. Statistical significance was calculated with unpaired two-tailed Student's t-tests. Significance is expressed as *p<0.05 compared to the vehicle-treated controls.

[0044] FIG. 7. Scheme of v-ATPase/mTORC1 regulation of autophagy and action of EN6.

[0045] FIG. 8. Transcript levels of genes unrelated to TFEB transcriptional programming. Gene expression of genes that are not TFEB target genes in Hela cells treated with EN6 (25 μ M) for 0 or 8 h, assessed by qRT-PCR from n=3 biological replicates/group.

DETAILED DESCRIPTION

5 I. Definitions

[0046] 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.

[0047] Where substituent groups are specified by their conventional chemical formulae,
10 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 $-\text{OCH}_2-$.

[0048] 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
15 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). 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-
20 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 ($-\text{O}-$).
25 An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an alkynyl moiety. An alkyl moiety may be fully saturated. An alkenyl may include more than one double bond and/or one or more triple bonds in addition to the one or more double bonds. An alkynyl may include more than one triple bond and/or one or more double bonds in addition to the one or more triple bonds.

[0049] The term “alkylene,” by itself or as part of another substituent, means, unless
30 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.

- 5 **[0050]** 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., N, S, Si, or P) may be placed at any
- 10 interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -S-CH₂-CH₂, -S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, -O-CH₃,
- 15 -O-CH₂-CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)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
- 20 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
- 25 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, a heteroalkyl (or
- 30 heteroalkylene) group will have from 2 to 24 atoms including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), with those groups having 10 or fewer atoms being preferred herein.

[0051] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'-$ 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.

[0052] 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-piperidiny, 2-piperidiny, 3-piperidiny, 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, a cycloalkyl (or cycloalkylene) group will have from 3 to 8 carbon atoms. In embodiments, a heterocycloalkyl (or heterocycloalkylene) group will have from 3 to 8 atoms including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S).

[0053] 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.

[0054] 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.

[0055] 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, quinoxalyl, 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-quinoxalyl, 5-quinoxalyl, 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. In embodiments, an aryl (or
5 arylene) group will have from 6 to 10 carbon atoms. In embodiments, a heteroaryl (or heteroarylene) group will have from 5 to 10 atoms including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S).

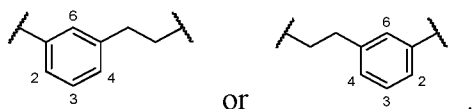
[0056] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different.

10 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,
15 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,
20 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.

[0057] The symbol “~” denotes the point of attachment of a chemical moiety to the
25 remainder of a molecule or chemical formula.

[0058] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0059] 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
30 group has the formula:



[0060] An alkylarylene moiety may be substituted (e.g., with a substituent group) on the alkylene moiety or the arylene linker (e.g., at carbons 2, 3, 4, or 6) with halogen, oxo, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂CH₃, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted C₁-C₅ alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0061] 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.

[0062] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R'', -SR', halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR''R''', -NR'C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R'', -ONR'R'', -NR'C(O)NR''NR''''R''', -CN, -NO₂, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R'', R''', and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' group when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term “alkyl” is meant to include groups including carbon atoms bound to

groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0063] 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',
 5 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
 10 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
 15 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.

[0064] 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
 20 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
 25 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
 30 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.

[0065] 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.

[0066] 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.

[0067] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0068] A “substituent group,” as used herein, means a group selected from the following moieties:

- 5 (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, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃,
- 10 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
- 15 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
- 20 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, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂,
- 25 -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, -NH₂SO₂H, -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,
 5 -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
 10 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
 15 heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0069] 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
 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.

[0070] 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-
 30 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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).

[0075] 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.

5 **[0076]** 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
10 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.

[0077] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted
15 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
20 optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group is different.

[0078] 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,
25 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
30 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.

[0079] In a recited claim or chemical formula description herein, each R substituent or L linker that is described as being “substituted” without reference as to the identity of any chemical moiety that composes the “substituted” group (also referred to herein as an “open substitution” on an R substituent or L linker or an “openly substituted” R substituent or L linker), the recited R substituent or L linker may, in embodiments, be substituted with one or more first substituent groups as defined below.

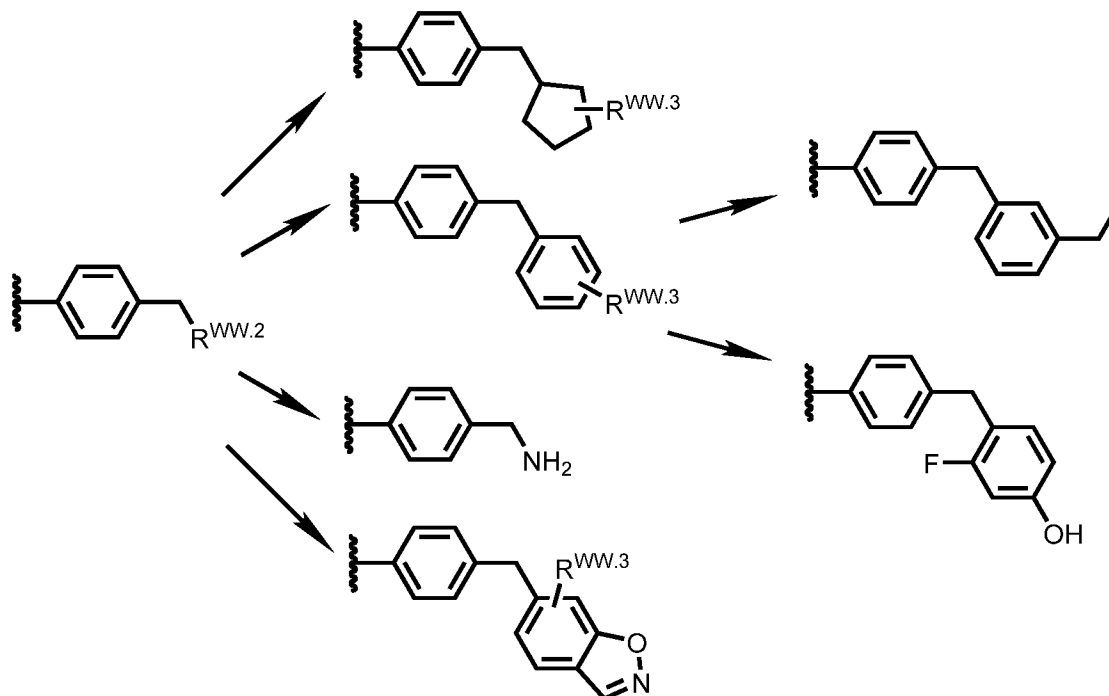
[0080] The first substituent group is denoted with a corresponding first decimal point numbering system such that, for example, R^1 may be substituted with one or more first substituent groups denoted by $R^{1.1}$, R^2 may be substituted with one or more first substituent groups denoted by $R^{2.1}$, R^3 may be substituted with one or more first substituent groups denoted by $R^{3.1}$, R^4 may be substituted with one or more first substituent groups denoted by $R^{4.1}$, R^5 may be substituted with one or more first substituent groups denoted by $R^{5.1}$, and the like up to or exceeding an R^{100} that may be substituted with one or more first substituent groups denoted by $R^{100.1}$. As a further example, R^{1A} may be substituted with one or more first substituent groups denoted by $R^{1A.1}$, R^{2A} may be substituted with one or more first substituent groups denoted by $R^{2A.1}$, R^{3A} may be substituted with one or more first substituent groups denoted by $R^{3A.1}$, R^{4A} may be substituted with one or more first substituent groups denoted by $R^{4A.1}$, R^{5A} may be substituted with one or more first substituent groups denoted by $R^{5A.1}$ and the like up to or exceeding an R^{100A} may be substituted with one or more first substituent groups denoted by $R^{100A.1}$. As a further example, L^1 may be substituted with one or more first substituent groups denoted by $R^{L1.1}$, L^2 may be substituted with one or more first substituent groups denoted by $R^{L2.1}$, L^3 may be substituted with one or more first substituent groups denoted by $R^{L3.1}$, L^4 may be substituted with one or more first substituent groups denoted by $R^{L4.1}$, L^5 may be substituted with one or more first substituent groups denoted by $R^{L5.1}$ and the like up to or exceeding an L^{100} which may be substituted with one or more first substituent groups denoted by $R^{L100.1}$. Thus, each numbered R group or L group (alternatively referred to herein as R^{WW} or L^{WW} wherein “WW” represents the stated superscript number of the subject R group or L group) described herein may be substituted with one or more first substituent groups referred to herein generally as $R^{WW.1}$ or $R^{LWW.1}$, respectively. In turn, each first substituent group (e.g., $R^{1.1}$, $R^{2.1}$, $R^{3.1}$, $R^{4.1}$, $R^{5.1}$... $R^{100.1}$, $R^{1A.1}$, $R^{2A.1}$, $R^{3A.1}$, $R^{4A.1}$, $R^{5A.1}$... $R^{100A.1}$, $R^{L1.1}$, $R^{L2.1}$, $R^{L3.1}$, $R^{L4.1}$, $R^{L5.1}$... $R^{L100.1}$) may be

further substituted with one or more second substituent groups (e.g., $R^{1.2}$, $R^{2.2}$, $R^{3.2}$, $R^{4.2}$, $R^{5.2}$... $R^{100.2}$; $R^{1A.2}$, $R^{2A.2}$, $R^{3A.2}$, $R^{4A.2}$, $R^{5A.2}$... $R^{100A.2}$; $R^{L1.2}$, $R^{L2.2}$, $R^{L3.2}$, $R^{L4.2}$, $R^{L5.2}$... $R^{L100.2}$, respectively). Thus, each first substituent group, which may alternatively be represented herein as $R^{WW.1}$ as described above, may be further substituted with one or more second substituent groups, which may alternatively be represented herein as $R^{WW.2}$.

[0081] Finally, each second substituent group (e.g., $R^{1.2}$, $R^{2.2}$, $R^{3.2}$, $R^{4.2}$, $R^{5.2}$... $R^{100.2}$; $R^{1A.2}$, $R^{2A.2}$, $R^{3A.2}$, $R^{4A.2}$, $R^{5A.2}$... $R^{100A.2}$; $R^{L1.2}$, $R^{L2.2}$, $R^{L3.2}$, $R^{L4.2}$, $R^{L5.2}$... $R^{L100.2}$) may be further substituted with one or more third substituent groups (e.g., $R^{1.3}$, $R^{2.3}$, $R^{3.3}$, $R^{4.3}$, $R^{5.3}$... $R^{100.3}$; $R^{1A.3}$, $R^{2A.3}$, $R^{3A.3}$, $R^{4A.3}$, $R^{5A.3}$... $R^{100A.3}$; $R^{L1.3}$, $R^{L2.3}$, $R^{L3.3}$, $R^{L4.3}$, $R^{L5.3}$... $R^{L100.3}$, respectively). Thus, each second substituent group, which may alternatively be represented herein as $R^{WW.2}$ as described above, may be further substituted with one or more third substituent groups, which may alternatively be represented herein as $R^{WW.3}$. Each of the first substituent groups may be optionally different. Each of the second substituent groups may be optionally different. Each of the third substituent groups may be optionally different.

[0082] Thus, as used herein, R^{WW} represents a substituent recited in a claim or chemical formula description herein which is openly substituted. “WW” represents the stated superscript number of the subject R group (1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). Likewise, L^{WW} is a linker recited in a claim or chemical formula description herein which is openly substituted. Again, “WW” represents the stated superscript number of the subject L group (1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). As stated above, in embodiments, each R^{WW} may be unsubstituted or independently substituted with one or more first substituent groups, referred to herein as $R^{WW.1}$; each first substituent group, $R^{WW.1}$, may be unsubstituted or independently substituted with one or more second substituent groups, referred to herein as $R^{WW.2}$; and each second substituent group may be unsubstituted or independently substituted with one or more third substituent groups, referred to herein as $R^{WW.3}$. Similarly, each L^{WW} linker may be unsubstituted or independently substituted with one or more first substituent groups, referred to herein as $R^{LWW.1}$; each first substituent group, $R^{LWW.1}$, may be unsubstituted or independently substituted with one or more second substituent groups, referred to herein as $R^{LWW.2}$; and each second substituent group may be unsubstituted or independently substituted with one or more third substituent groups, referred to herein as $R^{LWW.3}$. Each first substituent group is optionally different. Each second substituent group is optionally different. Each third substituent group is optionally different. For example, if R^{WW} is phenyl, the said phenyl group is optionally substituted by one or more $R^{WW.1}$ groups as defined herein below, e.g.,

when $R^{WW.1}$ is $R^{WW.2}$ -substituted alkyl, examples of groups so formed include but are not limited to itself optionally substituted by 1 or more $R^{WW.2}$, which $R^{WW.2}$ is optionally substituted by one or more $R^{WW.3}$. By way of example when $R^{WW.1}$ is alkyl, groups that could be formed, include but are not limited to:



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- [0083]** $R^{WW.1}$ is independently oxo, halogen, $-CX^{WW.1}_3$, $-CHX^{WW.1}_2$, $-CH_2X^{WW.1}$, $-OCX^{WW.1}_3$, $-OCH_2X^{WW.1}$, $-OCHX^{WW.1}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, $R^{WW.2}$ -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), $R^{WW.2}$ -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $R^{WW.2}$ -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), $R^{WW.2}$ -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $R^{WW.2}$ -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or $R^{WW.2}$ -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{WW.1}$ is independently oxo, halogen, $-CX^{WW.1}_3$, $-CHX^{WW.1}_2$, $-CH_2X^{WW.1}$, $-OCX^{WW.1}_3$, $-OCH_2X^{WW.1}$, $-OCHX^{WW.1}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl

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(e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW.1} is independently -F, -Cl, -Br, or -I.

[0084] R^{WW.2} is independently oxo, halogen, -CX^{WW.2}₃, -CHX^{WW.2}₂, -CH₂X^{WW.2}, -OCX^{WW.2}₃, -OCH₂X^{WW.2}, -OCHX^{WW.2}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, R^{WW.3}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{WW.3}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{WW.3}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{WW.3}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{WW.3}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{WW.3}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{WW.2} is independently oxo, halogen, -CX^{WW.2}₃, -CHX^{WW.2}₂, -CH₂X^{WW.2}, -OCX^{WW.2}₃, -OCH₂X^{WW.2}, -OCHX^{WW.2}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW.2} is independently -F, -Cl, -Br, or -I.

[0085] R^{WW.3} is independently oxo, halogen, -CX^{WW.3}₃, -CHX^{WW.3}₂, -CH₂X^{WW.3}, -OCX^{WW.3}₃, -OCH₂X^{WW.3}, -OCHX^{WW.3}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆,

C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW.3} is independently -F, -Cl, -Br, or -I.

[0086] Where two different R^{WW} substituents are joined together to form an openly substituted ring (e.g. substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl or substituted heteroaryl), in embodiments the openly substituted ring may be independently substituted with one or more first substituent groups, referred to herein as R^{WW.1}; each first substituent group, R^{WW.1}, may be unsubstituted or independently substituted with one or more second substituent groups, referred to herein as R^{WW.2}; and each second substituent group, R^{WW.2}, may be unsubstituted or independently substituted with one or more third substituent groups, referred to herein as R^{WW.3}; and each third substituent group, R^{WW.3}, is unsubstituted.

Each first substituent group is optionally different. Each second substituent group is optionally different. Each third substituent group is optionally different. In the context of two different R^{WW} substituents joined together to form an openly substituted ring, the “WW” symbol in the R^{WW.1}, R^{WW.2} and R^{WW.3} refers to the designated number of one of the two different R^{WW} substituents. For example, in embodiments where R^{100A} and R^{100B} are optionally joined together to form an openly substituted ring, R^{WW.1} is R^{100A.1}, R^{WW.2} is R^{100A.2}, and R^{WW.3} is R^{100A.3}. Alternatively, in embodiments where R^{100A} and R^{100B} are optionally joined together to form an openly substituted ring, R^{WW.1} is R^{100B.1}, R^{WW.2} is R^{100B.2}, and R^{WW.3} is R^{100B.3}. R^{WW.1}, R^{WW.2} and R^{WW.3} in this paragraph are as defined in the preceding paragraphs.

[0087] R^{LWW.1} is independently oxo, halogen, -CX^{LWW.1.3}, -CHX^{LWW.1.2}, -CH₂X^{LWW.1}, -OCX^{LWW.1.3}, -OCH₂X^{LWW.1}, -OCHX^{LWW.1.2}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, R^{LWW.2}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{LWW.2}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{LWW.2}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{LWW.2}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{LWW.2}-substituted or

unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{LWW.2}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{LWW.1} is independently oxo, halogen, -CX^{LWW.1}₃, -CHX^{LWW.1}₂, -CH₂X^{LWW.1}, -OCX^{LWW.1}₃, -OCH₂X^{LWW.1}, -OCHX^{LWW.1}₂, -CN, -OH, -NH₂,
 5 -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl
 10 (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{LWW.1} is independently -F, -Cl, -Br, or -I.

[0088] R^{LWW.2} is independently oxo, halogen, -CX^{LWW.2}₃, -CHX^{LWW.2}₂, -CH₂X^{LWW.2},
 15 -OCX^{LWW.2}₃, -OCH₂X^{LWW.2}, -OCHX^{LWW.2}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, R^{LWW.3}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{LWW.3}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5
 20 membered), R^{LWW.3}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{LWW.3}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{LWW.3}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{LWW.3}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6
 25 membered). In embodiments, R^{LWW.2} is independently oxo, halogen, -CX^{LWW.2}₃, -CHX^{LWW.2}₂, -CH₂X^{LWW.2}, -OCX^{LWW.2}₃, -OCH₂X^{LWW.2}, -OCHX^{LWW.2}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),
 30 unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl

(e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^{LWW.2}$ is independently -F, -Cl, -Br, or -I.

[0089] $R^{LWW.3}$ is independently oxo, halogen, $-CX^{LWW.3}_3$, $-CHX^{LWW.3}_2$, $-CH_2X^{LWW.3}$, $-OCX^{LWW.3}_3$, $-OCH_2X^{LWW.3}$, $-OCHX^{LWW.3}_2$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^{LWW.3}$ is independently -F, -Cl, -Br, or -I.

[0090] In the event that any R group recited in a claim or chemical formula description set forth herein (R^{WW} substituent) is not specifically defined in this disclosure, then that R group (R^{WW} group) is hereby defined as independently oxo, halogen, $-CX^{WW}_3$, $-CHX^{WW}_2$, $-CH_2X^{WW}$, $-OCX^{WW}_3$, $-OCH_2X^{WW}$, $-OCHX^{WW}_2$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, $R^{WW.1}$ -substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), $R^{WW.1}$ -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $R^{WW.1}$ -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), $R^{WW.1}$ -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $R^{WW.1}$ -substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or $R^{WW.1}$ -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW} is independently -F, -Cl, -Br, or -I. Again, “WW” represents the stated superscript number of the subject R group (e.g., 1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ are as defined above.

[0091] In the event that any L linker group recited in a claim or chemical formula description set forth herein (i.e., an L^{WW} substituent) is not explicitly defined, then that L group (L^{WW} group) is herein defined as independently a bond, -O-, -NH-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -S-, -SO₂NH-, $R^{LWW.1}$ -substituted or

unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{LWW.1}-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{LWW.1}-substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{LWW.1}-substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{LWW.1}-substituted or unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{LWW.1}-substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). Again, "WW" represents the stated superscript number of the subject L group (1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). R^{LWW.1}, as well as R^{LWW.2} and R^{LWW.3} are as defined above.

[0092] Certain compounds of the present disclosure possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of the present disclosure do not include those that are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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.

5 **[0097]** 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.

10 **[0098]** 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
15 present disclosure.

[0099] 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
20 not to be read as a single unit.

[0100] As used herein, the terms “bioconjugate” and “bioconjugate linker” refer to the resulting association between atoms or molecules of bioconjugate reactive groups or bioconjugate reactive moieties. The association can be direct or indirect. For example, a conjugate between a first bioconjugate reactive group (e.g., $-\text{NH}_2$, $-\text{COOH}$, $-\text{N}$ -
25 hydroxysuccinimide, or $-\text{maleimide}$) and a second bioconjugate reactive group (e.g., sulfhydryl, sulfur-containing amino acid, amine, amine sidechain containing amino acid, or carboxylate) provided herein can be direct, e.g., by covalent bond or linker (e.g., a first linker of 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,
30 dipole-induced dipole, London dispersion), ring stacking (pi effects), hydrophobic interactions and the like). In embodiments, bioconjugates or bioconjugate linkers are formed using bioconjugate chemistry (i.e., the association of two bioconjugate reactive groups)

including, but are not limited to nucleophilic substitutions (e.g., reactions of amines and alcohols with acyl halides, active esters), electrophilic substitutions (e.g., enamine reactions) and additions to carbon-carbon and carbon-heteroatom multiple bonds (e.g., Michael reaction, Diels-Alder addition). These and other useful reactions are discussed in, for example, March, ADVANCED ORGANIC CHEMISTRY, 3rd Ed., John Wiley & Sons, New York, 1985; Hermanson, BIOCONJUGATE TECHNIQUES, Academic Press, San Diego, 1996; and Feeney et al., MODIFICATION OF PROTEINS; Advances in Chemistry Series, Vol. 198, American Chemical Society, Washington, D.C., 1982. In embodiments, the first bioconjugate reactive group (e.g., maleimide moiety) is covalently attached to the second bioconjugate reactive group (e.g., a sulfhydryl). In embodiments, the first bioconjugate reactive group (e.g., haloacetyl moiety) is covalently attached to the second bioconjugate reactive group (e.g., a sulfhydryl). In embodiments, the first bioconjugate reactive group (e.g., pyridyl moiety) is covalently attached to the second bioconjugate reactive group (e.g., a sulfhydryl). In embodiments, the first bioconjugate reactive group (e.g., -N-hydroxysuccinimide moiety) is covalently attached to the second bioconjugate reactive group (e.g., an amine). In embodiments, the first bioconjugate reactive group (e.g., maleimide moiety) is covalently attached to the second bioconjugate reactive group (e.g., a sulfhydryl). In embodiments, the first bioconjugate reactive group (e.g., -sulfo-N-hydroxysuccinimide moiety) is covalently attached to the second bioconjugate reactive group (e.g., an amine).

[0101] Useful bioconjugate reactive moieties used for bioconjugate chemistries herein include, for example:

(a) carboxyl groups and various derivatives thereof including, but not limited to, N-hydroxysuccinimide esters, N-hydroxybenztriazole esters, acid halides, acyl imidazoles, thioesters, p-nitrophenyl esters, alkyl, alkenyl, alkynyl and aromatic esters;

(b) hydroxyl groups which can be converted to esters, ethers, aldehydes, etc.;

(c) haloalkyl groups wherein the halide can be later displaced with a nucleophilic group such as, for example, an amine, a carboxylate anion, thiol anion, carbanion, or an alkoxide ion, thereby resulting in the covalent attachment of a new group at the site of the halogen atom;

(d) dienophile groups which are capable of participating in Diels-Alder reactions such as, for example, maleimido or maleimide groups;

(e) aldehyde or ketone groups such that subsequent derivatization is possible via formation of carbonyl derivatives such as, for example, imines, hydrazones, semicarbazones or oximes, or via such mechanisms as Grignard addition or alkyllithium addition;

5 (f) sulfonyl halide groups for subsequent reaction with amines, for example, to form sulfonamides;

(g) thiol groups, which can be converted to disulfides, reacted with acyl halides, or bonded to metals such as gold, or react with maleimides;

(h) amine or sulfhydryl groups (e.g., present in cysteine), which can be, for example, acylated, alkylated or oxidized;

10 (i) alkenes, which can undergo, for example, cycloadditions, acylation, Michael addition, etc;

(j) epoxides, which can react with, for example, amines and hydroxyl compounds;

(k) phosphoramidites and other standard functional groups useful in nucleic acid synthesis;

15 (l) metal silicon oxide bonding;

(m) metal bonding to reactive phosphorus groups (e.g., phosphines) to form, for example, phosphate diester bonds;

(n) azides coupled to alkynes using copper catalyzed cycloaddition click chemistry; and

20 (o) biotin conjugate can react with avidin or streptavidin to form a avidin-biotin complex or streptavidin-biotin complex.

[0102] The bioconjugate reactive groups can be chosen such that they do not participate in, or interfere with, the chemical stability of the conjugate described herein. Alternatively, a reactive functional group can be protected from participating in the crosslinking reaction by the presence of a protecting group. In embodiments, the bioconjugate comprises a molecular entity derived from the reaction of an unsaturated bond, such as a maleimide, and a sulfhydryl group.

[0103] “Analog,” “analogue,” or “derivative” 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.

[0104] The terms “a” or “an,” as used in herein means one or more. In addition, the phrase “substituted with a[n],” as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is “substituted with an unsubstituted C₁-C₂₀ alkyl, or unsubstituted 2 to 20 membered heteroalkyl,” the group may contain one or more unsubstituted C₁-C₂₀ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0105] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as “R-substituted.” Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R¹³ substituents are present, each R¹³ substituent may be distinguished as R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc., wherein each of R^{13A}, R^{13B}, R^{13C}, R^{13D}, etc. is defined within the scope of the definition of R¹³ and optionally differently.

[0106] 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.

[0107] The term “pharmaceutically acceptable salts” is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the

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

[0108] Thus, the compounds of the present disclosure may exist as salts, such as with pharmaceutically acceptable acids. The present disclosure includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, propionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g., methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0109] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0110] In addition to salt forms, the present disclosure provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0111] Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the present disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

[0112] A polypeptide, or a cell is “recombinant” when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (e.g., non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, e.g., in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0113] As used herein, the term “about” means a range of values including the specified value, which a person of ordinary skill in the art would consider reasonably similar to the specified value. In embodiments, about means within a standard deviation using measurements generally acceptable in the art. In embodiments, about means a range extending to +/- 10% of the specified value. In embodiments, about includes the specified value.

[0114] “Co-administer” is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Co-administration is meant to include simultaneous or sequential administration of

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

[0115] A “cell” as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (e.g., spodoptera) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

[0116] The terms “treating” or “treatment” refers to any indicia of success in the treatment or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, the certain methods presented herein successfully treat cancer by decreasing the incidence of cancer and or causing remission of cancer. In some embodiments of the compositions or methods described herein, treating cancer includes slowing the rate of growth or spread of cancer cells, reducing metastasis, or reducing the growth of metastatic tumors. The term “treating” and conjugations thereof, include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing. In embodiments, the treating or treatment is no prophylactic treatment.

[0117] An “effective amount” is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g., achieve the effect for which it is

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

[0118] “Control” or “control experiment” is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity (e.g., signaling pathway) of a protein in the absence of a compound as described herein (including embodiments, examples, figures, or Tables).

[0119] “Contacting” is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g., chemical compounds including biomolecules, or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0120] The term “contacting” may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a cellular component (e.g., protein, ion, lipid, nucleic acid, nucleotide, amino acid, protein, particle, organelle, cellular compartment, microorganism, virus, lipid droplet, vesicle, small molecule, protein complex, protein aggregate, or macromolecule). In some embodiments contacting includes allowing a compound described herein to interact with a cellular component (e.g., protein, ion, lipid, nucleic acid, nucleotide, amino acid, protein, particle, virus, lipid droplet, organelle, cellular compartment, microorganism, vesicle, small molecule, protein complex, protein aggregate, or macromolecule) that is involved in a signaling pathway.

[0121] As defined herein, the term “inhibition,” “inhibit,” “inhibiting” and the like in reference to a cellular component-inhibitor interaction means negatively affecting (e.g., decreasing) the activity or function of the cellular component (e.g., decreasing the signaling pathway stimulated by a cellular component (e.g., protein, ion, lipid, virus, lipid droplet, nucleic acid, nucleotide, amino acid, protein, particle, organelle, cellular compartment, microorganism, vesicle, small molecule, protein complex, protein aggregate, or macromolecule)), relative to the activity or function of the cellular component in the absence of the inhibitor. In some embodiments inhibition refers to reduction of a disease or symptoms of disease. In some embodiments, inhibition refers to a reduction in the activity of a signal transduction pathway or signaling pathway (e.g., reduction of a pathway involving the cellular component). Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating the signaling pathway or enzymatic activity or the amount of a cellular component.

[0122] The term “modulator” refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of

the molecule (e.g., a target may be a cellular component (e.g., protein, ion, lipid, virus, lipid droplet, nucleic acid, nucleotide, amino acid, protein, particle, organelle, cellular compartment, microorganism, vesicle, small molecule, protein complex, protein aggregate, or macromolecule)) relative to the absence of the composition.

- 5 **[0123]** The term “modulate” is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. “Modulation” refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule.
- 10 **[0124]** “Patient” or “subject in need thereof” refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.
- 15 **[0125]** “Disease” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. In some embodiments, the disease is a disease related to (e.g., caused by) a cellular component (e.g., protein, ion, lipid, nucleic acid, nucleotide, amino acid, protein, particle, organelle, cellular compartment, microorganism, vesicle, small molecule, protein complex, protein aggregate, or
- 20 macromolecule).
- 25 **[0126]** As used herein, the term “cancer” refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g., humans), including leukemia, lymphoma, carcinomas and sarcomas. 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, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain
- 30 tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia,

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

[0127] 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 leukocythemetic 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.

[0128] 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,

- 5 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, cunateous T-cell lymphoma, peripheral T-cell lymphoma, anaplastic large cell lymphoma, mycosis fungoides, and precursor T-lymphoblastic lymphoma.

- [0129]** The term “sarcoma” generally refers to a tumor which is made up of a substance
10 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,
15 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
20 sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

- [0130]** 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
25 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.

- [0131]** The term “carcinoma” refers to a malignant new growth made up of epithelial cells
30 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, epierrmoid 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.

[0132] As used herein, the term “autoimmune disease” refers to a disease or condition in which a subject’s immune system has an aberrant immune response against a substance that does not normally elicit an immune response in a healthy subject. Examples of autoimmune diseases that may be treated with a compound, pharmaceutical composition, or method described herein include Acute Disseminated Encephalomyelitis (ADEM), Acute necrotizing hemorrhagic leukoencephalitis, Addison’s disease, Agammaglobulinemia, Alopecia areata,

Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome (APS), Autoimmune angioedema, Autoimmune aplastic anemia, Autoimmune dysautonomia, Autoimmune hepatitis, Autoimmune hyperlipidemia, Autoimmune immunodeficiency, Autoimmune inner ear disease (AIED), Autoimmune myocarditis,

5 Autoimmune oophoritis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune thrombocytopenic purpura (ATP), Autoimmune thyroid disease, Autoimmune urticaria, Axonal or neuronal neuropathies, Balo disease, Behcet's disease, Bullous pemphigoid, Cardiomyopathy, Castleman disease, Celiac disease, Chagas disease, Chronic fatigue syndrome, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent

10 multifocal osteomyelitis (CRMO), Churg-Strauss syndrome, Cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogans syndrome, Cold agglutinin disease, Congenital heart block, Cocksackie myocarditis, CREST disease, Essential mixed cryoglobulinemia, Demyelinating neuropathies, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis,

15 Eosinophilic esophagitis, Eosinophilic fasciitis, Erythema nodosum, Experimental allergic encephalomyelitis, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis (GPA) (formerly called Wegener's Granulomatosis), Graves' disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's

20 thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura, Herpes gestationis, Hypogammaglobulinemia, Idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, IgG4-related sclerosing disease, Immunoregulatory lipoproteins, Inclusion body myositis, Interstitial cystitis, Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis, Kawasaki syndrome, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus,

25 Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus (SLE), Lyme disease, chronic, Meniere's disease, Microscopic polyangiitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica (Devic's), Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism, PANDAS (Pediatric Autoimmune

30 Neuropsychiatric Disorders Associated with Streptococcus), Paraneoplastic cerebellar degeneration, Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonnage-Turner syndrome, Pars planitis (peripheral uveitis), Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Type I, II, & III autoimmune polyglandular syndromes, Polymyalgia

rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Progesterone dermatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Psoriasis, Psoriatic arthritis, Idiopathic pulmonary fibrosis, Pyoderma gangrenosum, Pure red cell aplasia, Raynauds phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy,

5 Reiter's syndrome, Relapsing polychondritis, Restless legs syndrome, Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia, Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP),

10 Tolosa-Hunt syndrome, Transverse myelitis, Type 1 diabetes, Ulcerative colitis, Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vesiculobullous dermatosis, Vitiligo, or Wegener's granulomatosis (i.e., Granulomatosis with Polyangiitis (GPA).

[0133] As used herein, the term “neurodegenerative disease” refers to a disease or

15 condition in which the function of a subject's nervous system becomes impaired. Examples of neurodegenerative diseases that may be treated with a compound, pharmaceutical composition, or method described herein include Alexander's disease, Alper's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, Ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Bovine spongiform encephalopathy

20 (BSE), Canavan disease, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, frontotemporal dementia, Gerstmann-Sträussler-Scheinker syndrome, Huntington's disease, HIV-associated dementia, Kennedy's disease, Krabbe's disease, kuru, Lewy body dementia, Machado-Joseph disease (Spinocerebellar ataxia type 3), Multiple sclerosis, Multiple System Atrophy, Narcolepsy, Neuroborreliosis, Parkinson's disease, Pelizaeus-

25 Merzbacher Disease, Pick's disease, Primary lateral sclerosis, Prion diseases, Refsum's disease, Sandhoff's disease, Schilder's disease, Subacute combined degeneration of spinal cord secondary to Pernicious Anaemia, Schizophrenia, Spinocerebellar ataxia (multiple types with varying characteristics), Spinal muscular atrophy, Steele-Richardson-Olszewski disease, or Tabes dorsalis.

30 **[0134]** As used herein, the term “metabolic disease” or “metabolic disorder” refers to a disease or condition in which a subject's metabolism or metabolic system (e.g., function of storing or utilizing energy) becomes impaired. Examples of metabolic diseases that may be treated with a compound, pharmaceutical composition, or method described herein include

diabetes (e.g., type I or type II), obesity, metabolic syndrome, or a mitochondrial disease (e.g., dysfunction of mitochondria or aberrant mitochondrial function).

[0135] The term “cellular component associated disease” (e.g., the cellular component may be a protein, ion, lipid, nucleic acid, nucleotide, amino acid, protein, particle, organelle, cellular compartment, microorganism, virus, vesicle, small molecule, protein complex, protein aggregate, or macromolecule; the disease may be a neurodegenerative disease, cancer, a metabolic disease, autoimmune disease, inflammatory disease, or infectious disease) (also referred to herein as “cellular component related disease”) refers to a disease caused by the cellular component. Other diseases that are associated with aberrant activity or level of the cellular component are well known in the art and determining such diseases are within the skill of a person of skill in the art.

[0136] “Pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0137] The term “preparation” is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0138] As used herein, the term “administering” means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional,

intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. By “co-administer” it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example cancer therapies such as chemotherapy, hormonal therapy, radiotherapy, or immunotherapy. The compounds of the invention can be administered alone or can be coadministered to the patient.

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

[0139] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating a disease associated with cells expressing a disease associated cellular component, or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0140] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another.

[0141] As a non-limiting example, the compounds described herein can be co-administered with conventional chemotherapeutic agents including alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine,

uramustine, thiotepa, nitrosoureas, etc.), anti-metabolites (e.g., 5-fluorouracil, azathioprine, methotrexate, leucovorin, capecitabine, cytarabine, floxuridine, fludarabine, gemcitabine, pemetrexed, raltitrexed, etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.), topoisomerase inhibitors (e.g.,
5 irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, etc.), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, etc.), platinum-based compounds (e.g., cisplatin, oxaloplatin, carboplatin, etc.), and the like.

[0142] The compounds described herein can also be co-administered with conventional
10 hormonal therapeutic agents including, but not limited to, steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, tamoxifen, and gonadotropin-releasing hormone agonists (GnRH) such as goserelin.

[0143] Additionally, the compounds described herein can be co-administered with
conventional immunotherapeutic agents including, but not limited to, immunostimulants
15 (e.g., Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, etc.), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), and radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ¹¹¹In,
20 ⁹⁰Y, or ¹³¹I, etc.).

[0144] In a further embodiment, the compounds described herein can be co-administered
with conventional radiotherapeutic agents including, but not limited to, radionuclides such as
⁴⁷Sc, ⁶⁴Cu, ⁶⁷Cu, ⁸⁹Sr, ⁸⁶Y, ⁸⁷Y, ⁹⁰Y, ¹⁰⁵Rh, ¹¹¹Ag, ¹¹¹In, ^{117m}Sn, ¹⁴⁹Pm, ¹⁵³Sm, ¹⁶⁶Ho, ¹⁷⁷Lu,
¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi, optionally conjugated to antibodies directed against tumor
25 antigens.

[0145] In therapeutic use for the treatment of a disease, compound utilized in the
pharmaceutical compositions of the present invention may be administered at the initial
dosage of about 0.001 mg/kg to about 1000 mg/kg daily. A daily dose range of about 0.01
mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 200 mg/kg, or about 1 mg/kg to
30 about 100 mg/kg, or about 10 mg/kg to about 50 mg/kg, can be used. The dosages, however,
may be varied depending upon the requirements of the patient, the severity of the condition
being treated, and the compound or drug being employed. For example, dosages can be

empirically determined considering the type and stage of cancer diagnosed in a particular patient. The dose administered to a patient, in the context of the present invention, should be sufficient to affect a beneficial therapeutic response in the patient over time. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a compound in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

[0146] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0147] The term “associated” or “associated with” in the context of a substance or substance activity or function associated with a disease (e.g., a protein associated disease, disease associated with a cellular component) means that the disease (e.g., neurodegenerative disease, cancer) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function or the disease or a symptom of the disease may be treated by modulating (e.g., inhibiting or activating) the substance (e.g., cellular component). For example, a neurodegenerative disease associated with a protein aggregate may be a neurodegenerative disease that results (entirely or partially) from aberrant protein aggregation or a neurodegenerative disease wherein a particular symptom of the disease is caused (entirely or partially) by aberrant protein aggregation. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a neurodegenerative disease associated with aberrant protein aggregation or a protein aggregate associated neurodegenerative disease, may be treated with a protein aggregate modulator or protein aggregate targeted autophagy degrader, in the instance where increased protein aggregation causes the neurodegenerative disease.

[0148] The term “aberrant” as used herein refers to different from normal. When used to describe enzymatic activity, aberrant refers to activity that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer

to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g., by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

5 **[0149]** “Anti-cancer agent” is used in accordance with its plain ordinary meaning and refers to a composition (e.g., compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In
 10 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. In embodiments, an anti-cancer agent is an inhibitor of K-Ras, RAF, MEK, Erk, PI3K, Akt, RTK, or mTOR. In embodiments, an anti-cancer agent is an MDM2 inhibitor or a genotoxic anti-cancer agent. In embodiments, an anti-cancer agent is nutlin-1, nutlin-2, nutlin-3, nutlin-3a, nutlin-3b,
 15 YH239-EE, MI-219, MI-773, MI-77301, MI-888, MX69, RG7112, RG7388, RITA, idasanutlin, DS-3032b, or AMG232. In embodiments, an anti-cancer agent is an alkylating agent, intercalating agent, or DNA replication inhibitor. 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-
 20 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., mechlorethamine, cyclophosphamide, chlorambucil, melphalan), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates
 25 (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,
 30 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),
 5 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), gossyphol, genasense,
 polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-
 related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid,
 10 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;
 15 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;
 20 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;
 25 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;
 30 combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8;
 cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatin; cypemycin;
 cytarabine ocfosfate; cytolytic factor; cytosstatin; 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; episteride; estramustine analogue; estrogen agonists; estrogen antagonists;
 etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim;
 5 finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin
 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;
 10 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;
 15 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;
 20 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
 25 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;
 30 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;

5 protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide;

10 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;

15 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;

20 tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors;

25 tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vaporeotide; 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;

30 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; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin

hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate;

5 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

10 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;

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

20 sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safinol; safinol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin;

25 tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; tricitabine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinat

30 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., TZT-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 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/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, Desaeyleleutherobin, 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.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In , ^{90}Y , or ^{131}I , etc.), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g., gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (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. A moiety of an anti-cancer agent is a monovalent anti-cancer agent (e.g., a monovalent form of an agent listed above).

[0150] “Chemotherapeutic” or “chemotherapeutic agent” is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0151] The term “electrophilic” as used herein refers to a chemical group that is capable of accepting electron density. An “electrophilic substituent,” “electrophilic chemical moiety,” or “electrophic moiety” refers to an electron-poor chemical group, substituent, or moiety (monovalent chemical group), which may react with an electron-donating group, such as a nucleophile, by accepting an electron pair or electron density to form a bond. In some

embodiments, the electrophilic substituent of the compound is capable of reacting with a cysteine residue. In some embodiments, the electrophilic substituent is capable of forming a covalent bond with a cysteine residue (e.g., ATP6V1A) and may be referred to as a “covalent cysteine modifier moiety” or “covalent cysteine modifier substituent.” The covalent bond
5 formed between the electrophilic substituent and the sulfhydryl group of the cysteine may be a reversible or irreversible bond. In some embodiments, the electrophilic substituent of the compound is capable of reacting with a lysine residue. In some embodiments, the electrophilic substituent of the compound is capable of reacting with a serine residue. In some embodiments, the electrophilic substituent of the compound is capable of reacting with
10 a methionine residue.

[0152] “Nucleophilic” as used herein refers to a chemical group that is capable of donating electron density.

[0153] An amino acid residue in a protein “corresponds” to a given residue when it occupies the same essential structural position within the protein as the given residue. For
15 example, a selected residue in a selected protein corresponds to C277 of human Vacuolar H⁺-ATPase protein when the selected residue occupies the same essential spatial or other structural relationship as C277 in human Vacuolar H⁺-ATPase protein. In some embodiments, where a selected protein is aligned for maximum homology with the human Vacuolar H⁺-ATPase protein, the position in the aligned selected protein aligning with C277
20 is said to correspond to C277. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, e.g., where the structure of the selected protein is aligned for maximum correspondence with the human Vacuolar H⁺-ATPase protein and the overall structures compared. In this case, an amino acid that occupies the same essential position as C277 in the structural model is said to correspond to the C277 residue.

[0154] An amino acid residue in a protein “corresponds” to a given residue when it occupies the same essential structural position within the protein as the given residue. For
25 example, a selected residue in a selected protein corresponds to C277 of human ATP6V1A protein when the selected residue occupies the same essential spatial or other structural relationship as C277 in human ATP6V1A protein. In some embodiments, where a selected
30 protein is aligned for maximum homology with the human ATP6V1A protein, the position in the aligned selected protein aligning with C277 is said to correspond to C277. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, e.g.,

where the structure of the selected protein is aligned for maximum correspondence with the human ATP6V1A protein and the overall structures compared. In this case, an amino acid that occupies the same essential position as C277 in the structural model is said to correspond to the C277 residue.

5 **[0155]** The term “isolated,” when applied to a nucleic acid or protein, denotes that the nucleic acid or protein is essentially free of other cellular components with which it is associated in the natural state. It can be, for example, in a homogeneous state and may be in either a dry or aqueous solution. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high
10 performance liquid chromatography. A protein that is the predominant species present in a preparation is substantially purified.

[0156] The term “amino acid” refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the
15 genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified
20 R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid. The terms “non-naturally occurring amino acid” and “unnatural amino acid” refer to amino acid
25 analogs, synthetic amino acids, and amino acid mimetics which are not found in nature.

[0157] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

30 **[0158]** The terms “polypeptide,” “peptide,” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may in embodiments be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid

polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers.

[0159] “Percentage of sequence identity” is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e., gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[0160] The terms “identical” or percent “identity,” in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (see, e.g., NCBI web site <http://www.ncbi.nlm.nih.gov/BLAST/> or the like). Such sequences are then said to be “substantially identical.” This definition also refers to, or may be applied to, the complement of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0161] “Percentage of sequence identity” is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e., gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the

number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

5 **[0162]** An amino acid or nucleotide base “position” is denoted by a number that sequentially identifies each amino acid (or nucleotide base) in the reference sequence based on its position relative to the N-terminus (or 5'-end). Due to deletions, insertions, truncations, fusions, and the like that must be taken into account when determining an optimal alignment, in general the amino acid residue number in a test sequence determined by simply counting
10 from the N-terminus will not necessarily be the same as the number of its corresponding position in the reference sequence. For example, in a case where a variant has a deletion relative to an aligned reference sequence, there will be no amino acid in the variant that corresponds to a position in the reference sequence at the site of deletion. Where there is an insertion in an aligned reference sequence, that insertion will not correspond to a numbered
15 amino acid position in the reference sequence. In the case of truncations or fusions there can be stretches of amino acids in either the reference or aligned sequence that do not correspond to any amino acid in the corresponding sequence.

[0163] The terms “numbered with reference to” or “corresponding to,” when used in the context of the numbering of a given amino acid or polynucleotide sequence, refers to the
20 numbering of the residues of a specified reference sequence when the given amino acid or polynucleotide sequence is compared to the reference sequence.

[0164] The term “protein complex” is used in accordance with its plain ordinary meaning and refers to a protein which is associated with an additional substance (e.g., another protein, protein subunit, or a compound). Protein complexes typically have defined quaternary
25 structure. The association between the protein and the additional substance may be a covalent bond. In embodiments, the association between the protein and the additional substance (e.g., compound) is via non-covalent interactions. In embodiments, a protein complex refers to a group of two or more polypeptide chains. Proteins in a protein complex are linked by non-covalent protein–protein interactions. A non-limiting example of a protein
30 complex is the proteasome.

[0165] The term “protein aggregate” is used in accordance with its plain ordinary meaning and refers to an aberrant collection or accumulation of proteins (e.g., misfolded proteins).

Protein aggregates are often associated with diseases (e.g., amyloidosis). Typically, when a protein misfolds as a result of a change in the amino acid sequence or a change in the native environment which disrupts normal non-covalent interactions, and the misfolded protein is not corrected or degraded, the unfolded/misfolded protein may aggregate. There are three main types of protein aggregates that may form: amorphous aggregates, oligomers, and amyloid fibrils. In embodiments, protein aggregates are termed aggresomes. In embodiments, the protein aggregate is TDP43, HTT, APP, SNCA, or MAPT. In embodiments, the protein aggregate includes the protein Beta amyloid, Amyloid precursor protein, IAPP (Amylin), Alpha-synuclein, PrPSc, PrPSc, Huntingtin, Calcitonin, Atrial natriuretic factor, Apolipoprotein AI, Serum amyloid A, Medin, Prolactin, Transthyretin, Lysozyme, Beta-2 microglobulin, Gelsolin, Keratoepithelin, Beta amyloid, Cystatin, Immunoglobulin light chain AL, TDP43, or S-IBM.

[0166] The term “vesicle” is used in accordance with its plain ordinary meaning and refers to a small membrane enclosed compartment within a cell. Vesicles are typically involved in transport, buoyancy control, or enzyme storage within a cell. Some vesicles, for example a lysosome, may include enzymes, proteins, polysaccharides, lipids, nucleic acids, or organelles within the compartment. Vesicles are typically formed within cells as a result of exocytosis or phagocytosis, however some vesicles are formed at the Golgi complex and transported to the cell membrane. Vesicles may be unilamellar or multilamellar.

[0167] The term “vacuolar H⁺-ATPase,” “V-type proton ATPase,” “vacuolar H⁺-ATPase protein complex,” or “v-ATPase” refers to an enzyme that acidifies a wide array of intracellular organelles (e.g., lysosomes) and pump protons across the plasma membranes of cells. V-ATPases, including ATP6V1A as a component, couple the energy of ATP hydrolysis to proton transport across intracellular and plasma membranes of eukaryotic cells.

[0168] The term “V-type proton ATPase catalytic subunit A” or “ATP6V1A” refers to a gene that encodes a component of vacuolar ATPase (v-ATPase), which is an enzyme that mediates amino acid-dependent recruitment of mTORC1 to the lysosome. In some embodiments ATP6V1A refers to UniProt P38606-1. In embodiments, ATP6V1A refers to human ATP6V1A. In embodiments, ATP6V1A refers to Entrez 523. In embodiments, ATP6V1A refers to RefSeq NM_001690.3. In embodiments, ATP6V1A refers to RefSeq NP_001681.2. In some embodiments, ATP6V1A has the sequence:

MDFSKLPKILDEDKSTFGYVHGVSGPVVTACDMAGAAMYELVRVGHSELVGEIIRLEGD

MATIQVYEETSGVSVGDPVLRGTGKPLSVELGPGIMGAIFDGIQRPLSDISSQTQSIYIPR
 GVNVSALSRLDIKWDFTPCKNLRVGSHITGGDIYGIVSENSLIHKIMLPPRNRGTVTYIA
 PPGNYDTSDVVLELEFEGVKEKFTMVQVWPVRQVRPVTEKLPANHPLLTGQRVLDALFPC
 VQGGTTAIPGAFGCGKTVISQSLSKYSNSDVIIYVGCGERGNEMSEVLRDFPELTMEVDG
 5 KVESIMKRTALVANTSNMPVAAREASIYTGITLSEYFRDMGYHVSMMADSTSRWAEALRE
 ISGRLEMPADSGYPAYLGARLASFYERAGRVKCLGNPEREGSVSIVGAVSPPGGDFSDP
 VTSATLGIVQVFWGLDKKLAQRKHFPNVNLISYSKYMRALDEYYDKHFTEFVPLRTKAK
 EILQEEEDLAEIVQLVGKASLAETDKITLEVAKLIKDDFLQQNGYTPYDRFCPFYKTVGM
 LSNMIAFYDMARRAVETTAQSDNKITWSIIREHMGDILYKLSSMKFKDPLKDGEAKIKSD
 10 YAQLLEDMQNAFRSLED (SEQ ID NO:1).

[0169] The term “mTOR” refers to the protein “mechanistic target of rapamycin
 (serine/threonine kinase)” or “mammalian target of rapamycin.” The term “mTOR” may
 refer to the nucleotide sequence or protein sequence of human mTOR (e.g., Entrez 2475,
 Uniprot P42345, RefSeq NM_004958, or RefSeq NP_004949). The term “mTOR” includes
 15 both the wild-type form of the nucleotide sequences or proteins as well as any mutants
 thereof. In some embodiments, “mTOR” is wild-type mTOR. In some embodiments,
 “mTOR” is one or more mutant forms. The term “mTOR” XYZ refers to a nucleotide
 sequence or protein of a mutant mTOR wherein the Y numbered amino acid of mTOR that
 normally has an X amino acid in the wildtype, instead has a Z amino acid in the mutant. In
 20 embodiments, an mTOR is the human mTOR. In embodiments, the mTOR has the following
 amino acid sequence:

MLGTGPAAATTAATTSSNVSVLQQFASGLKSRNEETRAKAAKELQHYVTMELREMSQEES
 TRFYDQLNHHIFELVSSDANERKGGILAIASLIGVEGGNATRIGRFANYLRNLLPSNDP
 VVMEMASKAIGRLAMAGDTFTA EYVEFEVKRALEWLGADRNEGRRHAAVLVLRELAISVP
 25 TFFFQQVQPPFDNIFVAVWDPKQAIREGAVAALRACLILTTQREPKE MQKPQWYRHTFEE
 AEKGFDETLAKEKGMNRDDRIHGALLILNELVRISMEGERLREEMEEITQQQLVHDKYC
 KDLMGFGTKPRHITPFTSFQAVQPQQSNALVGLLGYSSHQGLMGFGTSPSPAKSTLVESR
 CCRDLMEEKFDQVCQWVLKCRNSKNSLIQMTILNLLPRLAAFRPSAFTDTQYLQDTMNHV
 LSCVKKEKERTA AFQALGLLSVAVRSEFKVYLPRVLDIIRAALPPKDFAHKRQKAMQVDA
 30 TVFTCISMLARAMGPGIQQDIKELLEPMLAVGLSPALTAVLYDL SRQIPQLKKDIQDGLL
 KMLSLVLMHKPLRHPGMPKGLAHQLASPGLTTLPEASDVGSITLALRTLGSFEFEGHSLT
 QFVRHCADHFLNSEHKEIRMEAARTCSRLLTPSIHLISGHAHVVSQTAVQVVADVLSKLL
 VVGITDPDPDIRYCVLASLDERFDAHLAQAE NLQALFVALNDQVFEIRELAICTVGRLLS
 MNPAFVMPFLRKMLIQILTELEHSGIGRIKEQSARMLGHLVSNAPRLIRPYMEPILKALI
 35 LKCLKDPDPDPNPGVINNVLATIGELAQVSGLEMRKWVDELFIIMDMLQDSSLLAKRQVA

LWTLGQLVASTGYVVEPYRKYP TLLLEVLLNFLKTEQNQGTRREAIRVLGLLGALDPYKHK
 VNIGMIDQSRDASAVSLSESKSSQDSSDYSTSEMLVNMGNLPLDEFYPAVSMVALMRIFR
 DQSLSHHHTMVVQAITFIFKSLGLKCVQFLPQVMPTFLNVIRVCDGAIREFLFQQLGMLV
 SFVKSHIRPYMDEIVTLMREFWVMNTSIQSTIILLIEQIVVALGGEFKLYLPQLIPHMLR
 5 VFMHDNSPGRIVSIKLLAAIQLFGANLDDYLHLLLPIVKLFDAP EAPLPSRKA ALETVD
 RLTESLDFTDYASRIIHPIVRTLDQSP ELRSTAMDTLSSLVFQLGKKYQIFIPMVNKKVLV
 RHRINHQR YDVLICRIVKGYTLADEEEDPLIYQHRMLRSGQGDALASGPVETGPMKKLHV
 STINLQKAWGAARRVSKDDWLEWLRRLSLELLKDSSSPSLRSCWALAQAYNPMARDLFNA
 AFVSCWSELNEDQQDELIRSIELALTSQDIAEVTQTLLNLAEFMEHSDKGPLPLRDDNGI
 10 VLLGERAAKCRAYAKALHYKELEFQKGPTPAILES LISINNKLQQPEAAAGVLEYAMKHF
 GELEIQATWYEKLHEWEDALVAYDKKMDTNKDDPELMLGRMRCLEALGEWGQLHQQCCE
 KWTLVNDETQAKMARMAAAAWGLGQWDSMEEYTCMIPRDTHDGAFYRAVLALHQDLF
 SLAQQCIDKARDLLDAELTAMAGESYSRAYGAMV SCHMLSELEEVIQYKLVPERREIRQIW
 WERLQGCQRIVEDWQKILMVRS LVSPHEDMRTWLKYASLCGKSGRLALAHKTLVLLLGV
 15 DPSRQLDHPLPTVHPQVTYAYMKNMWKSARKIDAFQHMQH FVQTMQQQAQHA IATEDQQ
 HKQELHKL MARCFLKLGEWQLNLQGINESTIPKVLQYYSAATEHDRSWYKA WHAWAVMN
 FEAVLHYKHQNQARDEKKKLRHASGANITNATTAATTAATATTTASTE GSNSESEAESTENS
 PTPSPLQKKVTEDLSKTLLMYTVP AVQGFRRSISLSRGNNLQD TLRVLTWFDYGHWPDVN
 EALVEGVKAIQIDTWLQVIPQLIARIDTPRPLVGR LIHQLLTDIGRYHPQALIYPLTVAS
 20 KSTTTARHNAANKILKNMCEHSNTLVQQAMMVSEELIRVAILWHEMWHEGLEEASRLYFG
 ERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLME AQEWCRKYMKSGNVKDLTQ
 AWDLYYHVFRISKQLPQLTSLELQYVSPKLLMCRDLELAVPGTYDPNQPIIRIQSIAPSL
 QVITSKQRPRKLTLMGSNGHEFVFLKGHEDLRQDERVMQLFGLVNTLLANDPTSLRKNL
 SIQRYAVIPLSTNSGLIGWVPHCDTLHALIRDYREKKKILLNIEHRIMLRMAPDYDHLTL
 25 MQKVEVFEHAVNNTAGDDLAKLLWLKSPSSEVWFDRRTNYTRSLAVMSMVGYILGLGDRH
 PSNLMLDRLSGKILHIDFGDCFEVAMTREKFPEKIPFRLTRMLTNAMEVTGLDGNYRITC
 HTVMEVLREHKDSVMAVLEAFVYDPLLNWRLMDTNTKGNKRSRTRTDSYSAGQSVEILDG
 VELGEP AHKKTGTTPESIH SFIGDGLVKPEALNKKAIQIINRVRDKLTGRDFSHDDTLD
 VPTQVELLIKQATSHENLCQCYIGWCPFW (SEQ ID NO:2).

30 **[0170]** The term “mTORC1” refers to the protein complex including mTOR and Raptor
 (regulatory-associated protein of mTOR). mTORC1 may also include MLST8 (mammalian
 lethal with SEC13 protein 8), PRAS40, and/or DEPTOR. mTORC1 may function as a
 nutrient/energy/redox sensor and regulator of protein synthesis. The term “mTORC1
 pathway” or “mTORC1 signal transduction pathway” refers to a cellular pathway including
 35 mTORC1. An mTORC1 pathway includes the pathway components upstream and

downstream from mTORC1. An mTORC1 pathway is a signaling pathway that is modulated by modulation of mTORC1 activity. In embodiments, an mTORC1 pathway is a signaling pathway that is modulated by modulation of mTORC1 activity but not by modulation of mTORC2 activity. In embodiments, an mTORC1 pathway is a signaling pathway that is modulated to a greater extent by modulation of mTORC1 activity than by modulation of mTORC2 activity.

[0171] The term “mTORC2” refers to the protein complex including mTOR and RICTOR (rapamycin-insensitive companion of mTOR). mTORC2 may also include GβL, mSIN1 (mammalian stress-activated protein kinase interacting protein 1), Protor 1/2, DEPTOR, TTI1, and/or TEL2. mTORC2 may regulate cellular metabolism and the cytoskeleton. The term “mTORC2 pathway” or “mTORC2 signal transduction pathway” refers to a cellular pathway including mTORC2. An mTORC2 pathway includes the pathway components upstream and downstream from mTORC2. An mTORC2 pathway is a signaling pathway that is modulated by modulation of mTORC2 activity. In embodiments, an mTORC2 pathway is a signaling pathway that is modulated by modulation of mTORC2 activity but not by modulation of mTORC1 activity. In embodiments, an mTORC2 pathway is a signaling pathway that is modulated to a greater extent by modulation of mTORC2 activity than by modulation of mTORC1 activity.

[0172] The term “Sequestosome-1” or “SQSTM1” or “p62/SQSTM1” or “ubiquitin-binding protein p62” or “p62” refers to an autophagosome cargo protein (including homologs, isoforms, and functional fragments thereof) that targets other proteins that bind to it for selective autophagy. p62 harbors active nuclear import and export signals and shuttles between the nucleus and cytoplasm. The term “p62” refers to the nucleotide sequences or proteins of human p62. The term “p62” includes both the wild-type form of the nucleotide sequences or proteins as well as any mutants thereof. In some embodiments, “p62” is wild-type p62. In some embodiments, “p62” is one or more mutant forms. The term “p62” XYZ refers to a nucleotide sequence or protein of a mutant p62 wherein the Y numbered amino acid of p62 that has an X amino acid in the wildtype instead has a Z amino acid in the mutant. In embodiments, p62 is a functional fragment thereof. In some embodiments p62 refers to UniProt C9J6J8, having the sequence:

MASLTVKAYLLGKEDAAREIRRFSCCSPEPEAEAEAAAGPGPCERLLSRVAALFPAL
RPGGFQAHYRGGGFR (SEQ ID NO:3).

[0173] In embodiments, p62 refers to Entrez 8878. In embodiments, p62 refers to RefSeq NM_001142298.1, RefSeq NM_001142299.1, RefSeq NM_003900.4, RefSeq NP_001135770.1, RefSeq NP_001135771.1, or RefSeq NP_003891.1. In some embodiments p62 refers to UniProt Q13501, having the sequence:

5 MASLTVKAYLLGKEDAAREIRRFSCCSPEPEAEAEAAAGPGPCERLLSRVAALFPALRP
GGFQAHYRDEDGDLVAFSSDEELTMAMSYVKDDIFRIYIKEKKECRRDHRPPCAQEAPRN
MVHPNVICDGCNGPVVGTRYKCSVCPDYDLCSVCEGKGLHRGHTKLAFPSPFGHLSEGFS
HSRWLRKVKHGHFGWPGWEMGPPGNWSPRPPRAGEARPGPTAESASGPSSEDPSVNFLKNV
GESVAAALSPLGIEVDIDVEHGGKRSRLTPVSPESSSTEEKSSSQPSSCCSDPSKPGGNV
10 EGATQSLAEQMRKIALESEGRPEEQMESDNCSSGDDDDWTHLSSKEVDPSTGELQSLQMPE
SEGPSSLDPSQEGPTGLKEAALYPHLPPEADPRLIESLSQMLSMGFSDEGGWLTRLLQTK
NYDIGAALDTIQYSKHPPPL (SEQ ID NO:4).

[0174] In some embodiments p62 refers to the sequence:

RFSFCCSPEPEAEAEAAAGPGPCERL (SEQ ID NO:5).

15 **[0175]** The term “LC3B” or “microtubule-associated proteins 1A/1B light chain 3B” refers to a central protein in the autophagy pathway, where it functions, for example, in autophagy substrate selection. The term “LC3B” may refer to the nucleotide sequence or protein sequence of human LC3B. In embodiments, LC3B is LC3BII. In embodiments, LC3B is Entrez 81631, Uniprot Q9GZQ8, RefSeq NM_022818.4, or RefSeq NP_073729.1. In
20 embodiments, the LC3B has the following amino acid sequence:

MPSEKTFKQRRTFEQRVEDVRLIREQHPTKIPVIIERYKGEKQLPVLDKTKFLVPDHVNM
SELIKIIRRLQLNANQAFFLLVNGHSMVSVSTPISEVYESEKDEDGFLYMVYASQETFG
MKLSV (SEQ ID NO:6).

[0176] The term “4EBP1” or “eukaryotic translation initiation factor 4E-binding protein 1”
25 refers to a protein that interacts with eukaryotic translation initiation factor 4E, which is a component of the multisubunit complex that recruits 40S ribosomal subunits to the 5’ end of mRNAs. The term “4EBP1” may refer to the nucleotide sequence or protein sequence of human 4EBP1. In embodiments, 4EBP1 is Entrez 1978, Uniprot Q13541, RefSeq NM_004095.3, or RefSeq NP_004086.1. In embodiments, the 4EBP1 has the following
30 amino acid sequence:

MSGGSSCSQTPSRAIPATRRVVLGDGVQLPPGDYSTTPGGTLFSTTPGGTRIYYDRKFLM

ECRNSPVTKTPPRDLPTIPGVTSPSSDEPPMEASQSHLRNSPEDKRAGGEESQFEMDI (SEQ ID NO:7).

[0177] The term “TFEB” or “transcription factor EB” refers to a protein involved in lysosomal biogenesis. The TFEB protein coordinates, for example, expression of lysosomal hydrolases, membrane proteins, and genes involved in autophagy. The TFEB protein is encoded by the TFEB gene. The term “TFEB” may refer to the nucleotide sequence or protein sequence of human TFEB. In embodiments, TFEB is Entrez 7942, Uniprot P19484, RefSeq NM_001167827.2, RefSeq NM_001271943.1, RefSeq NM_001271944.1, RefSeq NM_001271945.1, RefSeq NM_007162.2, RefSeq NP_001161299.2, RefSeq NP_001258872.1, RefSeq NP_001258873.1, RefSeq NP_001258874.1, or RefSeq NP_009093.1. In embodiments, the TFEB has the following amino acid sequence:

MASRIGLRMQLMREQAQQEEQRERMQQQAVMHYMQQQQQQQQQQLGGPPTPAINTPVHF
QSPPPVPGEVLKVQSYLENPTSYHLQQSQHQKVREYLSEYGNKFAAHISPAQGSPKPPPA
ASPGVRAGHVLSSSAGNSAPNSPMAMLHIGSNPERELDDVIDNIMRLDDVLGYINPEMQM
PNTLPLSSSHLNVYSSDPQVTASLVGVTSSSCPADLTQKRELTAESRALAKERQKKDNH
NLIERRRRFNINDRIKELGMLIPKANDLDVRWNKGTILKASVDYIRRMQKDLQKSRELEN
HSRRLEMTNKQLWLRIQELQMQRVHGLPTTSPSGMNMAELAQQVVKQELPSEEGPGEAL
MLGAEVPDPEPLPALPPQAPLPLPTQPPSPFHHLDFSHLSFGGREDEGPPGYPEPLAPG
HGSPFPSLSKKDLMLLDDSLPLASDLLSTMSPEASKASSRRSSFSMEEGDVL (SEQ ID NO:8).

[0178] The term “TFE3” or “transcription factor E3” refers to a protein that activates expression of CD30L in T-cells. The TFE3 protein is encoded by the TFE3 gene. The term “TFE3” may refer to the nucleotide sequence or protein sequence of human TFE3. In embodiments, TFE3 is Entrez 7030, Uniprot P19532, RefSeq NM_001282142.1, RefSeq NM_006521.5, RefSeq NP_001269071.1, or RefSeq NP_006512.2. In embodiments, the TFE3 has the following amino acid sequence:

MSHAAEPARDGVEASAEGPRAVFVLLLEERRPADSAQLLSLNSLLPESGIVADIELENVLD
PDSFYELKSQPLPLRSSLPLSLQATPATPATLSASSSAGGSRTAMPSSSSSSRVLLRQQL
MRAQAQEQRERRERREQAAAAPFPSPAPASPAISVVGVSAGGHTLSRPPPAQVPREVLKVQ
THLENPTRYHLQQARRQQVKQYLSTTLGPKLASQALTPPPGPASAQPLPAPEAAHTTGPT
GSAPNSPMALLTIGSSSEKEIDDVIDEISLESSYNDEMLSYLPGGTTGLQLPSTLPVSG
NLLDVYSSQGVATPAITVSNSCPAELPNIKREISETAKALLKERQKKDNHNLIERRRRF
NINDRIKELGTLIPKSSDPEMRWNKGTILKASVDYIRKLQKEQQRSKDLESRQRSLEQAN

RSLQLRIQELELQAQIHGLPVPPTPGLLSLATTASDSLKPEQLDIEEEGRPGAATFHVG
GGPAQNAPHQQPPAPPSDALLDLHFPSDHLGLDLPFHLGLELMEEEEGVVGGLSGGA
LSPLRAASDPLLSSVSPAVSKASSRRSSFSMEEES (SEQ ID NO:9).

[0179] The term “autophagosome” is used in accordance with its plain ordinary meaning and refers to a vesicle that contains a cellular component slated to be degraded by autophagy. In embodiments, autophagosome formation is a multistep process that includes the biogenesis of the phagophore, followed by its elongation and closure. In embodiments, more than 15 autophagy-related ATG proteins, as well as class III PI3 kinases, may be required to construct the autophagosome, including the transmembrane ATG protein ATG9, along with membranes from multiple sources cellular sources.

[0180] “Nucleic acid” refers to nucleotides (e.g., deoxyribonucleotides or ribonucleotides) and polymers thereof in either single-, double- or multiple-stranded form, or complements thereof; or nucleosides (e.g., deoxyribonucleosides or ribonucleosides). In embodiments, “nucleic acid” does not include nucleosides. The terms “polynucleotide,” “oligonucleotide,” “oligo,” or the like refer, in the usual and customary sense, to a linear sequence of nucleotides. Oligonucleotides are typically from about 5, 6, 7, 8, 9, 10, 12, 15, 25, 30, 40, 50 or more nucleotides in length, up to about 100 nucleotides in length. Nucleic acids and polynucleotides are a polymers of any length, including longer lengths, e.g., 200, 300, 500, 1000, 2000, 3000, 5000, 7000, 10,000, etc. In certain embodiments the nucleic acids herein contain phosphodiester bonds. In other embodiments, nucleic acid analogs are included that may have alternate backbones, comprising, e.g., phosphoramidate, phosphorothioate, phosphorodithioate, or O-methylphosphoroamidite linkages (see, Eckstein, *Oligonucleotides and Analogues: A Practical Approach*, Oxford University Press); and peptide nucleic acid backbones and linkages. Other analog nucleic acids include those with positive backbones; non-ionic backbones, and non-ribose backbones, including those described in U.S. Patent Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, *Carbohydrate Modifications in Antisense Research*, Sanghui & Cook, eds. Nucleic acids containing one or more carbocyclic sugars are also included within one definition of nucleic acids. Modifications of the ribose-phosphate backbone may be done for a variety of reasons, e.g., to increase the stability and half-life of such molecules in physiological environments or as probes on a biochip. Mixtures of naturally occurring nucleic acids and analogs can be made; alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs may be made. A residue of a nucleic acid, as referred to

herein, is a monomer of the nucleic acid (e.g., a nucleotide). The term “nucleoside” refers, in the usual and customary sense, to a glycosylamine including a nucleobase and a five-carbon sugar (ribose or deoxyribose). Non limiting examples, of nucleosides include, cytidine, uridine, adenosine, guanosine, thymidine and inosine. Nucleosides may be modified at the base and/or the sugar. The term “nucleotide” refers, in the usual and customary sense, to a single unit of a polynucleotide, i.e., a monomer. Nucleotides can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of polynucleotides contemplated herein include single and double stranded DNA, single and double stranded RNA, and hybrid molecules having mixtures of single and double stranded DNA and RNA. Examples of nucleic acid, e.g., polynucleotides contemplated herein include any types of RNA, e.g., mRNA, siRNA, miRNA, and guide RNA and any types of DNA, genomic DNA, plasmid DNA, and minicircle DNA, and any fragments thereof. The term “duplex” in the context of polynucleotides refers, in the usual and customary sense, to double strandedness. Nucleic acids can be linear or branched. For example, nucleic acids can be a linear chain of nucleotides or the nucleic acids can be branched, e.g., such that the nucleic acids comprise one or more arms or branches of nucleotides. Optionally, the branched nucleic acids are repetitively branched to form higher ordered structures such as dendrimers and the like.

[0181] “Nucleotide,” as used herein, refers to a nucleoside-5'-polyphosphate compound, or a structural analog thereof, which can be incorporated (e.g., partially incorporated as a nucleoside-5'-monophosphate or derivative thereof) by a nucleic acid polymerase to extend a growing nucleic acid chain (such as a primer). Nucleotides may comprise bases such as A, C, G, T, U, or analogues thereof, and may comprise 2, 3, 4, 5, 6, 7, 8, or more phosphates in the phosphate group. Nucleotides may be modified at one or more of the base, sugar, or phosphate group. A nucleotide may have a label or tag attached (a “labeled nucleotide” or “tagged nucleotide”).

[0182] The terms also encompass nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphodiester derivatives including, e.g., phosphoramidate, phosphorodiamidate, phosphorothioate (also known as phosphothioate having double bonded sulfur replacing oxygen in the phosphate), phosphorodithioate, phosphonocarboxylic acids, phosphonocarboxylates, phosphonoacetic acid, phosphonoformic

acid, methyl phosphonate, boron phosphonate, or O-methylphosphoroamidite linkages (see, Eckstein, *Oligonucleotides and Analogues: A Practical Approach*, Oxford University Press) as well as modifications to the nucleotide bases such as in 5-methyl cytidine or

pseudouridine; and peptide nucleic acid backbones and linkages. Other analog nucleic acids

include those with positive backbones; non-ionic backbones, modified sugars, and non-ribose backbones (e.g., phosphorodiamidate morpholino oligos or locked nucleic acids (LNA) as known in the art), including those described in U.S. Patent Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, *Carbohydrate Modifications in Antisense Research*, Sanghui & Cook, eds. Nucleic acids containing one or more carbocyclic sugars are

also included within one definition of nucleic acids. Modifications of the ribose-phosphate backbone may be done for a variety of reasons, e.g., to increase the stability and half-life of such molecules in physiological environments or as probes on a biochip. Mixtures of naturally occurring nucleic acids and analogs can be made; alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs may be made. In embodiments, the internucleotide linkages in DNA are phosphodiester, phosphodiester derivatives, or a combination of both.

[0183] Nucleic acids can include nonspecific sequences. As used herein, the term “nonspecific sequence” refers to a nucleic acid sequence that contains a series of residues that are not designed to be complementary to or are only partially complementary to any other nucleic acid sequence. By way of example, a nonspecific nucleic acid sequence is a sequence of nucleic acid residues that does not function as an inhibitory nucleic acid when contacted with a cell or organism.

[0184] An “antisense nucleic acid” as referred to herein is a nucleic acid (e.g., DNA or RNA molecule) that is complementary to at least a portion of a specific target nucleic acid (e.g., a nucleic acid coding for one or more amino acids corresponding to C277 of human ATP6V1A protein) and is capable of reducing transcription of the target nucleic acid (e.g., mRNA from DNA), reducing the translation of the target nucleic acid (e.g., mRNA), altering transcript splicing (e.g., single stranded morpholino oligo), or interfering with the endogenous activity of the target nucleic acid. See, e.g., Weintraub, *Scientific American*, 262:40 (1990). Typically, synthetic antisense nucleic acids (e.g., oligonucleotides) are generally between 15 and 25 bases in length. Thus, antisense nucleic acids are capable of hybridizing to (e.g., selectively hybridizing to) a target nucleic acid (e.g., a nucleic acid coding for one or more amino acids corresponding to C277 of human ATP6V1A protein). In

embodiments, the antisense nucleic acid hybridizes to the target nucleic acid (e.g., a nucleic acid coding for one or more amino acids corresponding to C277 of human ATP6V1A

protein) *in vitro*. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid (e.g., a nucleic acid coding for one or more amino acids corresponding to C277 of

human ATP6V1A protein) in a cell. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid (e.g., a nucleic acid coding for one or more amino acids corresponding to C277 of human ATP6V1A protein) in an organism. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid (e.g., a nucleic acid coding for one or more amino acids corresponding to C277 of human ATP6V1A protein) under physiological conditions.

Antisense nucleic acids may comprise naturally occurring nucleotides or modified nucleotides such as, e.g., phosphorothioate, methylphosphonate, and -anomeric sugar-phosphate, backbonemodified nucleotides.

[0185] In the cell, the antisense nucleic acids hybridize to the corresponding RNA (e.g., a nucleic acid coding for one or more amino acids corresponding to C277 of human ATP6V1A protein) forming a double-stranded molecule. The antisense nucleic acids interfere with the endogenous behavior of the RNA (e.g., a nucleic acid coding for one or more amino acids corresponding to C277 of human ATP6V1A protein) and inhibit its function relative to the absence of the antisense nucleic acid. Furthermore, the double-stranded molecule may be degraded via the RNAi pathway. The use of antisense methods to inhibit the *in vitro*

translation of genes is well known in the art (Marcus-Sakura, *Anal. Biochem.*, 172:289, (1988)). Further, antisense molecules which bind directly to the DNA may be used.

Antisense nucleic acids may be single or double stranded nucleic acids. Non-limiting examples of antisense nucleic acids include siRNAs (including their derivatives or pre-cursors, such as nucleotide analogs), short hairpin RNAs (shRNA), micro RNAs (miRNA), saRNAs (small activating RNAs) and small nucleolar RNAs (snoRNA) or certain of their derivatives or pre-cursors.

[0186] The term “complement,” as used herein, refers to a nucleotide (e.g., RNA or DNA) or a sequence of nucleotides capable of base pairing with a complementary nucleotide or sequence of nucleotides. As described herein and commonly known in the art the

complementary (matching) nucleotide of adenosine is thymidine and the complementary (matching) nucleotide of guanine is cytosine. Thus, a complement may include a sequence of nucleotides that base pair with corresponding complementary nucleotides of a second nucleic acid sequence. The nucleotides of a complement may partially or completely match

the nucleotides of the second nucleic acid sequence. Where the nucleotides of the complement completely match each nucleotide of the second nucleic acid sequence, the complement forms base pairs with each nucleotide of the second nucleic acid sequence.

Where the nucleotides of the complement partially match the nucleotides of the second

5 nucleic acid sequence only some of the nucleotides of the complement form base pairs with nucleotides of the second nucleic acid sequence. Examples of complementary sequences include coding and a non-coding sequences, wherein the non-coding sequence contains complementary nucleotides to the coding sequence and thus forms the complement of the coding sequence. A further example of complementary sequences are sense and antisense
10 sequences, wherein the sense sequence contains complementary nucleotides to the antisense sequence and thus forms the complement of the antisense sequence.

[0187] As described herein the complementarity of sequences may be partial, in which only some of the nucleic acids match according to base pairing, or complete, where all the nucleic acids match according to base pairing. Thus, two sequences that are complementary to each
15 other, may have a specified percentage of nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region).

[0188] The term “antibody” refers to a polypeptide encoded by an immunoglobulin gene or functional fragments thereof that specifically binds and recognizes an antigen. The
20 recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon, and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively.

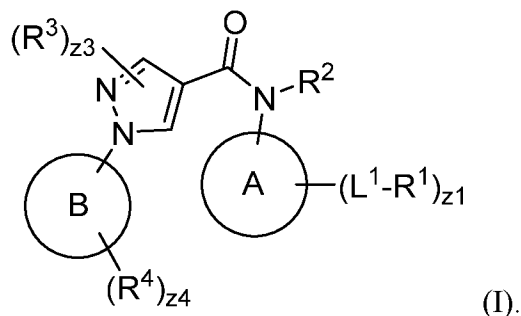
[0189] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one
25 “light” (about 25 kDa) and one “heavy” chain (about 50-70 kDa). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms “variable heavy chain,” “V_H,” or “VH” refer to the
30 variable region of an immunoglobulin heavy chain, including an Fv, scFv, dsFv, or Fab; while the terms “variable light chain,” “V_L,” or “VL” refer to the variable region of an immunoglobulin light chain, including of an Fv, scFv, dsFv, or Fab.

[0190] Examples of antibody functional fragments include, but are not limited to, complete antibody molecules, antibody fragments, such as Fv, single chain Fv (scFv), complementarity determining regions (CDRs), VL (light chain variable region), VH (heavy chain variable region), Fab, F(ab)₂' and any combination of those or any other functional portion of an immunoglobulin peptide capable of binding to target antigen (see, e.g., FUNDAMENTAL IMMUNOLOGY (Paul ed., 4th ed. 2001). As appreciated by one of skill in the art, various antibody fragments can be obtained by a variety of methods, for example, digestion of an intact antibody with an enzyme, such as pepsin; or de novo synthesis. Antibody fragments are often synthesized de novo either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, includes antibody fragments either produced by the modification of whole antibodies, or those synthesized de novo using recombinant DNA methodologies (e.g., single chain Fv) or those identified using phage display libraries (see, e.g., McCafferty *et al.*, (1990) *Nature* 348:552). The term "antibody" also includes bivalent or bispecific molecules, diabodies, triabodies, and tetrabodies. Bivalent and bispecific molecules are described in, e.g., Kostelny *et al.* (1992) *J. Immunol.* 148:1547, Pack and Pluckthun (1992) *Biochemistry* 31:1579, Hollinger *et al.* (1993), *PNAS. USA* 90:6444, Gruber *et al.* (1994) *J. Immunol.* 152:5368, Zhu *et al.* (1997) *Protein Sci.* 6:781, Hu *et al.* (1996) *Cancer Res.* 56:3055, Adams *et al.* (1993) *Cancer Res.* 53:4026, and McCartney, *et al.* (1995) *Protein Eng.* 8:301.

[0191] The term "irreversible covalent bond" is used in accordance with its plain ordinary meaning in the art and refers to the resulting association between atoms or molecules of (e.g., electrophilic chemical moiety and nucleophilic moiety) wherein the probability of dissociation is low. In embodiments, the irreversible covalent bond does not easily dissociate under normal biological conditions. In embodiments, the irreversible covalent bond is formed through a chemical reaction between two species (e.g., electrophilic chemical moiety and cysteine).

II. Compounds

[0192] In an aspect is provided a compound, or a pharmaceutically acceptable salt thereof, having the formula:



[0193] Ring A is a phenyl or 5 to 6 membered heteroaryl.

[0194] Ring B is a phenyl or 5 to 6 membered heteroaryl.

[0195] L^1 is independently a bond, $-S(O)_{2-}$, $-N(R^5)-$, $-O-$, $-S-$, $-C(O)-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)-$, $-N(R^5)C(O)NH-$, $-NHC(O)N(R^5)-$, $-C(O)O-$, $-OC(O)-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0196] R^5 is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, 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.

[0197] R^1 is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-SO_{nl}R^{1D}$, $-SO_{vl}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{ml}$, $-NR^{1A}R^{1B}$, $-C(O)R^{1C}$, $-C(O)OR^{1C}$, $-C(O)NR^{1A}R^{1B}$, $-OR^{1D}$, $-NR^{1A}SO_2R^{1D}$, $-NR^{1A}C(O)R^{1C}$, $-NR^{1A}C(O)OR^{1C}$, $-NR^{1A}OR^{1C}$, $-N_3$, E, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent $-L^1-R^1$ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0198] E is an electrophilic moiety.

[0199] R² is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0200] R³ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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.

[0201] R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R⁴ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0202] R^{1A}, R^{1B}, R^{1C}, and R^{1D} are independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,

substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

5 [0203] X^1 is independently -F, -Cl, -Br, or -I.

[0204] n_1 is independently an integer from 0 to 4.

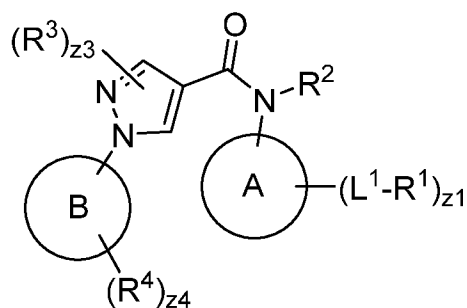
[0205] m_1 and v_1 are independently 1 or 2.

[0206] z_1 is independently an integer from 0 to 5.

[0207] z_3 is independently an integer from 0 to 2.

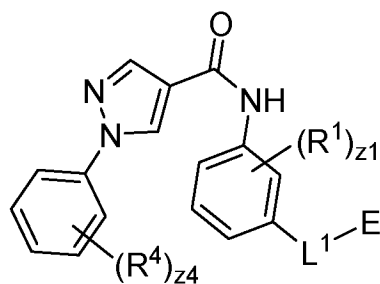
10 [0208] z_4 is independently an integer from 0 to 5.

[0209] In an aspect is provided a compound having the formula:



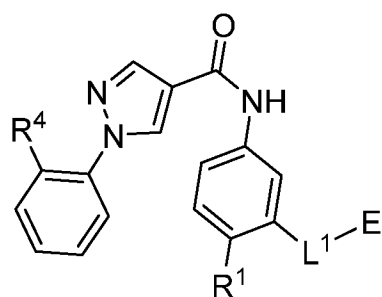
(I). Ring A, Ring B, L^1 , R^1 , R^2 , R^3 , z_3 , R^4 , and z_4 are as described herein, including in embodiments.

[0210] In embodiments, the compound has the formula:



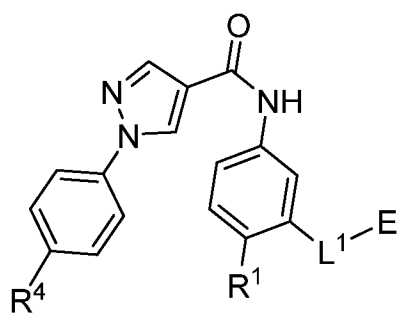
15 (II). L^1 , E, R^1 , z_1 , R^4 , and z_4 are as described herein, including in embodiments.

[0211] In embodiments, the compound has the formula:



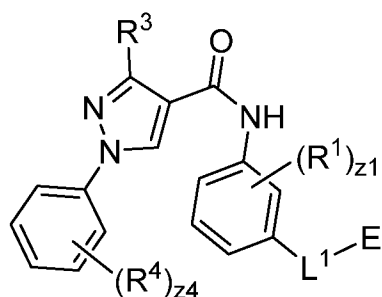
(III). L^1 , E, R^1 , and R^4 are as described herein, including in embodiments.

[0212] In embodiments, the compound has the formula:



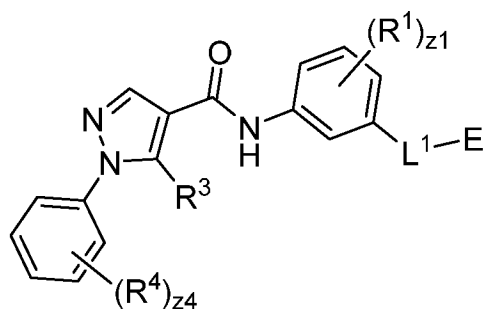
(IV). L^1 , E, R^1 , and R^4 are as described herein, including in
5 embodiments.

[0213] In embodiments, the compound has the formula:



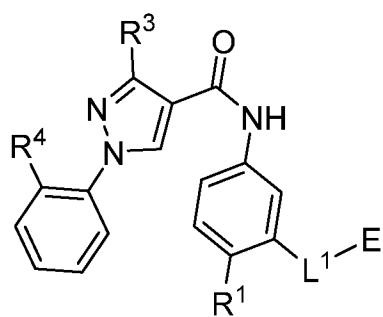
(V). L^1 , E, R^1 , z_1 , R^3 , R^4 , and z_4 are as described herein,
including in embodiments.

[0214] In embodiments, the compound has the formula:



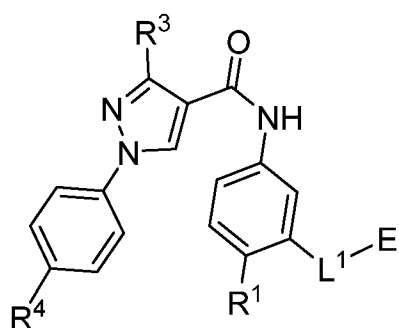
(VI). L^1 , E, R^1 , z_1 , R^3 , R^4 , and z_4 are as described
10 herein, including in embodiments.

[0215] In embodiments, the compound has the formula:



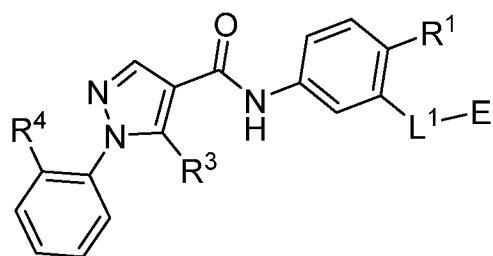
(VII). L^1 , E, R^1 , R^3 , and R^4 are as described herein, including in embodiments.

[0216] In embodiments, the compound has the formula:



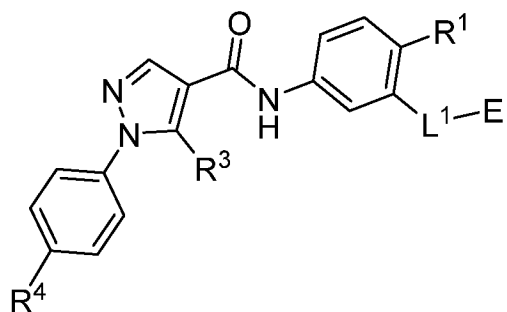
(VIII). L^1 , E, R^1 , R^3 , and R^4 are as described herein, including in embodiments.

[0217] In embodiments, the compound has the formula:



(IX). L^1 , E, R^1 , R^3 , and R^4 are as described herein, including in embodiments.

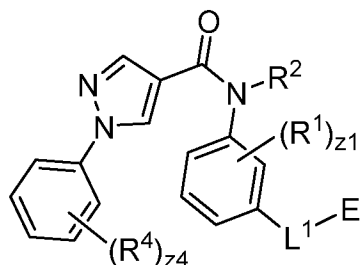
[0218] In embodiments, the compound has the formula:



(X). L^1 , E, R^1 , R^3 , and R^4 are as described herein,

including in embodiments.

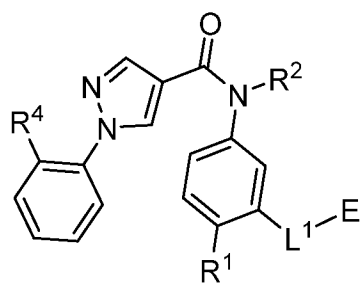
[0219] In embodiments, the compound has the formula:



(XI). L^1 , E, R^1 , $z1$, R^2 , R^4 , and $z4$ are as described herein,

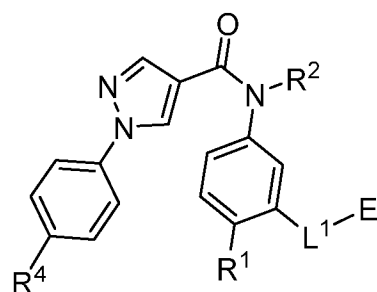
- 5 including in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

[0220] In embodiments, the compound has the formula:



- 10 (XII). L^1 , E, R^1 , R^2 , and R^4 are as described herein, including in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

- 15 [0221] In embodiments, the compound has the formula:

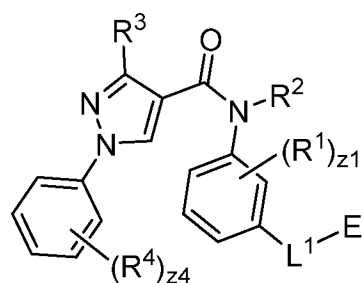


(XIII). L^1 , E, R^1 , R^2 , and R^4 are as described herein, including

in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is

5 independently C_3 - C_6 cycloalkyl.

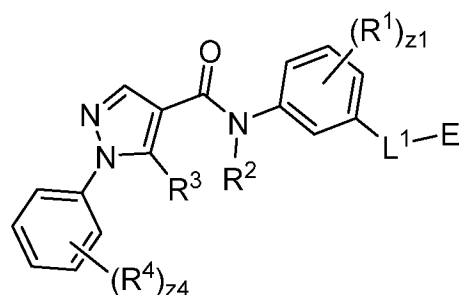
[0222] In embodiments, the compound has the formula:



(XIV). L^1 , E, R^1 , z_1 , R^2 , R^3 , R^4 , and z_4 are as described herein,

including in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In
embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is
10 independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted
ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

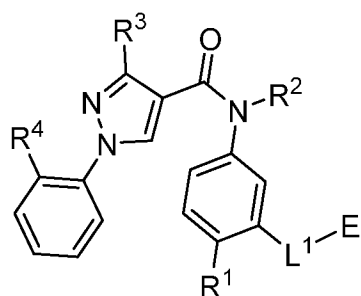
[0223] In embodiments, the compound has the formula:



(XV). L^1 , E, R^1 , z_1 , R^2 , R^3 , R^4 , and z_4 are as described

herein, including in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In
15 embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is
independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted
ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

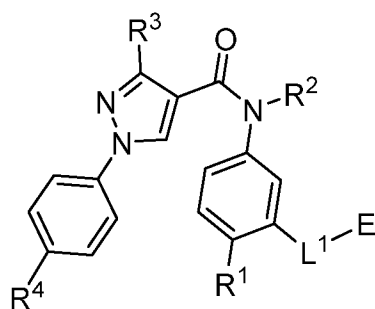
[0224] In embodiments, the compound has the formula:



(XVI). L^1 , E, R^1 , R^2 , R^3 , and R^4 are as described herein,

including in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In
embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is
5 independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted
ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

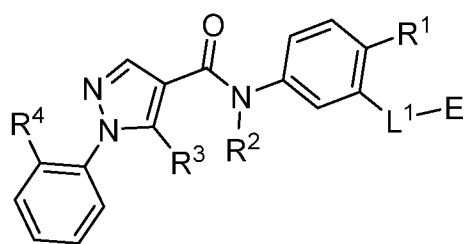
[0225] In embodiments, the compound has the formula:



(XVII). L^1 , E, R^1 , R^2 , R^3 , and R^4 are as described herein,

including in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In
10 embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is
independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted
ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

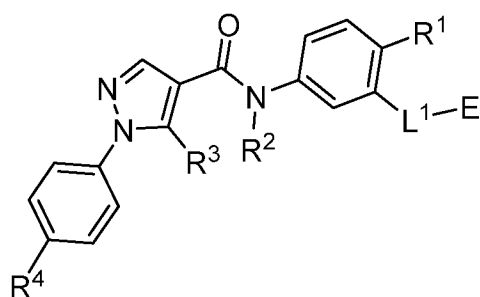
[0226] In embodiments, the compound has the formula:



(XVIII). L^1 , E, R^1 , R^2 , R^3 , and R^4 are as described

15 herein, including in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In
embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is
independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted
ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

[0227] In embodiments, the compound has the formula:



(XIX). L¹, E, R¹, R², R³, and R⁴ are as described

herein, including in embodiments. In embodiments, R² is independently C₁-C₆ alkyl. In
embodiments, R² is independently unsubstituted C₁-C₄ alkyl. In embodiments, R² is
5 independently unsubstituted methyl. In embodiments, R² is independently unsubstituted
ethyl. In embodiments, R² is independently C₃-C₆ cycloalkyl.

[0228] In embodiments, L¹ is independently a bond, -S(O)₂-, -N(R⁵)-, -O-, -S-, -C(O)-,
-C(O)N(R⁵)-, -N(R⁵)C(O)-, -N(R⁵)C(O)NH-, -NHC(O)N(R⁵)-, -C(O)O-, -OC(O)-, substituted
(e.g., substituted with at least one substituent group, size-limited substituent group, or lower
10 substituent group) or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted
(e.g., substituted with at least one substituent group, size-limited substituent group, or lower
substituent group) or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4
to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at
least one substituent group, size-limited substituent group, or lower substituent group) or
15 unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted
with at least one substituent group, size-limited substituent group, or lower substituent group)
or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6
membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least
one substituent group, size-limited substituent group, or lower substituent group) or
20 unsubstituted arylene (e.g., C₆-C₁₀ or phenylene), or substituted (e.g., substituted with at least
one substituent group, size-limited substituent group, or lower substituent group) or
unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0229] In embodiments, a substituted L¹ (e.g., substituted alkylene, substituted
heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted
25 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 L¹ is
substituted with a plurality of groups selected from substituent groups, size-limited

substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when L^1 is substituted, it is substituted with at least one substituent group. In embodiments, when L^1 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when L^1 is substituted, it is substituted with at least one lower substituent group.

[0230] In embodiments, L^1 is independently a bond, $-S(O)_2-$, $-NH-$, $-O-$, $-S-$, $-C(O)NH-$, $-NHC(O)-$, $-NHC(O)NH-$, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene.

[0231] In embodiments, L^1 is independently $-S(O)_2-$, $-NH-$, or substituted or unsubstituted 5 to 6 membered heterocycloalkylene.

[0232] In embodiments, L^1 is independently $-S(O)_2-$, $-NH-$, unsubstituted pyrrolidinylene, unsubstituted piperidinylene, or unsubstituted piperazinylene.

[0233] In embodiments, L^1 is independently $-NH-$.

[0234] In embodiments, L^1 is independently $-N(R^5)-$, and R^5 is as described herein, including in embodiments. In embodiments, L^1 is independently $-N(R^5)-$, and R^5 is independently hydrogen or unsubstituted alkyl. In embodiments, L^1 is independently $-N(R^5)-$, and R^5 is independently hydrogen or substituted or unsubstituted alkyl. In embodiments, L^1 is independently $-N(R^5)-$, and R^5 is independently hydrogen or unsubstituted alkyl. In embodiments, L^1 is independently $-N(R^5)-$, and R^5 is independently hydrogen or unsubstituted C_1 - C_4 alkyl. In embodiments, L^1 is independently $-N(R^5)-$, and R^5 is independently hydrogen or unsubstituted methyl.

[0235] In embodiments, R^1 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, $-N_3$, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to

6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0236] In embodiments, a substituted R¹ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R¹ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R¹ is substituted, it is substituted with at least one substituent group. In embodiments, when R¹ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R¹ is substituted, it is substituted with at least one lower substituent group.

[0237] In embodiments, R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0238] In embodiments, two adjacent R¹ substituents are joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0239] In embodiments, two adjacent R¹ substituents are joined to form a substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0240] In embodiments, a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by joining two adjacent R¹ substituents is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by two adjacent R¹ substituents is substituted, it is substituted with at least one substituent group. In embodiments, when a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by two adjacent R¹ substituents is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by two adjacent R¹ substituents is substituted, it is substituted with at least one lower substituent group.

[0241] In embodiments, R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -CI₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0242] In embodiments, R¹ is independently halogen. In embodiments, R¹ is independently -F. In embodiments, R¹ is independently -Cl. In embodiments, R¹ is independently -Br. In embodiments, R¹ is independently -I.

[0243] In embodiments, R¹ is independently halogen.

[0244] In embodiments, R¹ is -F.

[0245] In embodiments, R¹ is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OCX¹₃, -OCH₂X¹, -OCHX¹₂, -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, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹ is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OH, -SH, -OCX¹₃, -OCHX¹₂, -OCH₂X¹, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R¹ is independently halogen, -CF₃, -CHF₂, -CH₂F, -OH, -SH, -OCF₃, -OCHF₂, -OCH₂F, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R¹ is substituted or unsubstituted C₁-C₆ alkyl. In embodiments, R¹ is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R¹ is substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹ is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹ is substituted or unsubstituted phenyl. In embodiments, R¹ is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹ is independently halogen. In embodiments, R¹ is independently -CX¹₃. In embodiments, R¹ is independently -CHX¹₂. In embodiments, R¹ is independently -CH₂X¹. In embodiments, R¹ is independently -OCX¹₃. In embodiments, R¹ is independently -OCH₂X¹. In embodiments, R¹ is independently -OCHX¹₂. In embodiments, R¹ is independently -OCH₂X¹. In embodiments, R¹ is independently -CN. In embodiments, R¹ is independently -SO_mR^{1D}. In embodiments, R¹ is independently -SO_{v1}NR^{1A}R^{1B}. In embodiments, R¹ is independently -NHC(O)NR^{1A}R^{1B}. In embodiments, R¹ is independently -N(O)_{m1}. In embodiments, R¹ is independently -NR^{1A}R^{1B}. In embodiments, R¹ is independently -C(O)R^{1C}. In embodiments, R¹ is independently

-C(O)OR^{1C}. In embodiments, R¹ is independently -C(O)NR^{1A}R^{1B}. In embodiments, R¹ is independently -OR^{1D}. In embodiments, R¹ is independently -NR^{1A}SO₂R^{1D}. In embodiments, R¹ is independently -NR^{1A}C(O)R^{1C}. In embodiments, R¹ is independently -NR^{1A}C(O)OR^{1C}. In embodiments, R¹ is independently -NR^{1A}OR^{1C}. In embodiments, R¹ is independently -OH.

5 In embodiments, R¹ is independently -NH₂. In embodiments, R¹ is independently -COOH. In embodiments, R¹ is independently -CONH₂. In embodiments, R¹ is independently -NO₂. In embodiments, R¹ is independently -SH. In embodiments, R¹ is independently -CF₃. In embodiments, R¹ is independently -CHF₂. In embodiments, R¹ is independently -CH₂F. In embodiments, R¹ is independently -OCF₃. In embodiments, R¹ is independently -OCH₂F. In

10 embodiments, R¹ is independently -OCHF₂. In embodiments, R¹ is independently -OCH₃. In embodiments, R¹ is independently -OCH₂CH₃. In embodiments, R¹ is independently -OCH₂CH₂CH₃. In embodiments, R¹ is independently -OCH(CH₃)₂. In embodiments, R¹ is independently -OC(CH₃)₃. In embodiments, R¹ is independently -SCH₃. In embodiments, R¹ is independently -SCH₂CH₃. In embodiments, R¹ is independently -SCH₂CH₂CH₃. In

15 embodiments, R¹ is independently -SCH(CH₃)₂. In embodiments, R¹ is independently -SC(CH₃)₃. In embodiments, R¹ is independently -CH₃. In embodiments, R¹ is independently -CH₂CH₃. In embodiments, R¹ is independently -CH₂CH₂CH₃. In embodiments, R¹ is independently -CH(CH₃)₂. In embodiments, R¹ is independently -C(CH₃)₃. In embodiments, R¹ is independently -F. In embodiments, R¹ is independently

20 -Cl. In embodiments, R¹ is independently -Br. In embodiments, R¹ is independently -I. In embodiments, R¹ is independently unsubstituted methyl. In embodiments, R¹ is independently unsubstituted ethyl. In embodiments, R¹ is independently unsubstituted propyl. In embodiments, R¹ is independently unsubstituted n-propyl. In embodiments, R¹ is independently unsubstituted isopropyl. In embodiments, R¹ is independently unsubstituted

25 butyl. In embodiments, R¹ is independently unsubstituted n-butyl. In embodiments, R¹ is independently unsubstituted isobutyl. In embodiments, R¹ is independently unsubstituted tert-butyl. In embodiments, R¹ is independently unsubstituted pentyl.

[0246] In embodiments, two adjacent -L¹-R¹ substituents are joined to form a substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower

30 substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g.,

substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0247] In embodiments, a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by joining two adjacent -L¹-R¹ substituents is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by two adjacent -L¹-R¹ substituents is substituted, it is substituted with at least one substituent group. In embodiments, when a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by two adjacent -L¹-R¹ substituents is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by two adjacent -L¹-R¹ substituents is substituted, it is substituted with at least one lower substituent group.

[0248] In embodiments, two adjacent -L¹-R¹ substituents are joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, two adjacent -L¹-R¹ substituents are joined to form a substituted or unsubstituted cycloalkyl. In embodiments, two adjacent -L¹-R¹ substituents are joined to form a substituted or unsubstituted heterocycloalkyl. In embodiments, two adjacent -L¹-R¹ substituents are joined to form a substituted or unsubstituted aryl. In embodiments, two adjacent R¹ substituents are joined to form a substituted or unsubstituted heteroaryl. In embodiments, two adjacent -L¹-R¹ substituents are joined to form a substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, two adjacent -L¹-R¹ substituents are joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, two adjacent -L¹-R¹ substituents are joined to form a substituted or unsubstituted C₆-C₁₀ aryl. In embodiments,

two adjacent $-L^1-R^1$ substituents are joined to form a substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, two adjacent R^1 substituents are joined to form a substituted or unsubstituted C_3-C_6 cycloalkyl. In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form a substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form a substituted or unsubstituted phenyl. In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form a substituted or unsubstituted 5 to 6 membered heteroaryl. It will be understood that when two adjacent L^1 substituents are a bond, two adjacent $-L^1-R^1$ substituents that are joined are equivalent to two adjacent $-R^1$ substituents being joined and may be depicted as such in a formula.

[0249] In embodiments, R^{1A} , R^{1B} , R^{1C} , and R^{1D} are independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, 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.

[0250] In embodiments, R^{1A} is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),

substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0251] In embodiments, a substituted R^{1A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{1A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1A} is substituted, it is substituted with at least one lower substituent group.

[0252] In embodiments, R^{1A} is independently hydrogen. In embodiments, R^{1A} is independently -CX^{1A}₃. In embodiments, R^{1A} is independently -CHX^{1A}₂. In embodiments, R^{1A} is independently -CH₂X^{1A}. In embodiments, R^{1A} is independently -CN. In embodiments, R^{1A} is independently -COOH. In embodiments, R^{1A} is independently -CONH₂. X^{1A} is independently -F, -Cl, -Br, or -I.

[0253] In embodiments, R^{1A} is independently substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R^{1A} is independently substituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R^{1A} is independently unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R^{1A} is independently unsubstituted methyl. In embodiments, R^{1A} is independently unsubstituted ethyl. In embodiments, R^{1A} is independently unsubstituted propyl. In embodiments, R^{1A} is independently unsubstituted isopropyl. In embodiments, R^{1A} is independently unsubstituted tert-butyl. In embodiments, R^{1A} is 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^{1A} is independently substituted 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^{1A} is independently 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).

membered, or 4 to 5 membered). In embodiments, R^{1A} is independently substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, R^{1A} is independently substituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, R^{1A} is independently unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In

5 embodiments, R^{1A} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1A} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1A} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4

10 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1A} is independently substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl). In embodiments, R^{1A} is independently substituted aryl (e.g., C₆-C₁₀ or phenyl). In embodiments, R^{1A} is independently unsubstituted aryl (e.g., C₆-C₁₀ or phenyl). In embodiments, R^{1A} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9

15 membered, or 5 to 6 membered). In embodiments, R^{1A} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1A} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0254] In embodiments, R^{1B} is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃,
 20 -CI₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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,
 -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂,
 -OCHI₂, substituted (e.g., substituted with at least one substituent group, size-limited
 25 substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-
 C₄, or C₁-C₂), substituted (e.g., substituted with at least one substituent group, size-limited
 substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),
 substituted (e.g., substituted with at least one substituent group, size-limited substituent
 30 group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or
 C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited
 substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),

substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0255] In embodiments, a substituted R^{1B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{1B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1B} is substituted, it is substituted with at least one lower substituent group.

[0256] In embodiments, R^{1B} is independently hydrogen. In embodiments, R^{1B} is independently -CX^{1B}₃. In embodiments, R^{1B} is independently -CHX^{1B}₂. In embodiments, R^{1B} is independently -CH₂X^{1B}. In embodiments, R^{1B} is independently -CN. In embodiments, R^{1B} is independently -COOH. In embodiments, R^{1B} is independently -CONH₂. X^{1B} is independently -F, -Cl, -Br, or -I.

[0257] In embodiments, R^{1B} is independently substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R^{1B} is independently substituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R^{1B} is independently unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R^{1B} is independently unsubstituted methyl. In embodiments, R^{1B} is independently unsubstituted ethyl. In embodiments, R^{1B} is independently unsubstituted propyl. In embodiments, R^{1B} is independently unsubstituted isopropyl. In embodiments, R^{1B} is independently unsubstituted tert-butyl. In embodiments, R^{1B} is 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^{1B} is independently substituted 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^{1B} is independently 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^{1B} is independently substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, R^{1B} is independently substituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, R^{1B} is independently unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In
5 embodiments, R^{1B} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1B} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1B} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4
10 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1B} is independently substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl). In embodiments, R^{1B} is independently substituted aryl (e.g., C₆-C₁₀ or phenyl). In embodiments, R^{1B} is independently unsubstituted aryl (e.g., C₆-C₁₀ or phenyl). In embodiments, R^{1B} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
15 membered, or 5 to 6 membered). In embodiments, R^{1B} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1B} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0258] In embodiments, R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may be
20 joined to form a substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6
25 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered).

[0259] In embodiments, a substituted heterocycloalkyl formed by joining R^{1A} and R^{1B}
30 bonded to the same nitrogen is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted heterocycloalkyl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited

substituent group, and/or lower substituent group may optionally be different. In
embodiments, when a substituted heterocycloalkyl formed by joining R^{1A} and R^{1B} bonded to
the same nitrogen is substituted, it is substituted with at least one substituent group. In
embodiments, when a substituted heterocycloalkyl formed by joining R^{1A} and R^{1B} bonded to
5 the same nitrogen is substituted, it is substituted with at least one size-limited substituent
group. In embodiments, when a substituted heterocycloalkyl formed by joining R^{1A} and R^{1B}
bonded to the same nitrogen is substituted, it is substituted with at least one lower substituent
group.

[0260] In embodiments, R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may be
10 joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6
membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1A}
and R^{1B} substituents bonded to the same nitrogen atom may be joined to form a substituted
heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5
membered, or 5 to 6 membered). In embodiments, R^{1A} and R^{1B} substituents bonded to the
15 same nitrogen atom may be joined to form an unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered).

[0261] In embodiments, R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may be
joined to form a substituted (e.g., substituted with at least one substituent group, size-limited
substituent group, or lower substituent group) or unsubstituted heteroaryl (e.g., 5 to 10
20 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1A} and R^{1B}
substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl
(e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1A} and
 R^{1B} substituents bonded to the same nitrogen atom may be joined to form an unsubstituted
heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0262] In embodiments, a substituted heteroaryl formed by joining R^{1A} and R^{1B} bonded to
25 the same nitrogen is substituted with at least one substituent group, size-limited substituent
group, or lower substituent group; wherein if the substituted heteroaryl 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
30 substituent group may optionally be different. In embodiments, when a substituted heteroaryl
formed by joining R^{1A} and R^{1B} bonded to the same nitrogen is substituted, it is substituted
with at least one substituent group. In embodiments, when a substituted heteroaryl formed by

joining R^{1A} and R^{1B} bonded to the same nitrogen is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a substituted heteroaryl formed by joining R^{1A} and R^{1B} bonded to the same nitrogen is substituted, it is substituted with at least one lower substituent group.

5 **[0263]** In embodiments, R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may be joined to form a substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1A} and R^{1B} substituents bonded to
10 the same nitrogen atom may be joined to form an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0264] In embodiments, R^{1C} is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$,
15 $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted (e.g., substituted with at least one substituent group, size-limited
20 substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted (e.g., substituted with at least one substituent group, size-limited
25 substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or
30 substituted (e.g., substituted with at least one substituent group, 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).

[0265] In embodiments, a substituted R^{1C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{1C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1C} is substituted, it is substituted with at least one lower substituent group.

[0266] In embodiments, R^{1C} is independently hydrogen. In embodiments, R^{1C} is independently $-CX^{1C}_3$. In embodiments, R^{1C} is independently $-CHX^{1C}_2$. In embodiments, R^{1C} is independently $-CH_2X^{1C}$. In embodiments, R^{1C} is independently $-CN$. In embodiments, R^{1C} is independently $-COOH$. In embodiments, R^{1C} is independently $-CONH_2$. X^{1C} is independently $-F$, $-Cl$, $-Br$, or $-I$.

[0267] In embodiments, R^{1C} is independently substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In embodiments, R^{1C} is independently substituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In embodiments, R^{1C} is independently unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2). In embodiments, R^{1C} is independently unsubstituted methyl. In embodiments, R^{1C} is independently unsubstituted ethyl. In embodiments, R^{1C} is independently unsubstituted propyl. In embodiments, R^{1C} is independently unsubstituted isopropyl. In embodiments, R^{1C} is independently unsubstituted tert-butyl. In embodiments, R^{1C} is 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^{1C} is independently substituted 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^{1C} is independently substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6). In embodiments, R^{1C} is independently substituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6). In embodiments, R^{1C} is independently unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6). In embodiments, R^{1C} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In

embodiments, R^{1C} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1C} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1C} is

5 independently substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl). In embodiments, R^{1C} is independently substituted aryl (e.g., C₆-C₁₀ or phenyl). In embodiments, R^{1C} is independently unsubstituted aryl (e.g., C₆-C₁₀ or phenyl). In embodiments, R^{1C} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1C} is independently substituted

10 heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1C} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0268] In embodiments, R^{1D} is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -CI₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCI₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or

30 substituted (e.g., substituted with at least one substituent group, 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).

[0269] In embodiments, a substituted R^{1D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{1D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1D} is substituted, it is substituted with at least one lower substituent group.

[0270] In embodiments, R^{1D} is independently hydrogen. In embodiments, R^{1D} is independently $-CX^{1D}_3$. In embodiments, R^{1D} is independently $-CHX^{1D}_2$. In embodiments, R^{1D} is independently $-CH_2X^{1D}$. In embodiments, R^{1D} is independently $-CN$. In embodiments, R^{1D} is independently $-COOH$. In embodiments, R^{1D} is independently $-CONH_2$. X^{1D} is independently $-F$, $-Cl$, $-Br$, or $-I$.

[0271] In embodiments, R^{1D} is independently substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2). In embodiments, R^{1D} is independently substituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2). In embodiments, R^{1D} is independently unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2). In embodiments, R^{1D} is independently unsubstituted methyl. In embodiments, R^{1D} is independently unsubstituted ethyl. In embodiments, R^{1D} is independently unsubstituted propyl. In embodiments, R^{1D} is independently unsubstituted isopropyl. In embodiments, R^{1D} is independently unsubstituted tert-butyl. In embodiments, R^{1D} is 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^{1D} is independently substituted 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^{1D} is independently substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6). In embodiments, R^{1D} is independently substituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6). In embodiments, R^{1D} is independently unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6). In embodiments, R^{1D} is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In

embodiments, R^{1D} is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1D} is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R^{1D} is

5 independently substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl). In embodiments, R^{1D} is independently substituted aryl (e.g., C_6 - C_{10} or phenyl). In embodiments, R^{1D} is independently unsubstituted aryl (e.g., C_6 - C_{10} or phenyl). In embodiments, R^{1D} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1D} is independently substituted

10 heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{1D} is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0272] In embodiments, R^1 is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$,

15 $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NH SO_2H$, $-NHC=(O)H$, $-NHC(O)OH$, $-NHOH$, R^{10} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{10} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{10} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{10} -substituted or unsubstituted

20 heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{10} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or R^{10} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^1 is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$,

25 $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NH SO_2H$, $-NHC=(O)H$, $-NHC(O)OH$, $-NHOH$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered,

30 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), 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 $-I$. In embodiments, R^1 is independently unsubstituted methyl. In embodiments, R^1 is independently unsubstituted ethyl. In

embodiments, R^1 is independently R^{10} -substituted 2 membered heteroalkyl. In embodiments, R^1 is independently R^{10} -substituted methoxy.

[0273] In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form a R^{10} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{10} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{10} -substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or R^{10} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form an unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form a R^{10} -substituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6). In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form a R^{10} -substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form a R^{10} -substituted aryl (e.g., C_6-C_{10} or phenyl). In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form a R^{10} -substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form an unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6). In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form an unsubstituted aryl (e.g., C_6-C_{10} or phenyl). In embodiments, two adjacent $-L^1-R^1$ substituents are joined to form an unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0274] R^{10} is independently oxo, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-N_3$, R^{11} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{11} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{11} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{11} -substituted or

unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R¹¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or R¹¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁰ is independently -F, -Cl, -Br, or -I. In embodiments, R¹⁰ is independently unsubstituted methyl. In embodiments, R¹⁰ is independently unsubstituted ethyl.

[0275] R¹¹ is independently oxo, halogen, -CX¹¹₃, -CHX¹¹₂, -CH₂X¹¹, -OCX¹¹₃, -OCH₂X¹¹, -OCHX¹¹₂, -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, -N₃, R¹²-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R¹²-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), R¹²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R¹²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R¹²-substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or R¹²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹¹ is independently -F, -Cl, -Br, or -I. In embodiments, R¹¹ is independently unsubstituted methyl. In embodiments, R¹¹ is independently unsubstituted ethyl.

[0276] R¹² is independently oxo, halogen, -CX¹²₃, -CHX¹²₂, -CH₂X¹², -OCX¹²₃, -OCH₂X¹², -OCHX¹²₂, -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, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹² is independently -F, -Cl, -Br, or -I. In embodiments, R¹² is independently unsubstituted methyl. In embodiments, R¹² is independently unsubstituted ethyl.

[0277] In embodiments, n1 is 0. In embodiments, n1 is 1. In embodiments, n1 is 2. In embodiments, n1 is 3. In embodiments, n1 is 4. In embodiments, m1 is 1. In embodiments, m1 is 2. In embodiments, v1 is 1. In embodiments, v1 is 2.

[0278] In embodiments, z1 is independently an integer from 0 to 4. In embodiments, z1 is 0. In embodiments, z1 is 1. In embodiments, z1 is 2. In embodiments, z1 is 3. In embodiments, z1 is 4. In embodiments, z1 is 5.

[0279] In embodiments, R² is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0280] In embodiments, a substituted R² (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R² is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group

may optionally be different. In embodiments, when R^2 is substituted, it is substituted with at least one substituent group. In embodiments, when R^2 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^2 is substituted, it is substituted with at least one lower substituent group.

- 5 **[0281]** In embodiments, R^2 is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$,
 10 substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or
 15 unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^2 is independently hydrogen. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently unsubstituted propyl. In embodiments, R^2 is independently unsubstituted n-propyl. In
 20 embodiments, R^2 is independently unsubstituted isopropyl. In embodiments, R^2 is independently unsubstituted butyl. In embodiments, R^2 is independently unsubstituted n-butyl. In embodiments, R^2 is independently unsubstituted isobutyl. In embodiments, R^2 is independently unsubstituted tert-butyl. In embodiments, R^2 is independently unsubstituted pentyl.
- 25 **[0282]** In embodiments, R^2 is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$,
 30 unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0283] In embodiments, R^2 is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0284] In embodiments, R^2 is independently hydrogen. In embodiments, R^2 is independently $-CCl_3$. In embodiments, R^2 is independently $-CBr_3$. In embodiments, R^2 is independently $-CF_3$. In embodiments, R^2 is independently $-Cl_3$. In embodiments, R^2 is independently $-CH_2Cl$. In embodiments, R^2 is independently $-CH_2Br$. In embodiments, R^2 is independently $-CH_2F$. In embodiments, R^2 is independently $-CH_2I$. In embodiments, R^2 is independently $-CHCl_2$. In embodiments, R^2 is independently $-CHBr_2$. In embodiments, R^2 is independently $-CHF_2$. In embodiments, R^2 is independently $-CHI_2$. In embodiments, R^2 is independently unsubstituted C_1 - C_6 alkyl. In embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently unsubstituted propyl. In embodiments, R^2 is independently unsubstituted n-propyl. In embodiments, R^2 is independently unsubstituted isopropyl. In embodiments, R^2 is independently unsubstituted butyl. In embodiments, R^2 is independently unsubstituted n-butyl. In embodiments, R^2 is independently unsubstituted isobutyl. In embodiments, R^2 is independently unsubstituted tert-butyl. In embodiments, R^2 is independently unsubstituted pentyl. In embodiments, R^2 is independently unsubstituted hexyl. In embodiments, R^2 is independently unsubstituted C_3 - C_6 cycloalkyl.

[0285] In embodiments, R^3 and R^4 are independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$,

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.

[0286] In embodiments, R^3 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0287] In embodiments, a substituted R^3 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^3 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^3 is substituted, it is substituted with at least one substituent group. In embodiments, when R^3 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^3 is substituted, it is substituted with at least one lower substituent group.

[0288] In embodiments, R^3 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0289] In embodiments, R^3 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0290] In embodiments, R^3 is independently halogen. In embodiments, R^3 is independently $-F$. In embodiments, R^3 is independently $-Cl$. In embodiments, R^3 is independently $-Br$. In embodiments, R^3 is independently $-I$. In embodiments, R^3 is independently $-CCl_3$. In embodiments, R^3 is independently $-CBr_3$. In embodiments, R^3 is independently $-CF_3$. In embodiments, R^3 is independently $-Cl_3$. In embodiments, R^3 is independently $-CH_2Cl$. In embodiments, R^3 is independently $-CH_2Br$. In embodiments, R^3 is independently $-CH_2F$. In embodiments, R^3 is independently $-CH_2I$. In embodiments, R^3 is independently $-CHCl_2$. In embodiments, R^3 is independently $-CHBr_2$. In embodiments, R^3 is independently $-CHF_2$. In embodiments, R^3 is independently $-CHI_2$. In embodiments, R^3 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^3 is independently unsubstituted methyl. In embodiments, R^3

is independently unsubstituted methyl. In embodiments, R³ is independently unsubstituted ethyl. In embodiments, R³ is independently unsubstituted propyl. In embodiments, R³ is independently unsubstituted n-propyl. In embodiments, R³ is independently unsubstituted isopropyl. In embodiments, R³ is independently unsubstituted butyl. In embodiments, R³ is independently unsubstituted n-butyl. In embodiments, R³ is independently unsubstituted isobutyl. In embodiments, R³ is independently unsubstituted tert-butyl.

[0291] In embodiments, z3 is 0. In embodiments, z3 is 1. In embodiments, z3 is 2.

[0292] In embodiments, R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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); two adjacent R⁴ substituents may optionally be joined to form a substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g.,

C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0293] In embodiments, a substituted R⁴ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R⁴ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R⁴ is substituted, it is substituted with at least one substituent group. In embodiments, when R⁴ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R⁴ is substituted, it is substituted with at least one lower substituent group.

[0294] In embodiments, a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by joining two adjacent R⁴ substituents is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by two adjacent R⁴ substituents is substituted, it is substituted with at least one substituent group. In embodiments, when a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by two adjacent R⁴ substituents is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl formed by two adjacent R⁴ substituents is substituted, it is substituted with at least one lower substituent group.

[0295] In embodiments, R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl,

-OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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.

5 **[0296]** In embodiments, R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or
10 unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0297] In embodiments, R⁴ is independently halogen. In embodiments, R⁴ is independently -F. In embodiments, R⁴ is independently -Cl. In embodiments, R⁴ is independently -Br. In
embodiments, R⁴ is independently -I. In embodiments, R⁴ is independently -OH. In
embodiments, R⁴ is independently unsubstituted C₁-C₄ alkyl. In embodiments, R⁴ is
15 independently unsubstituted methyl. In embodiments, R⁴ is independently unsubstituted ethyl. In embodiments, R⁴ is independently unsubstituted propyl. In embodiments, R⁴ is independently unsubstituted n-propyl. In embodiments, R⁴ is independently unsubstituted isopropyl. In embodiments, R⁴ is independently unsubstituted butyl. In embodiments, R⁴ is independently unsubstituted n-butyl. In embodiments, R⁴ is independently unsubstituted
20 isobutyl. In embodiments, R⁴ is independently unsubstituted tert-butyl.

[0298] In embodiments, R⁴ is independently halogen.

[0299] In embodiments, R⁴ is independently -F.

[0300] In embodiments, R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂,
25 -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4
30 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6

membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0301] In embodiments, R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0302] In embodiments, z₄ is independently an integer from 0 to 5.

[0303] In embodiments, z₄ is 0. In embodiments, z₄ is 1. In embodiments, z₄ is 2. In embodiments, z₄ is 3. In embodiments, z₄ is 4. In embodiments, z₄ is 5.

[0304] In embodiments, R⁵ is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g.,

substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

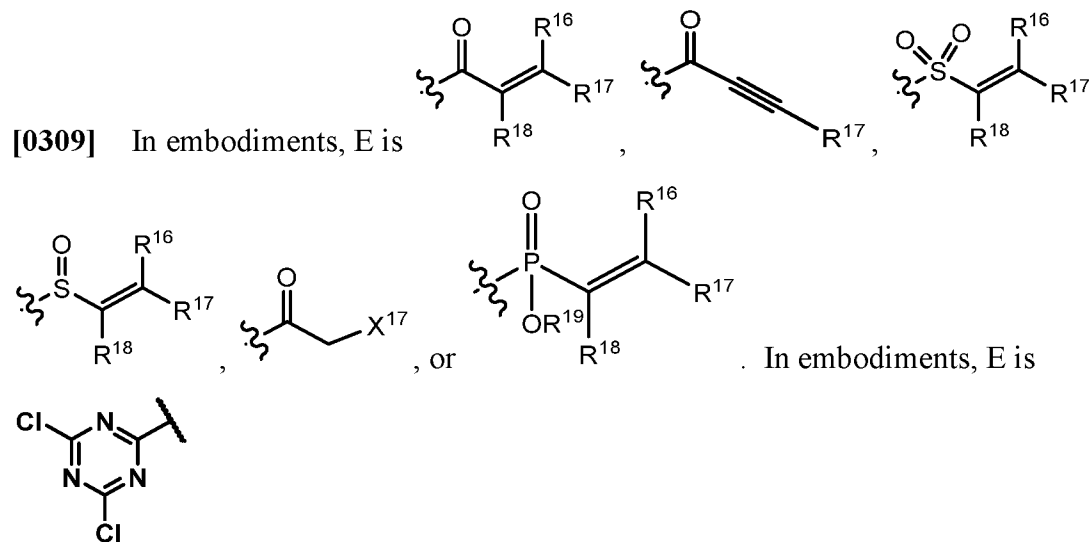
[0305] In embodiments, a substituted R⁵ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R⁵ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R⁵ is substituted, it is substituted with at least one substituent group. In embodiments, when R⁵ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R⁵ is substituted, it is substituted with at least one lower substituent group.

[0306] In embodiments, R⁵ is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R⁵ is independently hydrogen. In embodiments, R⁵ is independently unsubstituted methyl. In embodiments, R⁵ is independently unsubstituted ethyl. In embodiments, R⁵ is independently unsubstituted propyl. In embodiments, R⁵ is independently unsubstituted n-propyl. In embodiments, R⁵ is independently unsubstituted isopropyl. In embodiments, R⁵ is independently unsubstituted butyl. In embodiments, R⁵ is independently unsubstituted n-butyl. In embodiments, R⁵ is independently unsubstituted isobutyl. In embodiments, R⁵ is

independently unsubstituted tert-butyl. In embodiments, R⁵ is independently unsubstituted pentyl.

[0307] In embodiments, R⁵ is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0308] In embodiments, R⁵ is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).



[0310] R^{16} is independently hydrogen, halogen, $-CX^{16}_3$, $-CHX^{16}_2$, $-CH_2X^{16}$, $-CN$, $-SO_{n16}R^{16A}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHN R^{16A}R^{16B}$, $-ONR^{16A}R^{16B}$, $-NHC(O)NHN R^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16A}$, $-C(O)-OR^{16A}$, $-C(O)NR^{16A}R^{16B}$, $-OR^{16A}$, $-NR^{16A}SO_2R^{16B}$, $-NR^{16A}C(O)R^{16B}$, $-NR^{16A}C(O)OR^{16B}$, $-NR^{16A}OR^{16B}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, $-OCH_2X^{16}$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0311] R^{17} is independently hydrogen, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-CH_2X^{17}$, $-CN$, $-SO_{n17}R^{17A}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHN R^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC(O)NHN R^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17A}$, $-C(O)-OR^{17A}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17A}$, $-NR^{17A}SO_2R^{17B}$, $-NR^{17A}C(O)R^{17B}$, $-NR^{17A}C(O)OR^{17B}$, $-NR^{17A}OR^{17B}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, $-OCH_2X^{17}$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0312] R^{18} is independently hydrogen, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-CN$, $-SO_{n18}R^{18A}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHN R^{18A}R^{18B}$, $-ONR^{18A}R^{18B}$, $-NHC(O)NHN R^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-C(O)R^{18A}$, $-C(O)-OR^{18A}$, $-C(O)NR^{18A}R^{18B}$, $-OR^{18A}$, $-NR^{18A}SO_2R^{18B}$, $-NR^{18A}C(O)R^{18B}$, $-NR^{18A}C(O)OR^{18B}$, $-NR^{18A}OR^{18B}$, $-OCX^{18}_3$, $-OCHX^{18}_2$, $-OCH_2X^{18}$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),

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

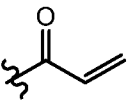
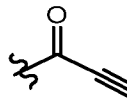
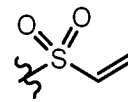
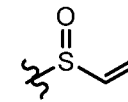
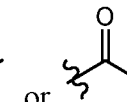
[0313] R¹⁹ is independently hydrogen, halogen, -CX¹⁹₃, -CHX¹⁹₂, -CH₂X¹⁹, -CN, -SO_{n19}R^{19A}, -SO_{v19}NR^{19A}R^{19B}, -NHN^{19A}R^{19B}, -ONR^{19A}R^{19B}, -NHC(O)NHN^{19A}R^{19B},
 5 -NHC(O)NR^{19A}R^{19B}, -N(O)_{m19}, -NR^{19A}R^{19B}, -C(O)R^{19A}, -C(O)-OR^{19A}, -C(O)NR^{19A}R^{19B},
 -OR^{19A}, -NR^{19A}SO₂R^{19B}, -NR^{19A}C(O)R^{19B}, -NR^{19A}C(O)OR^{19B}, -NR^{19A}OR^{19B}, -OCX¹⁹₃,
 -OCHX¹⁹₂, -OCH₂X¹⁹, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂),
 substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6
 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl
 10 (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to
 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
 substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted
 heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0314] R^{16A}, R^{16B}, R^{17A}, R^{17B}, R^{18A}, R^{18B}, R^{19A}, and R^{19B} are independently hydrogen, -CX₃,
 15 -CHX₂, -CH₂X, -CN, -OH, -COOH, -CONH₂, substituted or unsubstituted alkyl (e.g., C₁-C₈,
 C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to
 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or
 unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted
 heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5
 20 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or
 substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6
 membered); R^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be
 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be
 25 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be
 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be
 30 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl.

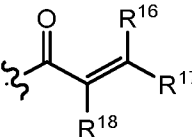
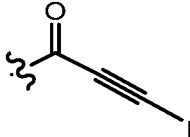
[0315] X, X¹⁶, X¹⁷, X¹⁸ and X¹⁹ are independently -F, -Cl, -Br, or -I.

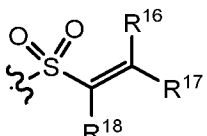
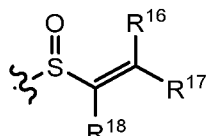
[0316] n₁₆, n₁₇, n₁₈, and n₁₉ are independently an integer from 0 to 4.

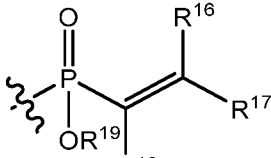
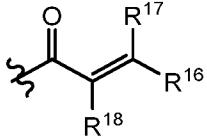
[0317] m16, m17, m18, m19, v16, v17, v18, and v19 are independently 1 or 2.

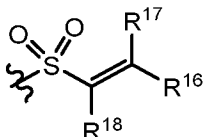
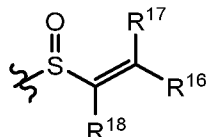
[0318] In embodiments, E is , , , , or .

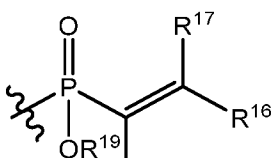
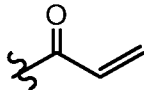
[0319] In embodiments, E is a covalent cysteine modifier moiety.

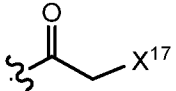
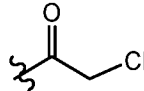
5 [0320] In embodiments, E is . In embodiments, E is . In

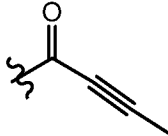
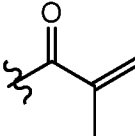
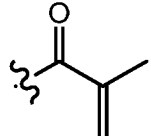
embodiments, E is . In embodiments, E is . In

embodiments, E is . In embodiments, E is . In

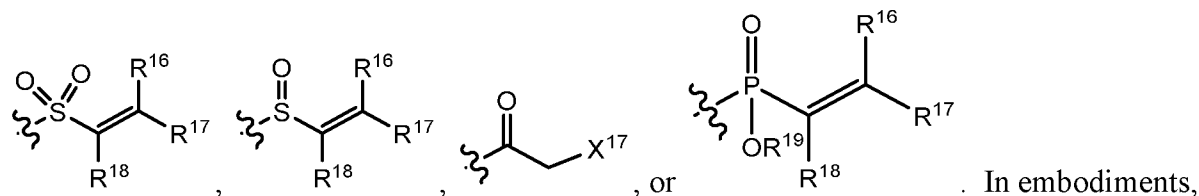
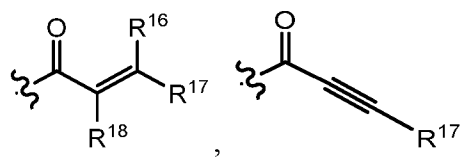
embodiments, E is . In embodiments, E is . In

embodiments, E is . In embodiments, E is . In

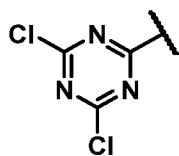
10 embodiments, E is . In embodiments, E is . In embodiments, E is

. In embodiments, E is . In embodiments, E is . R¹⁶, R¹⁷, R¹⁸, R¹⁹, and X¹⁷ are as described herein.

[0321] In embodiments, R^1 is independently

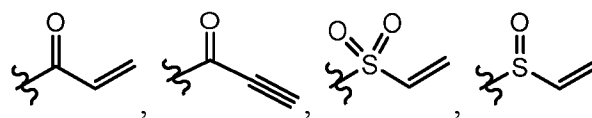


R^1 is independently

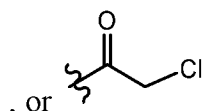


. R^{16} , R^{17} , R^{18} , R^{19} , and X^{17} are as described herein.

[0322] In embodiments, R^1 is independently

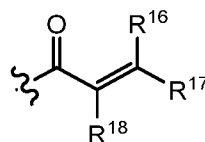


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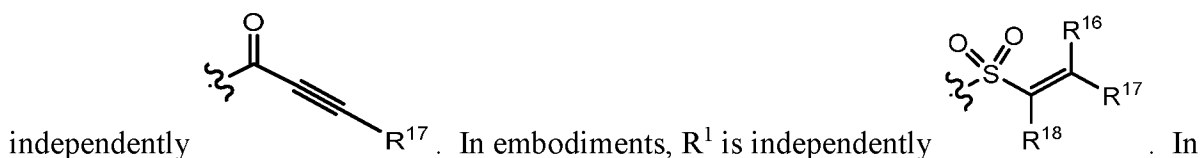


[0323] In embodiments, R^1 is independently a covalent cysteine modifier moiety.

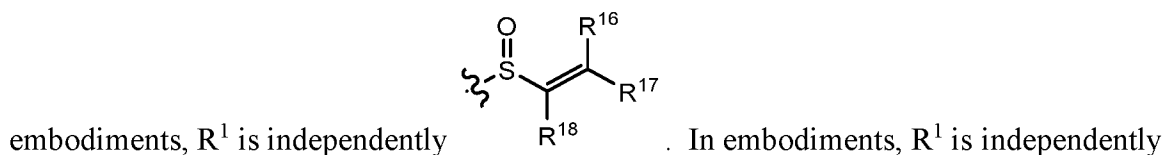
[0324] In embodiments, R^1 is independently



. In embodiments, R^1 is

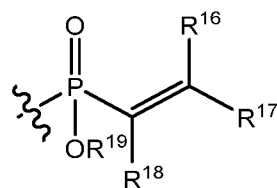


independently



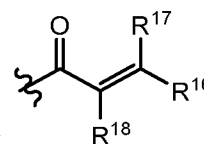
embodiments, R^1 is independently

. In embodiments, R^1 is independently

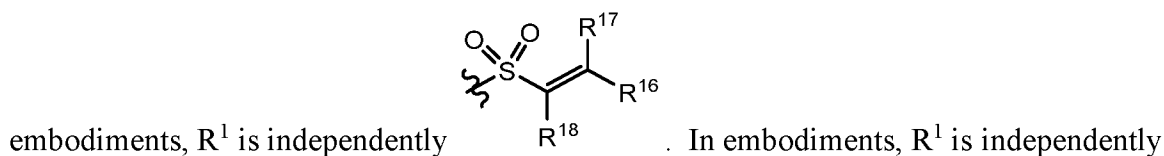


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. In embodiments, R^1 is independently

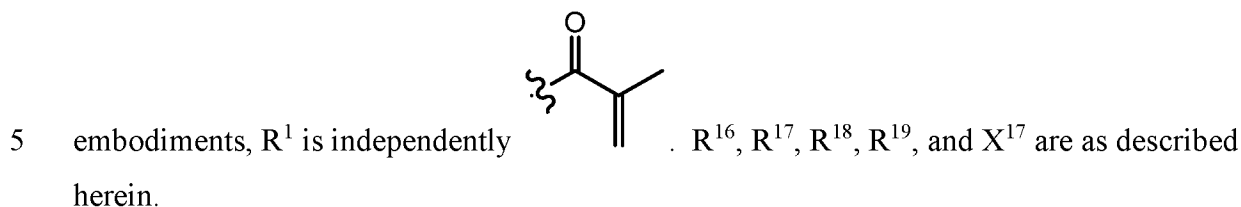
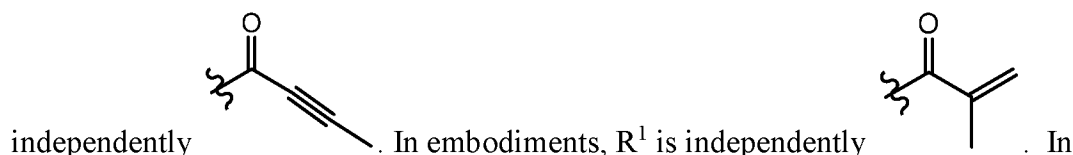
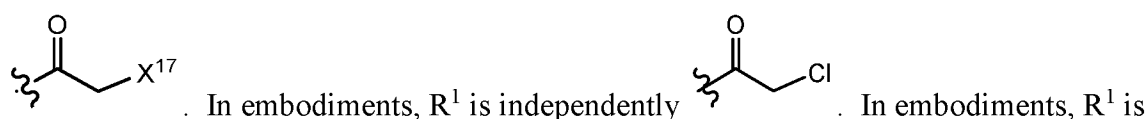
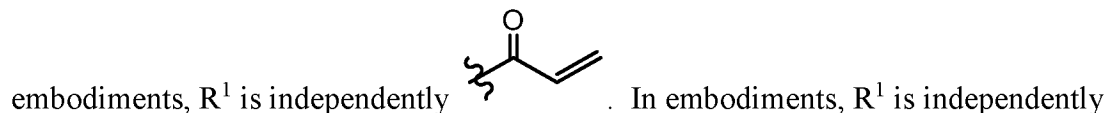
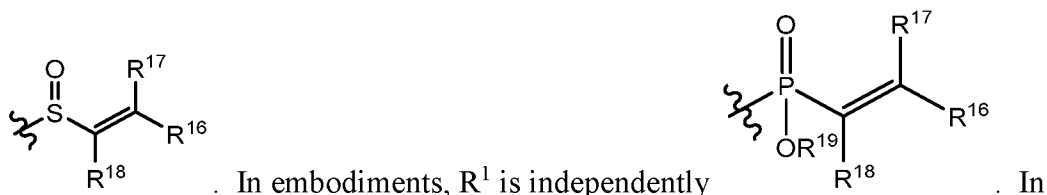


. In



embodiments, R^1 is independently

. In embodiments, R^1 is independently



[0325] X may independently be -F. X may independently be -Cl. X may independently be -Br. X may independently be -I. X¹⁶ may independently be -F. X¹⁶ may independently be -Cl. X¹⁶ may independently be -Br. X¹⁶ may independently be -I. X¹⁷ may

10 independently be -F. X¹⁷ may independently be -Cl. X¹⁷ may independently be -Br. X¹⁷ may independently be -I. X¹⁸ may independently be -F. X¹⁸ may independently be -Cl. X¹⁸ may independently be -Br. X¹⁸ may independently be -I. X¹⁹ may independently be -F. X¹⁹ may independently be -Cl. X¹⁹ may independently be -Br. X¹⁹ may independently be -I.

[0326] n₁₆ may independently be 0. n₁₆ may independently be 1. n₁₆ may independently be 2. n₁₆ may independently be 3. n₁₆ may independently be 4. n₁₇ may independently be 0. n₁₇ may independently be 1. n₁₇ may independently be 2. n₁₇ may independently be 3. n₁₇ may independently be 4. n₁₈ may independently be 0. n₁₈ may independently be 1. n₁₈ may independently be 2. n₁₈ may independently be 3. n₁₈ may independently be 4. n₁₉ may independently be 0. n₁₉ may independently be 1. n₁₉ may independently be 2. n₁₉ may independently be 3. n₁₉ may independently be 4.

20

[0327] v16 may independently be 1. v16 may independently be 2. v17 may independently be 1. v17 may independently be 2. v18 may independently be 1. v18 may independently be 2. v19 may independently be 1. v19 may independently be 2.

[0328] m16 may independently be 1. m16 may independently be 2. m17 may

5 independently be 1. m17 may independently be 2. m18 may independently be 1. m18 may independently be 2. m19 may independently be 1. m19 may independently be 2.

[0329] In embodiments, R^{16A} , R^{16B} , R^{17A} , R^{17B} , R^{18A} , R^{18B} , R^{19A} , and R^{19B} are

independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-COOH$, $-CONH_2$, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower

10 substituent group) or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at

least one substituent group, size-limited substituent group, or lower substituent group) or 15 unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one

substituent group, size-limited substituent group, or lower substituent group) or unsubstituted 20 aryl (e.g., C_6 - C_{10} or phenyl), or substituted (e.g., substituted with at least one substituent group, 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); R^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted (e.g.,

substituted with at least one substituent group, size-limited substituent group, or lower 25 substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted (e.g., substituted with at least one substituent group, 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);

R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be joined to 30 form a substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted (e.g., substituted with at least one substituent group, 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); R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted (e.g., substituted with at least one substituent group, 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); R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted (e.g., substituted with at least one substituent group, 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).

[0330] In embodiments, a substituted R^{16A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{16A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{16A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{16A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{16A} is substituted, it is substituted with at least one lower substituent group.

[0331] In embodiments, a substituted R^{16B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{16B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{16B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{16B} is substituted, it

is substituted with at least one size-limited substituent group. In embodiments, when R^{16B} is substituted, it is substituted with at least one lower substituent group.

[0332] In embodiments, a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{16A} and R^{16B} bonded to the same nitrogen is substituted with at least one

substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted heterocycloalkyl or the substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when a substituted

heterocycloalkyl or a substituted heteroaryl formed by joining R^{16A} and R^{16B} bonded to the same nitrogen is substituted, it is substituted with at least one substituent group. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{16A} and R^{16B} bonded to the same nitrogen is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{16A} and R^{16B} bonded to the same nitrogen is substituted, it is substituted with at least one lower substituent group.

[0333] In embodiments, a substituted R^{17A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or

lower substituent group; wherein if the substituted R^{17A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{17A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{17A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{17A} is substituted, it is substituted with at least one lower substituent group.

[0334] In embodiments, a substituted R^{17B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or

lower substituent group; wherein if the substituted R^{17B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower

substituent group may optionally be different. In embodiments, when R^{17B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{17B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{17B} is substituted, it is substituted with at least one lower substituent group.

5 **[0335]** In embodiments, a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{17A} and R^{17B} bonded to the same nitrogen is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted heterocycloalkyl or the substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower
10 substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{17A} and R^{17B} bonded to the same nitrogen is substituted, it is substituted with at least one substituent group. In
embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by
15 joining R^{17A} and R^{17B} bonded to the same nitrogen is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{17A} and R^{17B} bonded to the same nitrogen is substituted, it is substituted with at least one lower substituent group.

[0336] In embodiments, a substituted R^{18A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{18A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower
20 substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{18A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{18A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{18A} is substituted, it is substituted with at least one lower substituent group.

[0337] In embodiments, a substituted R^{18B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{18B} is substituted with a plurality of
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groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{18B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{18B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{18B} is substituted, it is substituted with at least one lower substituent group.

[0338] In embodiments, a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{18A} and R^{18B} bonded to the same nitrogen is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted heterocycloalkyl or the substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{18A} and R^{18B} bonded to the same nitrogen is substituted, it is substituted with at least one substituent group. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{18A} and R^{18B} bonded to the same nitrogen is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{18A} and R^{18B} bonded to the same nitrogen is substituted, it is substituted with at least one lower substituent group.

[0339] In embodiments, a substituted R^{19A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{19A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{19A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{19A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{19A} is substituted, it is substituted with at least one lower substituent group.

[0340] In embodiments, a substituted R^{19B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{19B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{19B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{19B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{19B} is substituted, it is substituted with at least one lower substituent group.

[0341] In embodiments, a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{19A} and R^{19B} bonded to the same nitrogen is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted heterocycloalkyl or the substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{19A} and R^{19B} bonded to the same nitrogen is substituted, it is substituted with at least one substituent group. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{19A} and R^{19B} bonded to the same nitrogen is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a substituted heterocycloalkyl or a substituted heteroaryl formed by joining R^{19A} and R^{19B} bonded to the same nitrogen is substituted, it is substituted with at least one lower substituent group.

[0342] In embodiments, R^{16} is independently hydrogen, halogen, $-CX^{16}_3$, $-CHX^{16}_2$, $-CH_2X^{16}$, $-CN$, $-SO_{n16}R^{16A}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHN R^{16A}R^{16B}$, $-ONR^{16A}R^{16B}$, $-NHC(O)NHN R^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16A}$, $-C(O)-OR^{16A}$, $-C(O)NR^{16A}R^{16B}$, $-OR^{16A}$, $-NR^{16A}SO_2R^{16B}$, $-NR^{16A}C(O)R^{16B}$, $-NR^{16A}C(O)OR^{16B}$, $-NR^{16A}OR^{16B}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, $-OCH_2X^{16}$, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or

unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0343] In embodiments, a substituted R¹⁶ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R¹⁶ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R¹⁶ is substituted, it is substituted with at least one substituent group. In embodiments, when R¹⁶ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R¹⁶ is substituted, it is substituted with at least one lower substituent group.

[0344] In embodiments, R¹⁶ is independently hydrogen. In embodiments, R¹⁶ is independently halogen. In embodiments, R¹⁶ is independently -CN. In embodiments, R¹⁶ is independently unsubstituted methyl. In embodiments, R¹⁶ is independently unsubstituted ethyl. In embodiments, R¹⁶ is independently unsubstituted propyl. In embodiments, R¹⁶ is independently unsubstituted isopropyl. In embodiments, R¹⁶ is independently unsubstituted butyl. In embodiments, R¹⁶ is independently unsubstituted tert-butyl. In embodiments, R¹⁶ is independently -CH₂Ph. In embodiments, R¹⁶ is independently -F. In embodiments, R¹⁶ is independently -Cl. In embodiments, R¹⁶ is independently -Br. In embodiments, R¹⁶ is independently -I. In embodiments, R¹⁶ is independently unsubstituted methoxy. In embodiments, R¹⁶ is independently unsubstituted ethoxy. In embodiments, R¹⁶ is independently -CF₃. In embodiments, R¹⁶ is independently -CCl₃. In embodiments, R¹⁶ is independently -CX¹⁶₃. In embodiments, R¹⁶ is independently -OH. In embodiments, R¹⁶ is independently -NH₂. In embodiments, R¹⁶ is independently -COOH. In embodiments, R¹⁶ is independently -CONH₂. In embodiments, R¹⁶ is independently -NO₂. In embodiments, R¹⁶ is independently -SH. In embodiments, R¹⁶ is independently -SO₃H. In embodiments, R¹⁶ is

independently $-\text{SO}_4\text{H}$. In embodiments, R^{16} is independently $-\text{SO}_2\text{NH}_2$. In embodiments, R^{16} is independently $-\text{NHNH}_2$. In embodiments, R^{16} is independently $-\text{ONH}_2$. In embodiments, R^{16} is independently $-\text{NHC}(\text{O})\text{NHNH}_2$. In embodiments, R^{16} is independently $-\text{NHC}(\text{O})\text{NH}_2$. In embodiments, R^{16} is independently $-\text{NHSO}_2\text{H}$. In embodiments, R^{16} is independently $-\text{NHC}(\text{O})\text{H}$. In embodiments, R^{16} is independently $-\text{NHC}(\text{O})\text{OH}$. In embodiments, R^{16} is independently $-\text{NHOH}$.

[0345] In embodiments, $\text{R}^{16\text{A}}$ is independently hydrogen. In embodiments, $\text{R}^{16\text{A}}$ is independently $-\text{CX}_3$. In embodiments, $\text{R}^{16\text{A}}$ is independently $-\text{CN}$. In embodiments, $\text{R}^{16\text{A}}$ is independently $-\text{COOH}$. In embodiments, $\text{R}^{16\text{A}}$ is independently $-\text{CONH}_2$. In embodiments, $\text{R}^{16\text{A}}$ is independently $-\text{CHX}_2$. In embodiments, $\text{R}^{16\text{A}}$ is independently $-\text{CH}_2\text{X}$. In embodiments, $\text{R}^{16\text{A}}$ is independently unsubstituted methyl. In embodiments, $\text{R}^{16\text{A}}$ is independently unsubstituted ethyl. In embodiments, $\text{R}^{16\text{A}}$ is independently unsubstituted propyl. In embodiments, $\text{R}^{16\text{A}}$ is independently unsubstituted isopropyl. In embodiments, $\text{R}^{16\text{A}}$ is independently unsubstituted butyl. In embodiments, $\text{R}^{16\text{A}}$ is independently unsubstituted tert-butyl.

[0346] In embodiments, $\text{R}^{16\text{B}}$ is independently hydrogen. In embodiments, $\text{R}^{16\text{B}}$ is independently $-\text{CX}_3$. In embodiments, $\text{R}^{16\text{B}}$ is independently $-\text{CN}$. In embodiments, $\text{R}^{16\text{B}}$ is independently $-\text{COOH}$. In embodiments, $\text{R}^{16\text{B}}$ is independently $-\text{CONH}_2$. In embodiments, $\text{R}^{16\text{B}}$ is independently $-\text{CHX}_2$. In embodiments, $\text{R}^{16\text{B}}$ is independently $-\text{CH}_2\text{X}$. In embodiments, $\text{R}^{16\text{B}}$ is independently unsubstituted methyl. In embodiments, $\text{R}^{16\text{B}}$ is independently unsubstituted ethyl. In embodiments, $\text{R}^{16\text{B}}$ is independently unsubstituted propyl. In embodiments, $\text{R}^{16\text{B}}$ is independently unsubstituted isopropyl. In embodiments, $\text{R}^{16\text{B}}$ is independently unsubstituted butyl. In embodiments, $\text{R}^{16\text{B}}$ is independently unsubstituted tert-butyl.

[0347] In embodiments, R^{17} is independently hydrogen, halogen, $-\text{CX}^{17}_3$, $-\text{CHX}^{17}_2$, $-\text{CH}_2\text{X}^{17}$, $-\text{CN}$, $-\text{SO}_{\text{nl}7}\text{R}^{17\text{A}}$, $-\text{SO}_{\text{v}17}\text{NR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{NHNR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{ONR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{NHC}(\text{O})\text{NHNR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{N}(\text{O})_{\text{ml}7}$, $-\text{NR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{C}(\text{O})\text{R}^{17\text{A}}$, $-\text{C}(\text{O})-\text{OR}^{17\text{A}}$, $-\text{C}(\text{O})\text{NR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{OR}^{17\text{A}}$, $-\text{NR}^{17\text{A}}\text{SO}_2\text{R}^{17\text{B}}$, $-\text{NR}^{17\text{A}}\text{C}(\text{O})\text{R}^{17\text{B}}$, $-\text{NR}^{17\text{A}}\text{C}(\text{O})\text{OR}^{17\text{B}}$, $-\text{NR}^{17\text{A}}\text{OR}^{17\text{B}}$, $-\text{OCX}^{17}_3$, $-\text{OCHX}^{17}_2$, $-\text{OCH}_2\text{X}^{17}$, substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower

substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0348] In embodiments, a substituted R¹⁷ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R¹⁷ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R¹⁷ is substituted, it is substituted with at least one substituent group. In embodiments, when R¹⁷ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R¹⁷ is substituted, it is substituted with at least one lower substituent group.

[0349] In embodiments, R¹⁷ is independently hydrogen. In embodiments, R¹⁷ is independently halogen. In embodiments, R¹⁷ is independently -CN. In embodiments, R¹⁷ is independently unsubstituted methyl. In embodiments, R¹⁷ is independently unsubstituted ethyl. In embodiments, R¹⁷ is independently unsubstituted propyl. In embodiments, R¹⁷ is independently unsubstituted isopropyl. In embodiments, R¹⁷ is independently unsubstituted butyl. In embodiments, R¹⁷ is independently unsubstituted tert-butyl. In embodiments, R¹⁷ is independently -CH₂Ph. In embodiments, R¹⁷ is independently -F. In embodiments, R¹⁷ is independently -Cl. In embodiments, R¹⁷ is independently -Br. In embodiments, R¹⁷ is independently -I. In embodiments, R¹⁷ is independently unsubstituted methoxy. In embodiments, R¹⁷ is independently unsubstituted ethoxy. In embodiments, R¹⁷ is independently -CF₃. In embodiments, R¹⁷ is independently -CCl₃. In embodiments, R¹⁷ is independently -CX¹⁷₃. In embodiments, R¹⁷ is independently -OH. In embodiments, R¹⁷ is

independently $-\text{NH}_2$. In embodiments, R^{17} is independently $-\text{COOH}$. In embodiments, R^{17} is independently $-\text{CONH}_2$. In embodiments, R^{17} is independently $-\text{NO}_2$. In embodiments, R^{17} is independently $-\text{SH}$. In embodiments, R^{17} is independently $-\text{SO}_3\text{H}$. In embodiments, R^{17} is independently $-\text{SO}_4\text{H}$. In embodiments, R^{17} is independently $-\text{SO}_2\text{NH}_2$. In embodiments, R^{17} is independently $-\text{NHNH}_2$. In embodiments, R^{17} is independently $-\text{ONH}_2$. In embodiments, R^{17} is independently $-\text{NHC}(\text{O})\text{NHNH}_2$. In embodiments, R^{17} is independently $-\text{NHC}(\text{O})\text{NH}_2$. In embodiments, R^{17} is independently $-\text{NHSO}_2\text{H}$. In embodiments, R^{17} is independently $-\text{NHC}(\text{O})\text{H}$. In embodiments, R^{17} is independently $-\text{NHC}(\text{O})\text{OH}$. In embodiments, R^{17} is independently $-\text{NHOH}$.

10 **[0350]** In embodiments, $\text{R}^{17\text{A}}$ is independently hydrogen. In embodiments, $\text{R}^{17\text{A}}$ is independently $-\text{CX}_3$. In embodiments, $\text{R}^{17\text{A}}$ is independently $-\text{CN}$. In embodiments, $\text{R}^{17\text{A}}$ is independently $-\text{COOH}$. In embodiments, $\text{R}^{17\text{A}}$ is independently $-\text{CONH}_2$. In embodiments, $\text{R}^{17\text{A}}$ is independently $-\text{CHX}_2$. In embodiments, $\text{R}^{17\text{A}}$ is independently $-\text{CH}_2\text{X}$. In embodiments, $\text{R}^{17\text{A}}$ is independently unsubstituted methyl. In embodiments, $\text{R}^{17\text{A}}$ is independently unsubstituted ethyl. In embodiments, $\text{R}^{17\text{A}}$ is independently unsubstituted propyl. In embodiments, $\text{R}^{17\text{A}}$ is independently unsubstituted isopropyl. In embodiments, $\text{R}^{17\text{A}}$ is independently unsubstituted butyl. In embodiments, $\text{R}^{17\text{A}}$ is independently unsubstituted tert-butyl.

20 **[0351]** In embodiments, $\text{R}^{17\text{B}}$ is independently hydrogen. In embodiments, $\text{R}^{17\text{B}}$ is independently $-\text{CX}_3$. In embodiments, $\text{R}^{17\text{B}}$ is independently $-\text{CN}$. In embodiments, $\text{R}^{17\text{B}}$ is independently $-\text{COOH}$. In embodiments, $\text{R}^{17\text{B}}$ is independently $-\text{CONH}_2$. In embodiments, $\text{R}^{17\text{B}}$ is independently $-\text{CHX}_2$. In embodiments, $\text{R}^{17\text{B}}$ is independently $-\text{CH}_2\text{X}$. In embodiments, $\text{R}^{17\text{B}}$ is independently unsubstituted methyl. In embodiments, $\text{R}^{17\text{B}}$ is independently unsubstituted ethyl. In embodiments, $\text{R}^{17\text{B}}$ is independently unsubstituted propyl. In embodiments, $\text{R}^{17\text{B}}$ is independently unsubstituted isopropyl. In embodiments, $\text{R}^{17\text{B}}$ is independently unsubstituted butyl. In embodiments, $\text{R}^{17\text{B}}$ is independently unsubstituted tert-butyl.

30 **[0352]** In embodiments, R^{18} is independently hydrogen, halogen, $-\text{CX}^{18}_3$, $-\text{CHX}^{18}_2$, $-\text{CH}_2\text{X}^{18}$, $-\text{CN}$, $-\text{SO}_{n18}\text{R}^{18\text{A}}$, $-\text{SO}_{v18}\text{NR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{NHNR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{ONR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{NHC}(\text{O})\text{NHNR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{N}(\text{O})_{m18}$, $-\text{NR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{C}(\text{O})\text{R}^{18\text{A}}$, $-\text{C}(\text{O})-\text{OR}^{18\text{A}}$, $-\text{C}(\text{O})\text{NR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{OR}^{18\text{A}}$, $-\text{NR}^{18\text{A}}\text{SO}_2\text{R}^{18\text{B}}$, $-\text{NR}^{18\text{A}}\text{C}(\text{O})\text{R}^{18\text{B}}$, $-\text{NR}^{18\text{A}}\text{C}(\text{O})\text{OR}^{18\text{B}}$, $-\text{NR}^{18\text{A}}\text{OR}^{18\text{B}}$, $-\text{OCX}^{18}_3$, $-\text{OCHX}^{18}_2$, $-\text{OCH}_2\text{X}^{18}$, substituted (e.g.,

substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one substituent group, size-limited substituent group, or lower substituent group) or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted (e.g., substituted with at least one substituent group, 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).

[0353] In embodiments, a substituted R¹⁸ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R¹⁸ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R¹⁸ is substituted, it is substituted with at least one substituent group. In embodiments, when R¹⁸ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R¹⁸ is substituted, it is substituted with at least one lower substituent group.

[0354] In embodiments, R¹⁸ is independently hydrogen. In embodiments, R¹⁸ is independently halogen. In embodiments, R¹⁸ is independently -CN. In embodiments, R¹⁸ is independently unsubstituted methyl. In embodiments, R¹⁸ is independently unsubstituted ethyl. In embodiments, R¹⁸ is independently unsubstituted propyl. In embodiments, R¹⁸ is independently unsubstituted isopropyl. In embodiments, R¹⁸ is independently unsubstituted butyl. In embodiments, R¹⁸ is independently unsubstituted tert-butyl. In embodiments, R¹⁸ is independently -CH₂Ph. In embodiments, R¹⁸ is independently -F. In embodiments, R¹⁸ is independently -Cl. In embodiments, R¹⁸ is independently -Br. In embodiments, R¹⁸ is independently -I. In embodiments, R¹⁸ is independently unsubstituted methoxy. In

embodiments, R^{18} is independently unsubstituted ethoxy. In embodiments, R^{18} is independently $-CF_3$. In embodiments, R^{18} is independently $-CCl_3$. In embodiments, R^{18} is independently $-CX^{18}_3$. In embodiments, R^{18} is independently $-OH$. In embodiments, R^{18} is independently $-NH_2$. In embodiments, R^{18} is independently $-COOH$. In embodiments, R^{18} is independently $-CONH_2$. In embodiments, R^{18} is independently $-NO_2$. In embodiments, R^{18} is independently $-SH$. In embodiments, R^{18} is independently $-SO_3H$. In embodiments, R^{18} is independently $-SO_4H$. In embodiments, R^{18} is independently $-SO_2NH_2$. In embodiments, R^{18} is independently $-NHNH_2$. In embodiments, R^{18} is independently $-ONH_2$. In embodiments, R^{18} is independently $-NHC(O)NHNH_2$. In embodiments, R^{18} is independently $-NHC(O)NH_2$. In embodiments, R^{18} is independently $-NHSO_2H$. In embodiments, R^{18} is independently $-NHC(O)H$. In embodiments, R^{18} is independently $-NHC(O)OH$. In embodiments, R^{18} is independently $-NHOH$.

[0355] In embodiments, R^{18A} is independently hydrogen. In embodiments, R^{18A} is independently $-CX_3$. In embodiments, R^{18A} is independently $-CN$. In embodiments, R^{18A} is independently $-COOH$. In embodiments, R^{18A} is independently $-CONH_2$. In embodiments, R^{18A} is independently $-CHX_2$. In embodiments, R^{18A} is independently $-CH_2X$. In embodiments, R^{18A} is independently unsubstituted methyl. In embodiments, R^{18A} is independently unsubstituted ethyl. In embodiments, R^{18A} is independently unsubstituted propyl. In embodiments, R^{18A} is independently unsubstituted isopropyl. In embodiments, R^{18A} is independently unsubstituted butyl. In embodiments, R^{18A} is independently unsubstituted tert-butyl.

[0356] In embodiments, R^{18B} is independently hydrogen. In embodiments, R^{18B} is independently $-CX_3$. In embodiments, R^{18B} is independently $-CN$. In embodiments, R^{18B} is independently $-COOH$. In embodiments, R^{18B} is independently $-CONH_2$. In embodiments, R^{18B} is independently $-CHX_2$. In embodiments, R^{18B} is independently $-CH_2X$. In embodiments, R^{18B} is independently unsubstituted methyl. In embodiments, R^{18B} is independently unsubstituted ethyl. In embodiments, R^{18B} is independently unsubstituted propyl. In embodiments, R^{18B} is independently unsubstituted isopropyl. In embodiments, R^{18B} is independently unsubstituted butyl. In embodiments, R^{18B} is independently unsubstituted tert-butyl.

[0357] In embodiments, R^{19} is independently hydrogen, halogen, $-CX^{19}_3$, $-CHX^{19}_2$, $-CH_2X^{19}$, $-CN$, $-SO_{n19}R^{19A}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHN R^{19A}R^{19B}$, $-ONR^{19A}R^{19B}$,

$-\text{NHC(O)NHN}^{\text{19A}}\text{R}^{\text{19B}}$, $-\text{NHC(O)NR}^{\text{19A}}\text{R}^{\text{19B}}$, $-\text{N(O)}_{\text{m19}}$, $-\text{NR}^{\text{19A}}\text{R}^{\text{19B}}$, $-\text{C(O)R}^{\text{19A}}$,
 $-\text{C(O)-OR}^{\text{19A}}$, $-\text{C(O)NR}^{\text{19A}}\text{R}^{\text{19B}}$, $-\text{OR}^{\text{19A}}$, $-\text{NR}^{\text{19A}}\text{SO}_2\text{R}^{\text{19B}}$, $-\text{NR}^{\text{19A}}\text{C(O)R}^{\text{19B}}$,
 $-\text{NR}^{\text{19A}}\text{C(O)OR}^{\text{19B}}$, $-\text{NR}^{\text{19A}}\text{OR}^{\text{19B}}$, $-\text{OCX}^{\text{19}}_3$, $-\text{OCHX}^{\text{19}}_2$, $-\text{OCH}_2\text{X}^{\text{19}}$, substituted (e.g.,
substituted with at least one substituent group, size-limited substituent group, or lower
5 substituent group) or unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, $\text{C}_1\text{-C}_4$, or $\text{C}_1\text{-C}_2$), substituted
(e.g., substituted with at least one substituent group, size-limited substituent group, or lower
substituent group) or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to
6 membered, 2 to 3 membered, or 4 to 5 membered), substituted (e.g., substituted with at
least one substituent group, size-limited substituent group, or lower substituent group) or
10 unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, $\text{C}_4\text{-C}_6$, or $\text{C}_5\text{-C}_6$), substituted (e.g., substituted
with at least one substituent group, size-limited substituent group, or lower substituent group)
or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered,
4 to 5 membered, or 5 to 6 membered), substituted (e.g., substituted with at least one
substituent group, size-limited substituent group, or lower substituent group) or unsubstituted
15 aryl (e.g., $\text{C}_6\text{-C}_{10}$ or phenyl), or substituted (e.g., substituted with at least one substituent
group, 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).

[0358] In embodiments, a substituted R^{19} (e.g., substituted alkyl, substituted heteroalkyl,
substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted
20 heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or
lower substituent group; wherein if the substituted R^{19} is substituted with a plurality of groups
selected from substituent groups, size-limited substituent groups, and lower substituent
groups; each substituent group, size-limited substituent group, and/or lower substituent group
may optionally be different. In embodiments, when R^{19} is substituted, it is substituted with at
25 least one substituent group. In embodiments, when R^{19} is substituted, it is substituted with at
least one size-limited substituent group. In embodiments, when R^{19} is substituted, it is
substituted with at least one lower substituent group.

[0359] In embodiments, R^{19} is independently hydrogen. In embodiments, R^{19} is
independently halogen. In embodiments, R^{19} is independently $-\text{CN}$. In embodiments, R^{19} is
30 independently unsubstituted methyl. In embodiments, R^{19} is independently unsubstituted
ethyl. In embodiments, R^{19} is independently unsubstituted propyl. In embodiments, R^{19} is
independently unsubstituted isopropyl. In embodiments, R^{19} is independently unsubstituted
butyl. In embodiments, R^{19} is independently unsubstituted tert-butyl. In embodiments, R^{19} is

independently $-\text{CH}_2\text{Ph}$. In embodiments, R^{19} is independently $-\text{F}$. In embodiments, R^{19} is independently $-\text{Cl}$. In embodiments, R^{19} is independently $-\text{Br}$. In embodiments, R^{19} is independently $-\text{I}$. In embodiments, R^{19} is independently unsubstituted methoxy. In embodiments, R^{19} is independently unsubstituted ethoxy. In embodiments, R^{19} is independently $-\text{CF}_3$. In embodiments, R^{19} is independently $-\text{CCl}_3$. In embodiments, R^{19} is independently $-\text{CX}^{19}_3$. In embodiments, R^{19} is independently $-\text{OH}$. In embodiments, R^{19} is independently $-\text{NH}_2$. In embodiments, R^{19} is independently $-\text{COOH}$. In embodiments, R^{19} is independently $-\text{CONH}_2$. In embodiments, R^{19} is independently $-\text{NO}_2$. In embodiments, R^{19} is independently $-\text{SH}$. In embodiments, R^{19} is independently $-\text{SO}_3\text{H}$. In embodiments, R^{19} is independently $-\text{SO}_4\text{H}$. In embodiments, R^{19} is independently $-\text{SO}_2\text{NH}_2$. In embodiments, R^{19} is independently $-\text{NHNH}_2$. In embodiments, R^{19} is independently $-\text{ONH}_2$. In embodiments, R^{19} is independently $-\text{NHC(O)NHNH}_2$. In embodiments, R^{19} is independently $-\text{NHC(O)NH}_2$. In embodiments, R^{19} is independently $-\text{NHSO}_2\text{H}$. In embodiments, R^{19} is independently $-\text{NHC(O)H}$. In embodiments, R^{19} is independently $-\text{NHC(O)OH}$. In embodiments, R^{19} is independently $-\text{NHOH}$.

[0360] In embodiments, $\text{R}^{19\text{A}}$ is independently hydrogen. In embodiments, $\text{R}^{19\text{A}}$ is independently $-\text{CX}_3$. In embodiments, $\text{R}^{19\text{A}}$ is independently $-\text{CN}$. In embodiments, $\text{R}^{19\text{A}}$ is independently $-\text{COOH}$. In embodiments, $\text{R}^{19\text{A}}$ is independently $-\text{CONH}_2$. In embodiments, $\text{R}^{19\text{A}}$ is independently $-\text{CHX}_2$. In embodiments, $\text{R}^{19\text{A}}$ is independently $-\text{CH}_2\text{X}$. In embodiments, $\text{R}^{19\text{A}}$ is independently unsubstituted methyl. In embodiments, $\text{R}^{19\text{A}}$ is independently unsubstituted ethyl. In embodiments, $\text{R}^{19\text{A}}$ is independently unsubstituted propyl. In embodiments, $\text{R}^{19\text{A}}$ is independently unsubstituted isopropyl. In embodiments, $\text{R}^{19\text{A}}$ is independently unsubstituted butyl. In embodiments, $\text{R}^{19\text{A}}$ is independently unsubstituted tert-butyl.

[0361] In embodiments, $\text{R}^{19\text{B}}$ is independently hydrogen. In embodiments, $\text{R}^{19\text{B}}$ is independently $-\text{CX}_3$. In embodiments, $\text{R}^{19\text{B}}$ is independently $-\text{CN}$. In embodiments, $\text{R}^{19\text{B}}$ is independently $-\text{COOH}$. In embodiments, $\text{R}^{19\text{B}}$ is independently $-\text{CONH}_2$. In embodiments, $\text{R}^{19\text{B}}$ is independently $-\text{CHX}_2$. In embodiments, $\text{R}^{19\text{B}}$ is independently $-\text{CH}_2\text{X}$. In embodiments, $\text{R}^{19\text{B}}$ is independently unsubstituted methyl. In embodiments, $\text{R}^{19\text{B}}$ is independently unsubstituted ethyl. In embodiments, $\text{R}^{19\text{B}}$ is independently unsubstituted propyl. In embodiments, $\text{R}^{19\text{B}}$ is independently unsubstituted isopropyl. In embodiments, $\text{R}^{19\text{B}}$ is independently unsubstituted butyl. In embodiments, $\text{R}^{19\text{B}}$ is independently unsubstituted tert-butyl.

[0362] In embodiments, when R^1 is substituted, R^1 is substituted with one or more first substituent groups denoted by $R^{1.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1.1}$ substituent group is substituted, the $R^{1.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1.2}$ substituent group is substituted, the $R^{1.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^1 , $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^1 , $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$, respectively.

[0363] In embodiments, when two adjacent R^1 substituents are optionally joined to form a moiety that is substituted (e.g., a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{1.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1.1}$ substituent group is substituted, the $R^{1.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1.2}$ substituent group is substituted, the $R^{1.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^1 , $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^1 , $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$, respectively.

[0364] In embodiments, when two adjacent $-L^1-R^1$ substituents are optionally joined to form a moiety that is substituted (e.g., a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{1.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1.1}$ substituent group is substituted, the $R^{1.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1.2}$ as explained in the definitions section above in the description of

“first substituent group(s)”. In embodiments, when an $R^{1.2}$ substituent group is substituted, the $R^{1.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $-L^1-R^1$, $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$ have values corresponding to the values of L^{WW} , R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein L^{WW} , R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to L^1 , R^1 , $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$, respectively.

[0365] In embodiments, when R^{1A} is substituted, R^{1A} is substituted with one or more first substituent groups denoted by $R^{1A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.1}$ substituent group is substituted, the $R^{1A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.2}$ substituent group is substituted, the $R^{1A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1A} , $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1A} , $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$, respectively.

[0366] In embodiments, when R^{1B} is substituted, R^{1B} is substituted with one or more first substituent groups denoted by $R^{1B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.1}$ substituent group is substituted, the $R^{1B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.2}$ substituent group is substituted, the $R^{1B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1B} , $R^{1B.1}$, $R^{1B.2}$, and $R^{1B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1B} , $R^{1B.1}$, $R^{1B.2}$, and $R^{1B.3}$, respectively.

[0367] In embodiments, when R^{1A} and R^{1B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{1A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.1}$ substituent group is substituted, the $R^{1A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.2}$ substituent group is substituted, the $R^{1A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1A} , $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1A} , $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$, respectively.

[0368] In embodiments, when R^{1A} and R^{1B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{1B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.1}$ substituent group is substituted, the $R^{1B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.2}$ substituent group is substituted, the $R^{1B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1B} , $R^{1B.1}$, $R^{1B.2}$, and $R^{1B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1B} , $R^{1B.1}$, $R^{1B.2}$, and $R^{1B.3}$, respectively.

[0369] In embodiments, when R^{1C} is substituted, R^{1C} is substituted with one or more first substituent groups denoted by $R^{1C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1C.1}$ substituent group is substituted, the $R^{1C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1C.2}$ as explained in the definitions section above in the description of

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

[0370] In embodiments, when R^{1D} is substituted, R^{1D} is substituted with one or more first substituent groups denoted by $R^{1D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1D.1}$ substituent group is substituted, the $R^{1D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1D.2}$ substituent group is substituted, the $R^{1D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1D} , $R^{1D.1}$, $R^{1D.2}$, and $R^{1D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1D} , $R^{1D.1}$, $R^{1D.2}$, and $R^{1D.3}$, respectively.

[0371] In embodiments, when R^2 is substituted, R^2 is substituted with one or more first substituent groups denoted by $R^{2.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2.1}$ substituent group is substituted, the $R^{2.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2.2}$ substituent group is substituted, the $R^{2.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^2 , $R^{2.1}$, $R^{2.2}$, and $R^{2.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^2 , $R^{2.1}$, $R^{2.2}$, and $R^{2.3}$, respectively.

[0372] In embodiments, when R^3 is substituted, R^3 is substituted with one or more first substituent groups denoted by $R^{3.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3.1}$ substituent group is substituted, the $R^{3.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3.2}$ substituent group is substituted, the $R^{3.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^3 , $R^{3.1}$, $R^{3.2}$, and $R^{3.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^3 , $R^{3.1}$, $R^{3.2}$, and $R^{3.3}$, respectively.

[0373] In embodiments, when R^4 is substituted, R^4 is substituted with one or more first substituent groups denoted by $R^{4.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4.1}$ substituent group is substituted, the $R^{4.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4.2}$ substituent group is substituted, the $R^{4.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^4 , $R^{4.1}$, $R^{4.2}$, and $R^{4.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^4 , $R^{4.1}$, $R^{4.2}$, and $R^{4.3}$, respectively.

[0374] In embodiments, when two adjacent R^4 substituents are optionally joined to form a moiety that is substituted (e.g., a substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{4.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4.1}$ substituent group is substituted, the $R^{4.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4.2}$ substituent group is substituted, the $R^{4.2}$ substituent group is substituted with one or more third substituent groups denoted by

$R^{4.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^4 , $R^{4.1}$, $R^{4.2}$, and $R^{4.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^4 , $R^{4.1}$, $R^{4.2}$, and $R^{4.3}$, respectively.

[0375] In embodiments, when R^5 is substituted, R^5 is substituted with one or more first substituent groups denoted by $R^{5.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5.1}$ substituent group is substituted, the $R^{5.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5.2}$ substituent group is substituted, the $R^{5.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^5 , $R^{5.1}$, $R^{5.2}$, and $R^{5.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^5 , $R^{5.1}$, $R^{5.2}$, and $R^{5.3}$, respectively.

[0376] In embodiments, when R^{10} is substituted, R^{10} is substituted with one or more first substituent groups denoted by $R^{10.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10.1}$ substituent group is substituted, the $R^{10.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{10.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10.2}$ substituent group is substituted, the $R^{10.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{10.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{10} , $R^{10.1}$, $R^{10.2}$, and $R^{10.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{10} , $R^{10.1}$, $R^{10.2}$, and $R^{10.3}$, respectively.

[0377] In embodiments, when R^{11} is substituted, R^{11} is substituted with one or more first substituent groups denoted by $R^{11.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.1}$ substituent group

is substituted, the $R^{11.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.2}$ substituent group is substituted, the $R^{11.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{11} , $R^{11.1}$, $R^{11.2}$, and $R^{11.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{11} , $R^{11.1}$, $R^{11.2}$, and $R^{11.3}$, respectively.

[0378] In embodiments, when R^{12} is substituted, R^{12} is substituted with one or more first substituent groups denoted by $R^{12.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.1}$ substituent group is substituted, the $R^{12.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.2}$ substituent group is substituted, the $R^{12.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{12} , $R^{12.1}$, $R^{12.2}$, and $R^{12.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{12} , $R^{12.1}$, $R^{12.2}$, and $R^{12.3}$, respectively.

[0379] In embodiments, when R^{16} is substituted, R^{16} is substituted with one or more first substituent groups denoted by $R^{16.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16.1}$ substituent group is substituted, the $R^{16.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{16.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16.2}$ substituent group is substituted, the $R^{16.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{16.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{16} , $R^{16.1}$, $R^{16.2}$, and $R^{16.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{16} , $R^{16.1}$, $R^{16.2}$, and $R^{16.3}$, respectively.

[0380] In embodiments, when R^{16A} is substituted, R^{16A} is substituted with one or more first substituent groups denoted by $R^{16A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16A.1}$ substituent group is substituted, the $R^{16A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{16A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16A.2}$ substituent group is substituted, the $R^{16A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{16A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{16A} , $R^{16A.1}$, $R^{16A.2}$, and $R^{16A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{16A} , $R^{16A.1}$, $R^{16A.2}$, and $R^{16A.3}$, respectively.

[0381] In embodiments, when R^{16B} is substituted, R^{16B} is substituted with one or more first substituent groups denoted by $R^{16B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16B.1}$ substituent group is substituted, the $R^{16B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{16B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16B.2}$ substituent group is substituted, the $R^{16B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{16B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{16B} , $R^{16B.1}$, $R^{16B.2}$, and $R^{16B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{16B} , $R^{16B.1}$, $R^{16B.2}$, and $R^{16B.3}$, respectively.

[0382] In embodiments, when R^{16A} and R^{16B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{16A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16A.1}$ substituent group is substituted, the $R^{16A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{16A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16A.2}$ substituent group is substituted, the $R^{16A.2}$ substituent group is substituted with one or more third substituent groups denoted

by $R^{16A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{16A} , $R^{16A.1}$, $R^{16A.2}$, and $R^{16A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{16A} , $R^{16A.1}$, $R^{16A.2}$, and $R^{16A.3}$, respectively.

[0383] In embodiments, when R^{16A} and R^{16B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{16B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16B.1}$ substituent group is substituted, the $R^{16B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{16B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16B.2}$ substituent group is substituted, the $R^{16B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{16B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{16B} , $R^{16B.1}$, $R^{16B.2}$, and $R^{16B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{16B} , $R^{16B.1}$, $R^{16B.2}$, and $R^{16B.3}$, respectively.

[0384] In embodiments, when R^{17} is substituted, R^{17} is substituted with one or more first substituent groups denoted by $R^{17.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17.1}$ substituent group is substituted, the $R^{17.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{17.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17.2}$ substituent group is substituted, the $R^{17.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{17.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{17} , $R^{17.1}$, $R^{17.2}$, and $R^{17.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{17} , $R^{17.1}$, $R^{17.2}$, and $R^{17.3}$, respectively.

[0385] In embodiments, when R^{17A} is substituted, R^{17A} is substituted with one or more first substituent groups denoted by $R^{17A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17A.1}$ substituent group is substituted, the $R^{17A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{17A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17A.2}$ substituent group is substituted, the $R^{17A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{17A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{17A} , $R^{17A.1}$, $R^{17A.2}$, and $R^{17A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{17A} , $R^{17A.1}$, $R^{17A.2}$, and $R^{17A.3}$, respectively.

[0386] In embodiments, when R^{17B} is substituted, R^{17B} is substituted with one or more first substituent groups denoted by $R^{17B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17B.1}$ substituent group is substituted, the $R^{17B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{17B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17B.2}$ substituent group is substituted, the $R^{17B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{17B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{17B} , $R^{17B.1}$, $R^{17B.2}$, and $R^{17B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{17B} , $R^{17B.1}$, $R^{17B.2}$, and $R^{17B.3}$, respectively.

[0387] In embodiments, when R^{17A} and R^{17B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{17A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17A.1}$ substituent group is substituted, the $R^{17A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{17A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17A.2}$ substituent group is substituted, the $R^{17A.2}$ substituent group is substituted with one or more third substituent groups denoted

by $R^{17A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{17A} , $R^{17A.1}$, $R^{17A.2}$, and $R^{17A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{17A} , $R^{17A.1}$, $R^{17A.2}$, and $R^{17A.3}$, respectively.

[0388] In embodiments, when R^{17A} and R^{17B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{17B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17B.1}$ substituent group is substituted, the $R^{17B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{17B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17B.2}$ substituent group is substituted, the $R^{17B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{17B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{17B} , $R^{17B.1}$, $R^{17B.2}$, and $R^{17B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{17B} , $R^{17B.1}$, $R^{17B.2}$, and $R^{17B.3}$, respectively.

[0389] In embodiments, when R^{18} is substituted, R^{18} is substituted with one or more first substituent groups denoted by $R^{18.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18.1}$ substituent group is substituted, the $R^{18.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{18.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18.2}$ substituent group is substituted, the $R^{18.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{18.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{18} , $R^{18.1}$, $R^{18.2}$, and $R^{18.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{18} , $R^{18.1}$, $R^{18.2}$, and $R^{18.3}$, respectively.

[0390] In embodiments, when R^{18A} is substituted, R^{18A} is substituted with one or more first substituent groups denoted by $R^{18A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18A.1}$ substituent group is substituted, the $R^{18A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{18A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18A.2}$ substituent group is substituted, the $R^{18A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{18A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{18A} , $R^{18A.1}$, $R^{18A.2}$, and $R^{18A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{18A} , $R^{18A.1}$, $R^{18A.2}$, and $R^{18A.3}$, respectively.

[0391] In embodiments, when R^{18B} is substituted, R^{18B} is substituted with one or more first substituent groups denoted by $R^{18B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18B.1}$ substituent group is substituted, the $R^{18B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{18B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18B.2}$ substituent group is substituted, the $R^{18B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{18B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{18B} , $R^{18B.1}$, $R^{18B.2}$, and $R^{18B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{18B} , $R^{18B.1}$, $R^{18B.2}$, and $R^{18B.3}$, respectively.

[0392] In embodiments, when R^{18A} and R^{18B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{18A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18A.1}$ substituent group is substituted, the $R^{18A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{18A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18A.2}$ substituent group is substituted, the $R^{18A.2}$ substituent group is substituted with one or more third substituent groups denoted

by $R^{18A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{18A} , $R^{18A.1}$, $R^{18A.2}$, and $R^{18A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{18A} , $R^{18A.1}$, $R^{18A.2}$, and $R^{18A.3}$, respectively.

[0393] In embodiments, when R^{18A} and R^{18B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{18B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18B.1}$ substituent group is substituted, the $R^{18B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{18B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{18B.2}$ substituent group is substituted, the $R^{18B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{18B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{18B} , $R^{18B.1}$, $R^{18B.2}$, and $R^{18B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{18B} , $R^{18B.1}$, $R^{18B.2}$, and $R^{18B.3}$, respectively.

[0394] In embodiments, when R^{19} is substituted, R^{19} is substituted with one or more first substituent groups denoted by $R^{19.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19.1}$ substituent group is substituted, the $R^{19.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{19.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19.2}$ substituent group is substituted, the $R^{19.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{19.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{19} , $R^{19.1}$, $R^{19.2}$, and $R^{19.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{19} , $R^{19.1}$, $R^{19.2}$, and $R^{19.3}$, respectively.

[0395] In embodiments, when R^{19A} is substituted, R^{19A} is substituted with one or more first substituent groups denoted by $R^{19A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19A.1}$ substituent group is substituted, the $R^{19A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{19A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19A.2}$ substituent group is substituted, the $R^{19A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{19A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{19A} , $R^{19A.1}$, $R^{19A.2}$, and $R^{19A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{19A} , $R^{19A.1}$, $R^{19A.2}$, and $R^{19A.3}$, respectively.

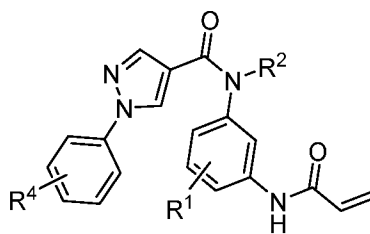
[0396] In embodiments, when R^{19B} is substituted, R^{19B} is substituted with one or more first substituent groups denoted by $R^{19B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19B.1}$ substituent group is substituted, the $R^{19B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{19B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19B.2}$ substituent group is substituted, the $R^{19B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{19B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{19B} , $R^{19B.1}$, $R^{19B.2}$, and $R^{19B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{19B} , $R^{19B.1}$, $R^{19B.2}$, and $R^{19B.3}$, respectively.

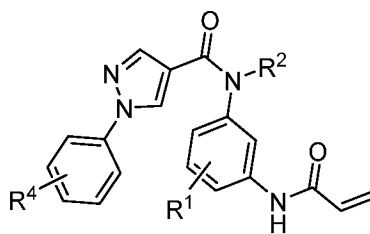
[0397] In embodiments, when R^{19A} and R^{19B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{19A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19A.1}$ substituent group is substituted, the $R^{19A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{19A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19A.2}$ substituent group is substituted, the $R^{19A.2}$ substituent group is substituted with one or more third substituent groups denoted

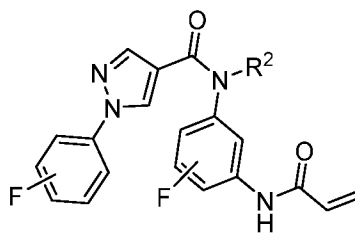
by $R^{19A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{19A} , $R^{19A.1}$, $R^{19A.2}$, and $R^{19A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{19A} , $R^{19A.1}$, $R^{19A.2}$, and $R^{19A.3}$, respectively.

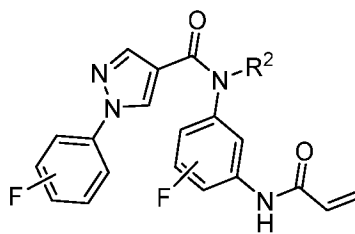
[0398] In embodiments, when R^{19A} and R^{19B} substituents that are bonded to the same nitrogen atom are joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{19B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19B.1}$ substituent group is substituted, the $R^{19B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{19B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{19B.2}$ substituent group is substituted, the $R^{19B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{19B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{19B} , $R^{19B.1}$, $R^{19B.2}$, and $R^{19B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{19B} , $R^{19B.1}$, $R^{19B.2}$, and $R^{19B.3}$, respectively.

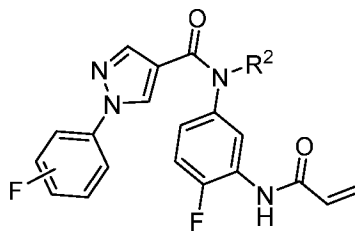
[0399] In embodiments, when L^1 is substituted, L^1 is substituted with one or more first substituent groups denoted by $R^{L1.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{L1.1}$ substituent group is substituted, the $R^{L1.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{L1.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{L1.2}$ substituent group is substituted, the $R^{L1.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{L1.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, L^1 , $R^{L1.1}$, $R^{L1.2}$, and $R^{L1.3}$ have values corresponding to the values of L^{WW} , $R^{LWW.1}$, $R^{LWW.2}$, and $R^{LWW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein L^{WW} , $R^{LWW.1}$, $R^{LWW.2}$, and $R^{LWW.3}$ are L^1 , $R^{L1.1}$, $R^{L1.2}$, and $R^{L1.3}$, respectively.

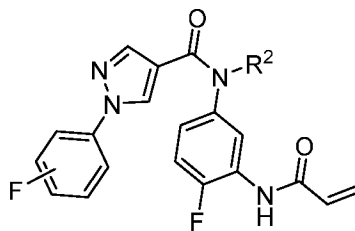


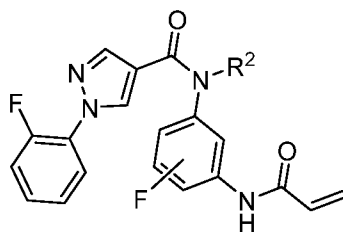
[0400] In embodiments, the compound is , wherein R^1 , R^2 , and R^4 are as described herein, including in embodiments. In embodiments, R^1 and R^4 are each independently halogen. In embodiments, R^2 is independently C_1 - C_6 alkyl. In embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

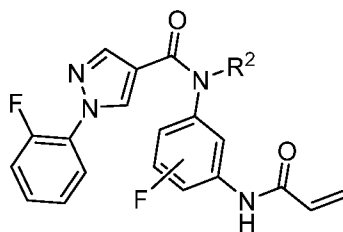


[0401] In embodiments, the compound is , wherein R^2 is as described herein, including in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

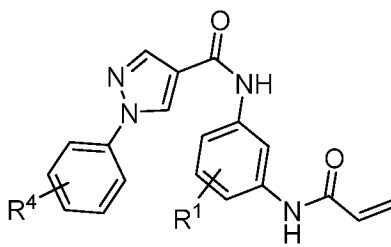


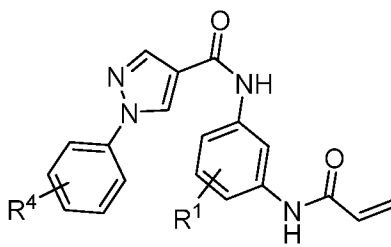
[0402] In embodiments, the compound is , wherein R^2 is as described herein, including in embodiments. In embodiments, R^2 is independently C_1 - C_6 alkyl. In embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

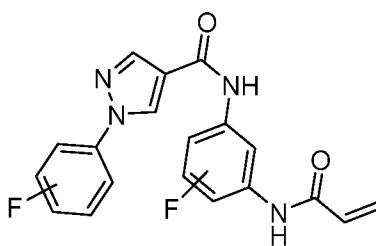


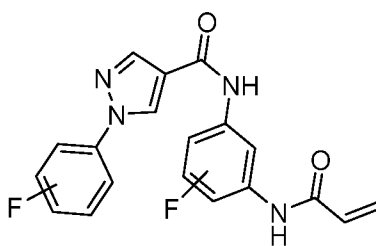
[0403] In embodiments, the compound is , wherein R^2 is as described herein, including in embodiments. In embodiments, R^2 is independently C_1 - C_6

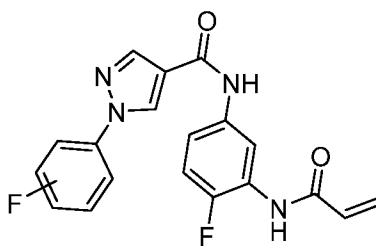
alkyl. In embodiments, R^2 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently C_3 - C_6 cycloalkyl.

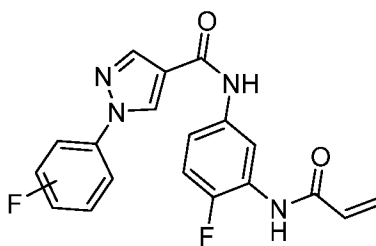


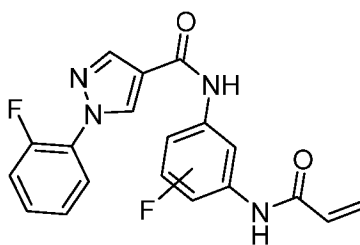
[0404] In embodiments, the compound is , wherein R^1 and R^4 are each independently halogen.

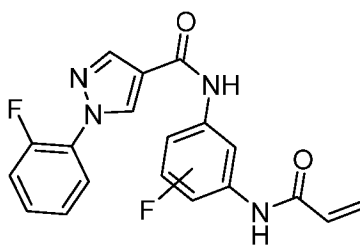


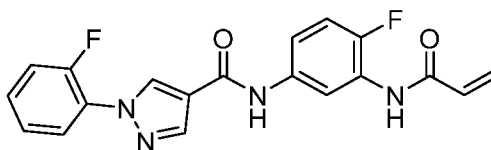
[0405] In embodiments, the compound is .

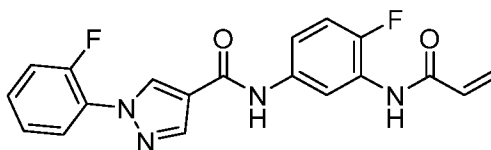


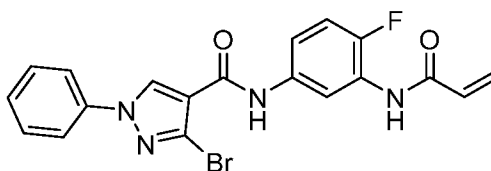
[0406] In embodiments, the compound is .

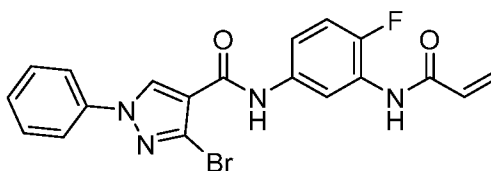


[0407] In embodiments, the compound is .

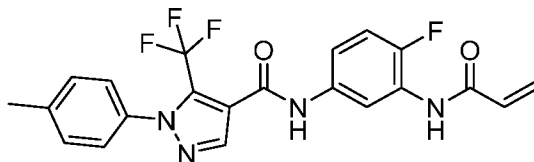


[0408] In embodiments, the compound is .

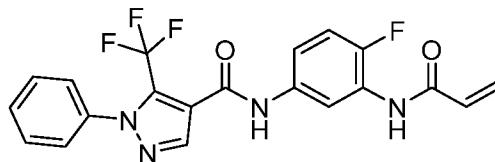


10 [0409] In embodiments, the compound is .

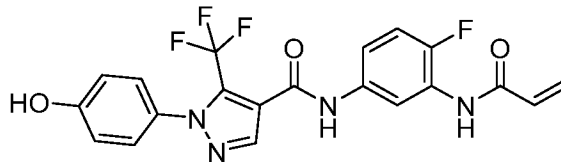
[0410] In embodiments, the compound is



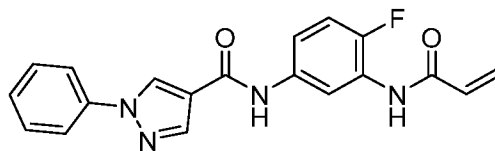
[0411] In embodiments, the compound is



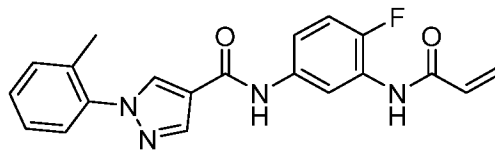
[0412] In embodiments, the compound is



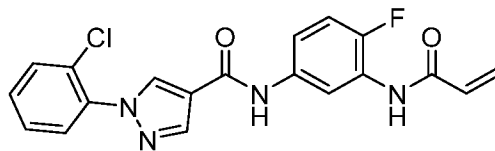
[0413] In embodiments, the compound is



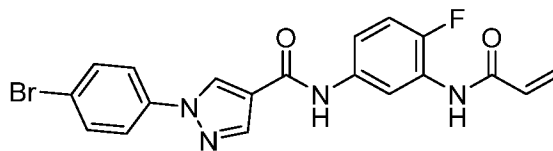
5 [0414] In embodiments, the compound is



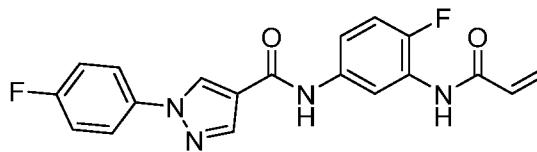
[0415] In embodiments, the compound is



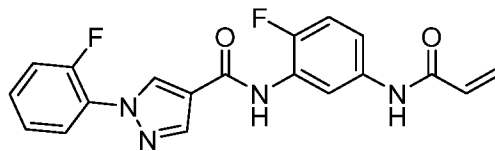
[0416] In embodiments, the compound is

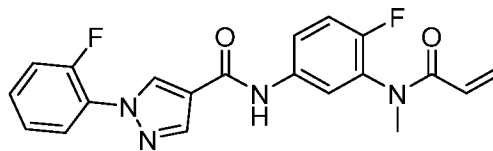


[0417] In embodiments, the compound is

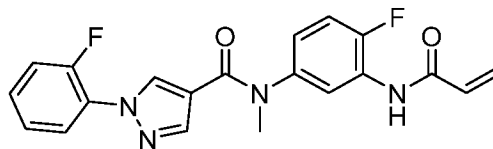


[0418] In embodiments, the compound is



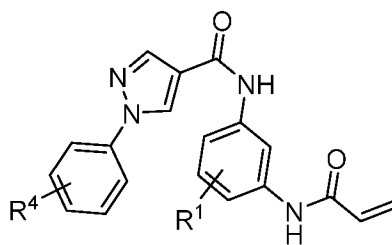


[0419] In embodiments, the compound is

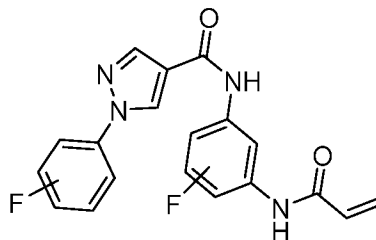


[0420] In embodiments, the compound is

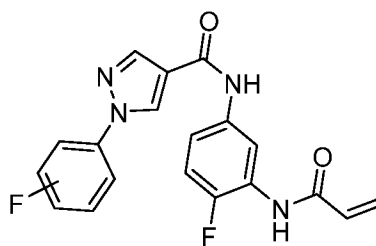
[0421] In embodiments, the compound is a compound described herein. In embodiments, the compound, or a pharmaceutically acceptable salt thereof, is the compound described
5 herein. In embodiments, the compound, or a pharmaceutically acceptable salt thereof, is the pharmaceutically acceptable salt of a compound described herein.



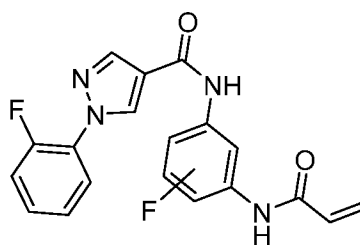
[0422] In embodiments, the compound is not and R^4 are each independently halogen.



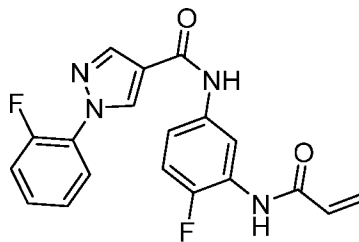
[0423] In embodiments, the compound is not



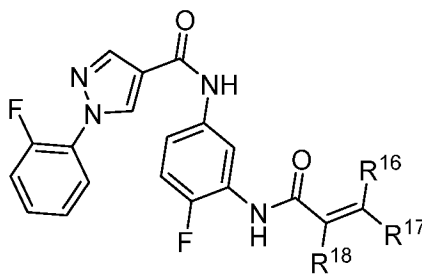
10 [0424] In embodiments, the compound is not



[0425] In embodiments, the compound is not



[0426] In embodiments, the compound is not



[0427] In embodiments, the compound is not R¹⁶, R¹⁷, and R¹⁸ are as defined herein, wherein

[0428] In embodiments, R¹ is not -F. In embodiments, R⁴ is not -F. In embodiments, when R¹ is independently -F, R⁴ is not -F. In embodiments, when R⁴ is independently -F, R¹ is not -F.

III. Pharmaceutical compositions

[0429] In an aspect is provided a pharmaceutical composition including a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0430] In an aspect is provided a pharmaceutical composition including a compound described herein and a pharmaceutically acceptable excipient.

[0431] In embodiments, the pharmaceutical composition includes an effective amount of the compound. In embodiments, the pharmaceutical composition includes a therapeutically effective amount of the compound. In embodiments, the pharmaceutical composition includes a second agent (e.g., an anti-cancer agent). In embodiments of the pharmaceutical compositions, the pharmaceutical composition includes a second agent in a therapeutically effective amount.

IV. Methods of use

[0432] In an aspect is provided a method for treating cancer in a subject in need thereof, the method including administering to the subject in need thereof a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0433] In an aspect is provided a method for treating cancer in a subject in need thereof, the method including administering to the subject in need thereof a therapeutically effective amount of a compound described herein.

[0434] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in a method of treating cancer including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

[0435] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer, the use including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

[0436] In embodiments, the cancer is renal cell carcinoma, follicular lymphoma, glioblastoma, colorectal cancer, endometrial cancer, or lung cancer.

[0437] In embodiments, the cancer is renal cell carcinoma. In embodiments, the cancer is follicular lymphoma. In embodiments, the cancer is glioblastoma. In embodiments, the cancer is colorectal cancer. In embodiments, the cancer is endometrial cancer. In embodiments, the cancer is lung cancer. In embodiments, the cancer is pancreatic cancer. In embodiments, the cancer is melanoma. In embodiments, the cancer is breast cancer. In embodiments, the cancer is acute myeloid leukemia. In embodiments, the cancer is endometrial cancer. In embodiments, the cancer is non-Hodgkin lymphoma. In embodiments, the cancer is mantle cell lymphoma. In embodiments, the method includes immunomodulation. In embodiments, the method includes cancer immunotherapy.

[0438] In an aspect is provided a method for treating a neurodegenerative disease, the method including administering to a subject in need thereof an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0439] In an aspect is provided a method for treating a neurodegenerative disease, the method including administering to a subject in need thereof an effective amount of a compound described herein. In embodiments, the compound is included in a therapeutically effective amount. In embodiments, the method is a method of treating nerve damage, the method including administering to a subject in need thereof an effective amount of a compound described herein. In embodiments, the neurodegenerative disease is Huntington

Disease. In embodiments, the neurodegenerative disease is Alzheimer Disease. In
embodiments, the neurodegenerative disease is Parkinson's Disease. In embodiments, the
neurodegenerative disease is frontotemporal dementia. In embodiments, the method includes
reducing protein aggregates (e.g., in the brain). In embodiments, the method includes
5 reducing TDP-43 aggregates (e.g., in the brain). In embodiments, the neurodegenerative
disease is amyotrophic lateral sclerosis. In embodiments, the neurodegenerative disease is
chronic traumatic encephalopathy. In embodiments, the neurodegenerative disease is
traumatic brain injury (e.g., concussion).

[0440] In an aspect is provided a compound described herein, or a pharmaceutically
10 acceptable salt thereof, for use in a method of treating a neurodegenerative disease including
administering to a subject in need thereof a therapeutically effective amount of the
compound, or a pharmaceutically acceptable salt thereof.

[0441] In an aspect is provided use of a compound described herein, or a pharmaceutically
acceptable salt thereof, in the manufacture of a medicament for the treatment of a
15 neurodegenerative disease, the use including administering to a subject in need thereof a
therapeutically effective amount of the compound, or a pharmaceutically acceptable salt
thereof.

[0442] In an aspect is provided a method for treating a metabolic disease, the method
including administering to a subject in need thereof an effective amount of a compound
20 described herein, or a pharmaceutically acceptable salt thereof.

[0443] In an aspect is provided a method for treating a metabolic disease, the method
including administering to a subject in need thereof an effective amount of a compound
described herein. In embodiments, the compound is included in a therapeutically effective
amount. In embodiments, the metabolic disease is diabetes. In embodiments, the metabolic
25 disease is type I diabetes. In embodiments, the metabolic disease is type II diabetes. In
embodiments, the metabolic disease is obesity. In embodiments, the metabolic disease is
metabolic syndrome. In embodiments, the metabolic disease is a mitochondrial disease (e.g.,
dysfunction of mitochondria or aberrant mitochondrial function).

[0444] In an aspect is provided a compound described herein, or a pharmaceutically
30 acceptable salt thereof, for use in a method of treating a metabolic disease including
administering to a subject in need thereof a therapeutically effective amount of the
compound, or a pharmaceutically acceptable salt thereof.

[0445] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a metabolic disease, the use including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

5 [0446] In an aspect is provided a method for treating aging, the method including administering to a subject in need thereof an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0447] In an aspect is provided a method for treating aging, the method including administering to a subject in need thereof an effective amount of a compound described
10 herein.

[0448] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in a method of treating aging including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

15 [0449] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of aging, the use including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

[0450] In another aspect is provided a method of extending lifespan (e.g., increased 1 day, increased 2 days, increased 3 days, increased 7 days, increased 1 month, increased 6 months, increased 12 months, increased 2 years, increased 5 years, etc.) or inducing longevity, the
20 method including administering to a subject in need thereof an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0451] In another aspect is provided a method of extending lifespan (e.g., increased 1 day, increased 2 days, increased 3 days, increased 7 days, increased 1 month, increased 6 months, increased 12 months, increased 2 years, increased 5 years, etc.) or inducing longevity, the
25 method including administering to a subject in need thereof an effective amount of a compound described herein.

[0452] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in a method of extending lifespan (e.g., increased 1 day, increased 2 days, increased 3 days, increased 7 days, increased 1 month, increased 6 months,
30

increased 12 months, increased 2 years, increased 5 years, etc.) or inducing longevity, including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

[0453] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for extending lifespan (e.g., increased 1 day, increased 2 days, increased 3 days, increased 7 days, increased 1 month, increased 6 months, increased 12 months, increased 2 years, increased 5 years, etc.) or inducing longevity, the use including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

[0454] In an aspect is provided a method of reducing the level of activity of mTORC1 in a subject in need thereof, the method including administering to the subject in need thereof an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0455] In an aspect is provided a method of reducing the level of activity of mTORC1 in a subject in need thereof, the method including administering to the subject in need thereof an effective amount of a compound described herein.

[0456] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in reducing the level of activity of mTORC1 including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

[0457] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of activity of mTORC1, the use including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

[0458] In an aspect is provided a method of reducing the level of activity of mTORC1 in a cell, the method including contacting a Vacuolar H⁺-ATPase in the cell with a compound as described herein, or a pharmaceutically acceptable salt thereof.

[0459] In an aspect is provided a method of reducing the level of activity of mTORC1 in a cell, the method including contacting a Vacuolar H⁺-ATPase in the cell with a compound as described herein.

[0460] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in reducing the level of activity of mTORC1 in a cell including contacting a Vacuolar H⁺-ATPase in the cell with the compound, or a pharmaceutically acceptable salt thereof.

5 **[0461]** In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of activity of mTORC1 in a cell, the use including contacting a Vacuolar H⁺-ATPase in the cell with the compound, or a pharmaceutically acceptable salt thereof.

[0462] In embodiments, the method includes dephosphorylation and/or nuclear
10 translocation of TFEB (e.g., RefSeq NM_007162.2 or RefSeq NP_009093.1) in a cell or subject. In embodiments, the method includes increasing the level of TFEB transcriptional targets in a cell or subject. In embodiments, the method includes increasing the level of CTSA (e.g., RefSeq NM_000308.3 or RefSeq NP_000299.2), CTSB (e.g., RefSeq
NM_001908.4 or RefSeq NP_001899.1), CTSF (e.g., RefSeq NM_003793.3 or RefSeq
15 NP_003784.2), HEXB (e.g., RefSeq NM_000521.4 or RefSeq NP_000512.2), CLN3 (e.g., RefSeq NM_000086.2 or RefSeq NP_000077.1), CLCN7 (e.g., RefSeq NM_001287.5 or RefSeq NP_001278.1), ATP6V0D1 (e.g., RefSeq NM_004691.4 or RefSeq NP_004682.2), ATP6V0E1 (e.g., RefSeq NM_003945.3 or RefSeq NP_003936.1), LAMP1 (e.g., RefSeq
NM_005561.3 or RefSeq NP_005552.3), or p62 (e.g., RefSeq NM_003900.4 or RefSeq
20 NP_003891.1) in a cell or subject. In embodiments, the method includes increasing the level of LC3BII in a cell or subject.

[0463] In embodiments, the method includes dephosphorylation and/or nuclear
translocation of TFE3 (e.g., RefSeq NM_006521.5 or RefSeq NP_006512.2) in a cell or
subject. In embodiments, the method includes increasing the level of TFE3 transcriptional
25 targets in a cell or subject.

[0464] In an aspect is provided a method of reducing the level of activity of a Vacuolar H⁺-ATPase, the method including contacting the Vacuolar H⁺-ATPase with a compound described herein, or a pharmaceutically acceptable salt thereof.

[0465] In an aspect is provided a method of reducing the level of activity of a Vacuolar H⁺-ATPase, the method including contacting the Vacuolar H⁺-ATPase with a compound
30 described herein.

[0466] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in reducing the level of activity of a Vacuolar H⁺-ATPase including contacting the Vacuolar H⁺-ATPase with the compound, or a pharmaceutically acceptable salt thereof.

- 5 [0467] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of activity of a Vacuolar H⁺-ATPase, the use including contacting the Vacuolar H⁺-ATPase with the compound, or a pharmaceutically acceptable salt thereof.

- 10 [0468] In an aspect is provided a method of reducing the level of activity of a Vacuolar H⁺-ATPase protein complex, the method including contacting an ATP6V1A in the Vacuolar H⁺-ATPase protein complex with a compound described herein, or a pharmaceutically acceptable salt thereof.

- 15 [0469] In an aspect is provided a method of reducing the level of activity of a Vacuolar H⁺-ATPase protein complex, the method including contacting an ATP6V1A in the Vacuolar H⁺-ATPase protein complex with a compound described herein.

[0470] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in reducing the level of activity of a Vacuolar H⁺-ATPase protein complex including contacting an ATP6V1A in the Vacuolar H⁺-ATPase protein complex with the compound, or a pharmaceutically acceptable salt thereof.

- 20 [0471] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of activity of a Vacuolar H⁺-ATPase protein complex, the use including contacting an ATP6V1A in the Vacuolar H⁺-ATPase protein complex with the compound, or a pharmaceutically acceptable salt thereof.

- 25 [0472] In an aspect is provided a method of reducing the level of activity of mTORC1 in a cell, the method including contacting an ATP6V1A in the cell with a compound as described herein, or a pharmaceutically acceptable salt thereof.

- 30 [0473] In an aspect is provided a method of reducing the level of activity of mTORC1 in a cell, the method including contacting an ATP6V1A in the cell with a compound as described herein.

[0474] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in reducing the level of activity of mTORC1 in a cell including contacting an ATP6V1A in the cell with the compound, or a pharmaceutically acceptable salt thereof.

5 [0475] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of activity of mTORC1 in a cell, the use including contacting an ATP6V1A in the cell with the compound, or a pharmaceutically acceptable salt thereof.

10 [0476] In an aspect is provided a method of reducing the level of activity of an ATP6V1A, the method including contacting the ATP6V1A with a compound described herein, or a pharmaceutically acceptable salt thereof.

[0477] In an aspect is provided a method of reducing the level of activity of an ATP6V1A, the method including contacting the ATP6V1A with a compound described herein.

15 [0478] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in reducing the level of activity of an ATP6V1A including contacting the ATP6V1A with the compound, or a pharmaceutically acceptable salt thereof.

[0479] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for reducing the level of activity of an ATP6V1A, the use including contacting the ATP6V1A with the compound, or a
20 pharmaceutically acceptable salt thereof.

[0480] In embodiments, the method includes reducing the activity of mTORC1 more than reducing the activity of mTORC2 (e.g., at least 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 100000, 1000000-fold more).

25 In embodiments, the method includes reducing the activity of mTORC1 more than reducing the activity of mTORC2 (e.g., about 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 100000, 1000000-fold more). In embodiments, the method includes reducing the activity of mTORC1 more than reducing the
30 activity of mTORC2 (e.g., 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20,

30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 100000, 1000000-fold more).

[0481] In embodiments, the method includes reducing (e.g., reduced relative to a control) mTORC1 signaling by preventing mTORC1 localization to the lysosome. In embodiments, the method includes modulating (e.g., preventing the formation) of the Ragulator complex. In embodiments, the method includes reducing (e.g., reduced relative to a control) mTORC1 signaling by causing an accumulation of Ragulator complex in the lysosome. In embodiments, the method includes preventing the activation of the Ragulator complex. In embodiments, the method includes preventing the binding of mTORC1 to the Ragulator complex. In embodiments, the method includes preventing the formation of the Ragulator complex.

[0482] In embodiments, the method includes inhibiting the activation of the Ragulator complex. In embodiments, the method includes inhibiting the binding of mTORC1 to the Ragulator complex. In embodiments, the method includes inhibiting the formation of the Ragulator complex. In embodiments, the method includes inhibiting the amino-acid-induced localization of mTORC1 to the lysosome. In embodiments, the method includes inhibiting the binding between the Vacuolar H⁺-ATPase protein complex and the Ragulator. In embodiments, the method includes inhibiting the activity of Rag activity. In embodiments, the method includes inhibiting the GTPase activity of Rag. In embodiments, the method includes inhibiting the Rag GTPase-induced localization of mTORC1 to the lysosome. In embodiments, the method includes increased acidification of a lysosome. In embodiments, the method includes inhibiting the phosphorylation of 4EBP1. In embodiments, the method includes inhibiting the phosphorylation of S6. In embodiments, the method includes inhibiting the activity of Vacuolar H⁺-ATPase protein complex. In embodiments, the method includes increasing autophagy. In embodiments, the method includes inhibiting the Rag-A/B Rag-C/D complex interaction with Raptor in mTORC1. In embodiments, the method includes inhibiting the phosphorylation of ULK1 kinase. In embodiments, the method includes increasing the nuclear translocation and/or activation of TFEB transcription factor.

[0483] In an aspect is provided a method for increasing autophagy in a subject in need thereof, the method including administering to the subject in need thereof a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0484] In an aspect is provided a method for increasing autophagy in a subject in need thereof, the method including administering to the subject in need thereof a therapeutically effective amount of a compound described herein.

[0485] In an aspect is provided a compound described herein, or a pharmaceutically acceptable salt thereof, for use in a method of increasing autophagy including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

[0486] In an aspect is provided use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing autophagy, the use including administering to a subject in need thereof a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof.

V. Vacuolar H⁺-ATPase

[0487] In an aspect is provided a Vacuolar H⁺-ATPase protein complex covalently bonded to a compound described herein, or a pharmaceutically acceptable salt thereof, which may be referred to herein as a Vacuolar H⁺-ATPase protein complex-compound complex.

[0488] In an aspect is provided a Vacuolar H⁺-ATPase protein complex covalently bonded to a compound described herein, which may be referred to herein as a Vacuolar H⁺-ATPase protein complex-compound complex. In embodiments, the Vacuolar H⁺-ATPase protein complex is a human Vacuolar H⁺-ATPase protein complex. In embodiments, the compound is provided in a therapeutically effective amount. In embodiments, the compound contacts an amino acid corresponding to C277 of human ATP6V1A in the Vacuolar H⁺-ATPase protein complex. In embodiments, the compound covalently binds an amino acid corresponding to C277 of human ATP6V1A in the Vacuolar H⁺-ATPase protein complex.

[0489] In embodiments, an ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) is covalently bonded to a compound (e.g., compound described herein or a portion of a compound described herein). In embodiments, an ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) is irreversibly covalently bonded to a compound (e.g., compound described herein or a portion of a compound described herein). In embodiments, an ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) is reversibly covalently bonded to a compound (e.g., compound described herein or a portion of a

compound described herein). In embodiments, an ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) is covalently bonded to a portion of a compound (e.g., compound described herein). In embodiments, an ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) is irreversibly covalently bonded to a portion of a compound described herein. In embodiments, an ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) is reversibly covalently bonded to a portion of a compound described herein. In embodiments, the compound described herein is bonded to a cysteine residue (e.g., residue corresponding to Cys277 of human ATP6V1A) of the ATP6V1A protein (e.g., human ATP6V1A protein).

[0490] In embodiments, the ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) covalently bonded to a compound described herein is the product of a reaction between the ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) and a compound described herein. It will be understood that the covalently bonded ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) and compound described herein are the remnants of the reactant ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) and compound, wherein each reactant now participates in the covalent bond between the ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) and compound. In embodiments of the covalently bonded ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) and compound described herein, the remnant of the E substituent is a linker including a covalent bond between the ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) and the remainder of the compound described herein. It will be understood by a person of ordinary skill in the art that when an ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human Vacuolar H⁺-ATPase protein complex) is covalently bonded to a compound described herein, the compound described herein forms a remnant of the pre-reacted compound wherein a bond connects the remnant of the compound to the remnant of the ATP6V1A in a Vacuolar H⁺-ATPase protein complex (e.g., human ATP6V1A in a human

Vacuolar H⁺-ATPase protein complex) (e.g., cysteine sulfur, sulfur of amino acid corresponding to C277 of human ATP6V1A in a Vacuolar H⁺-ATPase protein complex).

[0491] In an aspect is provided an ATP6V1A protein covalently bonded to a compound described herein, or a pharmaceutically acceptable salt thereof, which may be referred to herein as an ATP6V1A protein-compound complex.

[0492] In an aspect is provided an ATP6V1A protein covalently bonded to a compound described herein, which may be referred to herein as an ATP6V1A protein-compound complex. In embodiments, the ATP6V1A protein is a human ATP6V1A protein. In embodiments, human ATP6V1A protein has a sequence described herein. In embodiments, the compound is provided in a therapeutically effective amount. In embodiments, the compound contacts an amino acid corresponding to C277 of human ATP6V1A. In embodiments, the compound covalently binds an amino acid corresponding to C277 of human ATP6V1A.

[0493] In embodiments, an ATP6V1A protein (e.g., human ATP6V1A) is covalently bonded to a compound (e.g., compound described herein or a portion of a compound described herein). In embodiments, an ATP6V1A protein (e.g., human ATP6V1A) is irreversibly covalently bonded to a compound (e.g., compound described herein or a portion of a compound described herein). In embodiments, the ATP6V1A protein (e.g., human ATP6V1A) is reversibly covalently bonded to a compound (e.g., compound described herein or a portion of a compound described herein). In embodiments, the ATP6V1A protein (e.g., human ATP6V1A) is covalently bonded to a portion of a compound (e.g., compound described herein). In embodiments, the ATP6V1A protein (e.g., human ATP6V1A) is irreversibly covalently bonded to a portion of a compound described herein. In embodiments, the ATP6V1A protein (e.g., human ATP6V1A) is reversibly covalently bonded to a portion of a compound described herein. In embodiments, the compound described herein is bonded to a cysteine residue (e.g., residue corresponding to Cys277 of human ATP6V1A) of the ATP6V1A protein (e.g., human ATP6V1A).

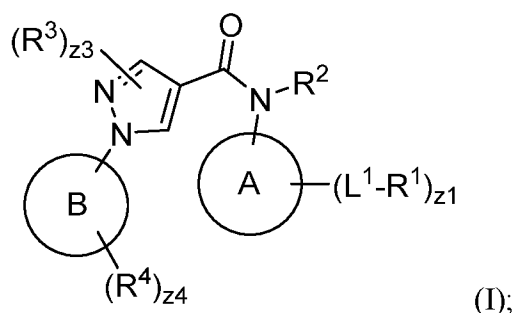
[0494] In embodiments, the ATP6V1A protein covalently bonded to a compound described herein is the product of a reaction between the ATP6V1A protein and a compound described herein. It will be understood that the covalently bonded ATP6V1A protein and compound described herein are the remnants of the reactant ATP6V1A protein and compound, wherein each reactant now participates in the covalent bond between the ATP6V1A protein and or

compound. In embodiments of the covalently bonded ATP6V1A protein and compound described herein, the remnant of the E substituent is a linker including a covalent bond between the ATP6V1A protein and the remainder of the compound described herein. It will be understood by a person of ordinary skill in the art that when a ATP6V1A protein is covalently bonded to a compound described herein, the compound described herein forms a remnant of the pre-reacted compound wherein a bond connects the remnant of the compound to the remnant of the ATP6V1A protein (e.g., cysteine sulfur, sulfur of amino acid corresponding to C277 of human ATP6V1A).

[0495] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

VI. Embodiments

[0496] Embodiment P1. A compound having the formula:



wherein,

Ring A is a phenyl or 5 to 6 membered heteroaryl;

Ring B is a phenyl or 5 to 6 membered heteroaryl;

L^1 is independently a bond, $-S(O)_2-$, $-N(R^5)-$, $-O-$, $-S-$, $-C(O)-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)-$, $-N(R^5)C(O)NH-$, $-NHC(O)N(R^5)-$, $-C(O)O-$, $-OC(O)-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R⁵ is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl;

R¹ is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OCX¹₃, -OCH₂X¹, -OCHX¹₂, -CN, -SO_{nl}R^{1D}, -SO_{v1}NR^{1A}R^{1B}, -NHC(O)NR^{1A}R^{1B}, -N(O)_{m1}, -NR^{1A}R^{1B}, -C(O)R^{1C}, -C(O)-OR^{1C}, -C(O)NR^{1A}R^{1B}, -OR^{1D}, -NR^{1A}SO₂R^{1D}, -NR^{1A}C(O)R^{1C}, -NR^{1A}C(O)OR^{1C}, -NR^{1A}OR^{1C}, -N₃, E, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent -L¹-R¹ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

R² is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl;

R³ and R⁴ are independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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} , and R^{1D} are independently hydrogen, halogen, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{CF}_3$, $-\text{Cl}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{Br}$, $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{I}$, $-\text{CHCl}_2$, $-\text{CHBr}_2$, $-\text{CHF}_2$, $-\text{CHI}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}(\text{O})\text{NHNH}_2$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NH}\text{SO}_2\text{H}$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCF}_3$, $-\text{OCl}_3$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{F}$, $-\text{OCH}_2\text{I}$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHF}_2$, $-\text{OCHI}_2$, 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;

X^1 is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$;

n_1 is independently an integer from 0 to 4;

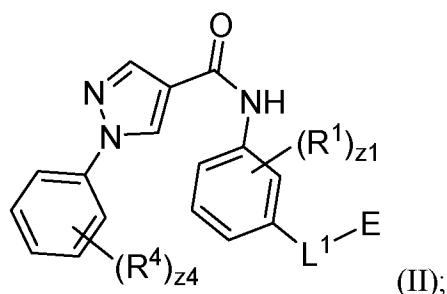
m_1 and v_1 are independently 1 or 2;

z_1 is independently an integer from 0 to 6;

z_3 is independently an integer from 0 to 2; and

z_4 is independently an integer from 0 to 6.

[0497] Embodiment P2. The compound of embodiment P1, having the formula:



wherein,

L^1 is independently a bond, $-\text{S}(\text{O})_2-$, $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{NHC}(\text{O})-$, $-\text{NHC}(\text{O})\text{NH}-$, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene;

R^1 is independently halogen, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{CF}_3$, $-\text{Cl}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{Br}$, $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{I}$, $-\text{CHCl}_2$, $-\text{CHBr}_2$, $-\text{CHF}_2$, $-\text{CHI}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}(\text{O})\text{NHNH}_2$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NH}\text{SO}_2\text{H}$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{OCCl}_3$, $-\text{OCBr}_3$, $-\text{OCF}_3$, $-\text{OCl}_3$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$,

-OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R¹ substituents may optionally be joined to form a

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

E is an electrophilic moiety;

R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H,

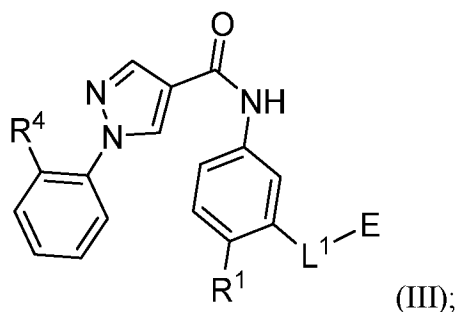
10 -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or

15 unsubstituted heteroaryl;

z₁ is independently an integer from 0 to 4; and

z₄ is independently an integer from 0 to 5.

[0498] Embodiment P3. The compound of embodiment P1, having the formula:



20 wherein,

L¹ is independently a bond, -S(O)₂-, -NH-, -O-, -S-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene;

R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H,

25

-SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety; and

R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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.

[0499] Embodiment P4. The compound of one of embodiments P1 to P3, wherein R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0500] Embodiment P5. The compound of one of embodiments P1 to P3, wherein R¹ is independently halogen.

[0501] Embodiment P6. The compound of one of embodiments P1 to P3, wherein R¹ is -F.

[0502] Embodiment P7. The compound of one of embodiments P1 to P6, wherein R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F,

-OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0503] Embodiment P8. The compound of one of embodiments P1 to P6, wherein R⁴ is independently halogen.

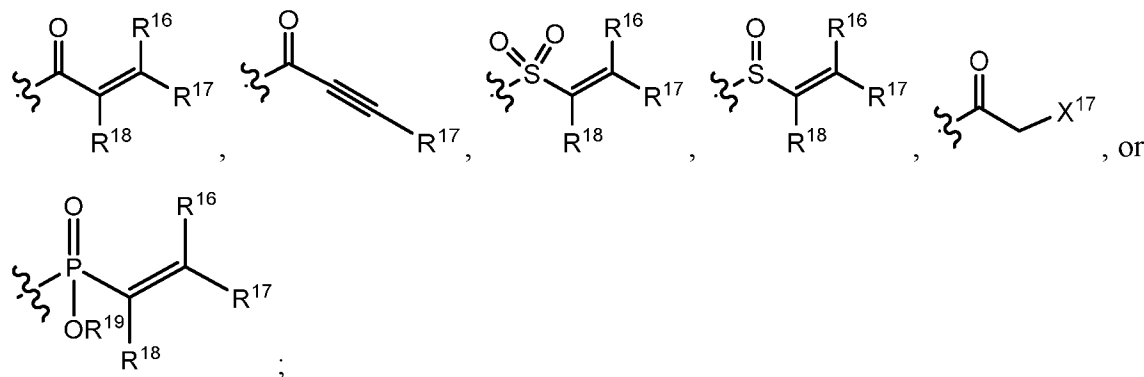
5 **[0504]** Embodiment P9. The compound of one of embodiments P1 to P6, wherein R⁴ is -F.

[0505] Embodiment P10. The compound of one of embodiments P1 to P9, wherein L¹ is independently -S(O)₂-, -NH-, or substituted or unsubstituted 5 to 6 membered heterocycloalkylene.

10 **[0506]** Embodiment P11. The compound of one of embodiments P1 to P9, wherein L¹ is independently -S(O)₂-, -NH-, unsubstituted pyrrolidinylene, unsubstituted piperidinylene, or unsubstituted piperazinylene.

[0507] Embodiment P12. The compound of one of embodiments P1 to P9, wherein L¹ is independently -NH-.

15 **[0508]** Embodiment P13. The compound of one of embodiments P1 to P12 wherein E is



wherein R¹⁶ is independently hydrogen, halogen, -CX¹⁶₃, -CHX¹⁶₂, -CH₂X¹⁶, -CN, -SO_{n16}R^{16A}, -SO_{v16}NR^{16A}R^{16B}, -NHN^{16A}R^{16B}, -ONR^{16A}R^{16B}, -NHC(O)NHN^{16A}R^{16B},
 20 -NHC(O)NR^{16A}R^{16B}, -N(O)_{m16}, -NR^{16A}R^{16B}, -C(O)R^{16A}, -C(O)-OR^{16A}, -C(O)NR^{16A}R^{16B}, -OR^{16A}, -NR^{16A}SO₂R^{16B}, -NR^{16A}C(O)R^{16B}, -NR^{16A}C(O)OR^{16B}, -NR^{16A}OR^{16B}, -OCX¹⁶₃, -OCHX¹⁶₂, -OCH₂X¹⁶, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

- R^{17} is independently hydrogen, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-CH_2X^{17}$, $-CN$, $-SO_{n17}R^{17A}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHN R^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC(O)NHN R^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17A}$, $-C(O)-OR^{17A}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17A}$, $-NR^{17A}SO_2R^{17B}$, $-NR^{17A}C(O)R^{17B}$, $-NR^{17A}C(O)OR^{17B}$, $-NR^{17A}OR^{17B}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, $-OCH_2X^{17}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;
- R^{18} is independently hydrogen, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-CN$, $-SO_{n18}R^{18A}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHN R^{18A}R^{18B}$, $-ONR^{18A}R^{18B}$, $-NHC(O)NHN R^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-C(O)R^{18A}$, $-C(O)-OR^{18A}$, $-C(O)NR^{18A}R^{18B}$, $-OR^{18A}$, $-NR^{18A}SO_2R^{18B}$, $-NR^{18A}C(O)R^{18B}$, $-NR^{18A}C(O)OR^{18B}$, $-NR^{18A}OR^{18B}$, $-OCX^{18}_3$, $-OCHX^{18}_2$, $-OCH_2X^{18}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;
- R^{19} is independently hydrogen, halogen, $-CX^{19}_3$, $-CHX^{19}_2$, $-CH_2X^{19}$, $-CN$, $-SO_{n19}R^{19A}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHN R^{19A}R^{19B}$, $-ONR^{19A}R^{19B}$, $-NHC(O)NHN R^{19A}R^{19B}$, $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-C(O)R^{19A}$, $-C(O)-OR^{19A}$, $-C(O)NR^{19A}R^{19B}$, $-OR^{19A}$, $-NR^{19A}SO_2R^{19B}$, $-NR^{19A}C(O)R^{19B}$, $-NR^{19A}C(O)OR^{19B}$, $-NR^{19A}OR^{19B}$, $-OCX^{19}_3$, $-OCHX^{19}_2$, $-OCH_2X^{19}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;
- R^{16A} , R^{16B} , R^{17A} , R^{17B} , R^{18A} , R^{18B} , R^{19A} , and R^{19B} are independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-COOH$, $-CONH_2$, 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^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may

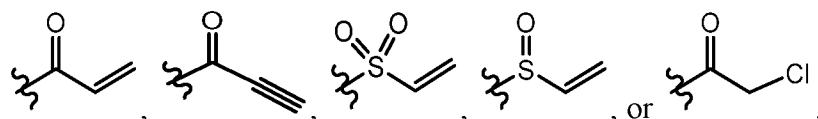
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X^1 , X^{16} , X^{17} , X^{18} , and X^{19} is independently -F, -Cl, -Br, or -I;

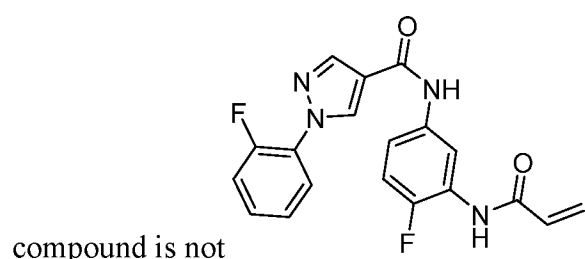
n_{16} , n_{17} , n_{18} , and n_{19} are independently an integer from 0 to 4; and

5 m_{16} , m_{17} , m_{18} , m_{19} , v_{16} , v_{17} , v_{18} , and v_{19} are independently 1 or 2.

[0509] Embodiment P14. The compound of one of embodiments P1 to P12, wherein E is



[0510] Embodiment P15. The compound of one of embodiments P1 to P14, wherein the



10 **[0511]** Embodiment P16. A pharmaceutical composition comprising a compound of one of embodiments P1 to P15 and a pharmaceutically acceptable excipient.

[0512] Embodiment P17. A method for treating cancer in a subject in need thereof, said method comprising administering to the subject in need thereof a therapeutically effective amount of a compound of one of embodiments P1 to P15.

15 **[0513]** Embodiment P18. The method of embodiment P17, wherein said cancer is renal cell carcinoma, follicular lymphoma, glioblastoma, colorectal cancer, endometrial, or lung cancer.

[0514] Embodiment P19. A method of reducing the level of activity of mTORC1 in a subject in need thereof, the method comprising administering to the subject in need thereof an
20 effective amount of a compound of one of embodiments P1 to P15.

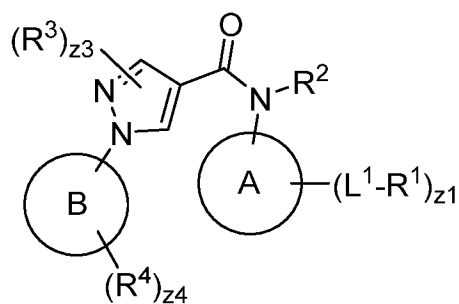
[0515] Embodiment P20. A method of reducing the level of activity of mTORC1 in a cell, the method comprising contacting a Vacuolar H^+ -ATPase protein complex in said cell with a compound of one of embodiments P1 to P15.

[0516] Embodiment P21. A method of reducing the level of activity of mTORC1 in a cell, the method comprising contacting an ATP6V1A in said cell with a compound of one of embodiments P1 to P15.

[0517] Embodiment P22. A method of reducing the level of activity of a Vacuolar H⁺-ATPase protein complex, the method comprising contacting an ATP6V1A in the Vacuolar H⁺-ATPase protein complex with a compound of one of embodiments P1 to P15.

VII. Additional embodiments

[0518] Embodiment 1. A compound, or a pharmaceutically acceptable salt thereof, having the formula:



wherein

Ring A is a phenyl or 5 to 6 membered heteroaryl;

Ring B is a phenyl or 5 to 6 membered heteroaryl;

L¹ is independently a bond, -S(O)₂-, -N(R⁵)-, -O-, -S-, -C(O)-, -C(O)N(R⁵)-,

-N(R⁵)C(O)-, -N(R⁵)C(O)NH-, -NHC(O)N(R⁵)-, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R⁵ is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl,

-CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl,

unsubstituted aryl, or unsubstituted heteroaryl;

R^1 is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-SO_{nl}R^{1D}$, $-SO_{vl}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{ml}$, $-NR^{1A}R^{1B}$, $-C(O)R^{1C}$, $-C(O)-OR^{1C}$, $-C(O)NR^{1A}R^{1B}$, $-OR^{1D}$, $-NR^{1A}SO_2R^{1D}$, $-NR^{1A}C(O)R^{1C}$, $-NR^{1A}C(O)OR^{1C}$, $-NR^{1A}OR^{1C}$, $-N_3$, E, substituted or unsubstituted alkyl, substituted or unsubstituted

- 5 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
two adjacent $-L^1-R^1$ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- 10 E is an electrophilic moiety;

R^2 is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl;

- R^3 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, 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^4 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, 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; two adjacent R⁴ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{1A}, R^{1B}, R^{1C}, and R^{1D} are independently hydrogen, halogen, -CCl₃, -CBr₃,

- 5 -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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;
- 10

X¹ is independently -F, -Cl, -Br, or -I;

n1 is independently an integer from 0 to 4;

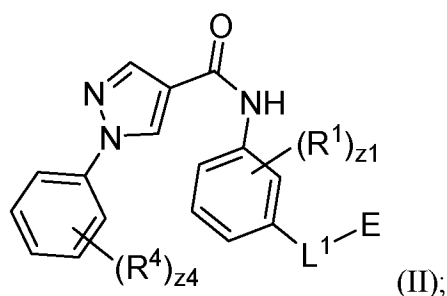
m1 and v1 are independently 1 or 2;

- 15 z1 is independently an integer from 0 to 5;

z3 is independently an integer from 0 to 2; and

z4 is independently an integer from 0 to 5.

[0519] Embodiment 2. The compound of embodiment 1, having the formula:



- 20 wherein

L¹ is independently a bond, -S(O)₂-, -NH-, -O-, -S-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene;

R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R¹ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

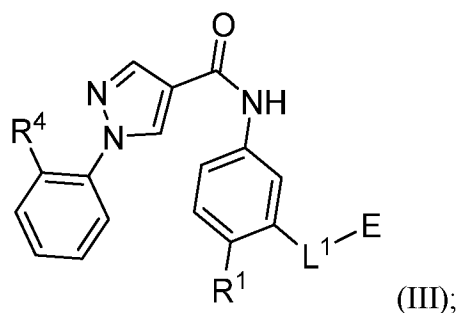
E is an electrophilic moiety;

R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R⁴ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

z₁ is independently an integer from 0 to 4; and

z₄ is independently an integer from 0 to 5.

[0520] Embodiment 3. The compound of embodiment 1, having the formula:



wherein

L^1 is independently a bond, $-S(O)_2-$, $-NH-$, $-O-$, $-S-$, $-C(O)NH-$, $-NHC(O)-$, $-NHC(O)NH-$, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene;

R^1 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$,

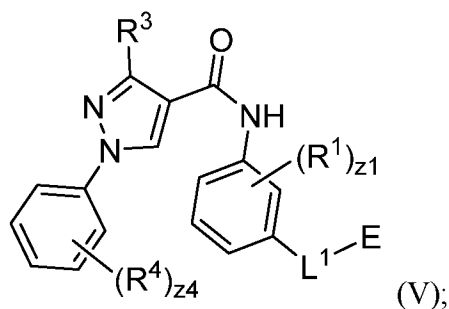
5 $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety; and

R^4 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$,

15 $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, 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.

[0521] Embodiment 4. The compound of embodiment 1, having the formula:



wherein

L^1 is independently a bond, $-S(O)_2-$, $-NH-$, $-O-$, $-S-$, $-C(O)NH-$, $-NHC(O)-$,

25 $-NHC(O)NH-$, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene;

R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

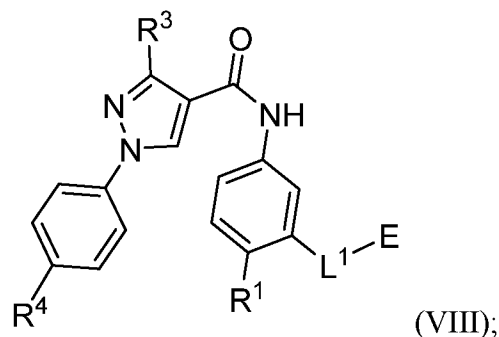
R³ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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 independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R⁴ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

z₁ is independently an integer from 0 to 4; and

z₄ is independently an integer from 0 to 5.

[0522] Embodiment 5. The compound of embodiment 1, having the formula:



wherein

L¹ is independently a bond, -S(O)₂-, -NH-, -O-, -S-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene;

R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

R³ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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

R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl,

-OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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.

5 **[0523]** Embodiment 6. The compound of one of embodiments 1, 4, and 5, wherein R³ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F,
10 -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0524] Embodiment 7. The compound of one of embodiments 1, 4, and 5, wherein R³ is independently halogen, -CCl₃, -CBr₃, -CF₃, or -Cl₃.

15 **[0525]** Embodiment 8. The compound of one of embodiments 1, 4, and 5, wherein R³ is independently -Br or -CF₃.

[0526] Embodiment 9. The compound of one of embodiments 1 to 8, wherein R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H,
20 -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0527] Embodiment 10. The compound of one of embodiments 1 to 8, wherein R¹ is independently halogen.

25 **[0528]** Embodiment 11. The compound of one of embodiments 1 to 8, wherein R¹ is independently -F.

[0529] Embodiment 12. The compound of one of embodiments 1 to 11, wherein R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H,
30 -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F,

-OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl.

[0530] Embodiment 13. The compound of one of embodiments 1 to 11, wherein R⁴ is independently halogen.

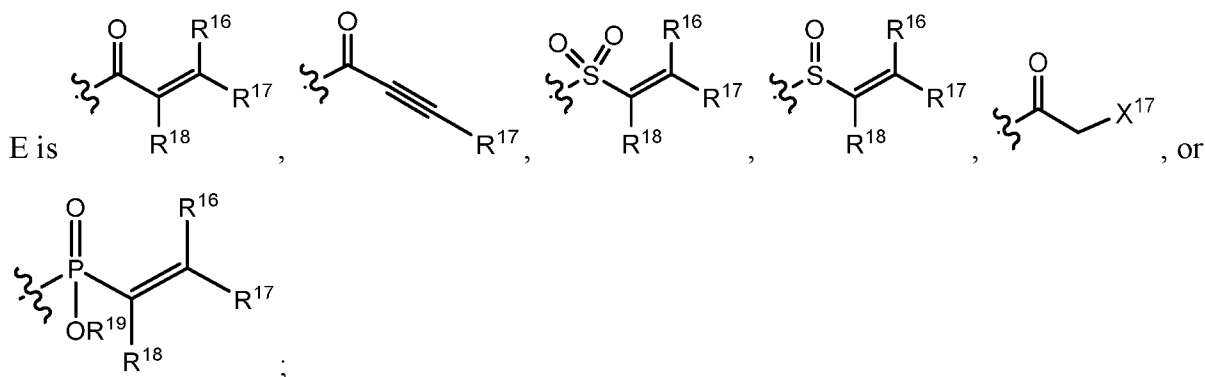
5 **[0531]** Embodiment 14. The compound of one of embodiments 1 to 11, wherein R⁴ is independently -F.

[0532] Embodiment 15. The compound of one of embodiments 1 to 14, wherein L¹ is independently -S(O)₂-, -NH-, or substituted or unsubstituted 5 to 6 membered heterocycloalkylene.

10 **[0533]** Embodiment 16. The compound of one of embodiments 1 to 14, wherein L¹ is independently -S(O)₂-, -NH-, unsubstituted pyrrolidinylene, unsubstituted piperidinylene, or unsubstituted piperazinylene.

[0534] Embodiment 17. The compound of one of embodiments 1 to 14, wherein L¹ is independently -NH-.

15 **[0535]** Embodiment 18. The compound of one of embodiments 1 to 17, wherein



wherein R¹⁶ is independently hydrogen, halogen, -CX¹⁶₃, -CHX¹⁶₂, -CH₂X¹⁶,
 -CN, -SO_{n16}R^{16A}, -SO_{v16}NR^{16A}R^{16B}, -NHN^{16A}R^{16B}, -ONR^{16A}R^{16B}, -NHC(O)NHN^{16A}R^{16B},
 20 -NHC(O)NR^{16A}R^{16B}, -N(O)_{m16}, -NR^{16A}R^{16B}, -C(O)R^{16A}, -C(O)-OR^{16A}, -C(O)NR^{16A}R^{16B},
 -OR^{16A}, -NR^{16A}SO₂R^{16B}, -NR^{16A}C(O)R^{16B}, -NR^{16A}C(O)OR^{16B}, -NR^{16A}OR^{16B}, -OCX¹⁶₃,
 -OCHX¹⁶₂, -OCH₂X¹⁶, substituted or unsubstituted alkyl, substituted or unsubstituted
 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R^{17} is independently hydrogen, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-CH_2X^{17}$, $-CN$, $-SO_{n17}R^{17A}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHN R^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC(O)NHN R^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17A}$, $-C(O)-OR^{17A}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17A}$, $-NR^{17A}SO_2R^{17B}$, $-NR^{17A}C(O)R^{17B}$, $-NR^{17A}C(O)OR^{17B}$, $-NR^{17A}OR^{17B}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, $-OCH_2X^{17}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R^{18} is independently hydrogen, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-CH_2X^{18}$, $-CN$, $-SO_{n18}R^{18A}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHN R^{18A}R^{18B}$, $-ONR^{18A}R^{18B}$, $-NHC(O)NHN R^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-C(O)R^{18A}$, $-C(O)-OR^{18A}$, $-C(O)NR^{18A}R^{18B}$, $-OR^{18A}$, $-NR^{18A}SO_2R^{18B}$, $-NR^{18A}C(O)R^{18B}$, $-NR^{18A}C(O)OR^{18B}$, $-NR^{18A}OR^{18B}$, $-OCX^{18}_3$, $-OCHX^{18}_2$, $-OCH_2X^{18}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R^{19} is independently hydrogen, halogen, $-CX^{19}_3$, $-CHX^{19}_2$, $-CH_2X^{19}$, $-CN$, $-SO_{n19}R^{19A}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHN R^{19A}R^{19B}$, $-ONR^{19A}R^{19B}$, $-NHC(O)NHN R^{19A}R^{19B}$, $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-C(O)R^{19A}$, $-C(O)-OR^{19A}$, $-C(O)NR^{19A}R^{19B}$, $-OR^{19A}$, $-NR^{19A}SO_2R^{19B}$, $-NR^{19A}C(O)R^{19B}$, $-NR^{19A}C(O)OR^{19B}$, $-NR^{19A}OR^{19B}$, $-OCX^{19}_3$, $-OCHX^{19}_2$, $-OCH_2X^{19}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R^{16A} , R^{16B} , R^{17A} , R^{17B} , R^{18A} , R^{18B} , R^{19A} , and R^{19B} are independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-COOH$, $-CONH_2$, 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^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may

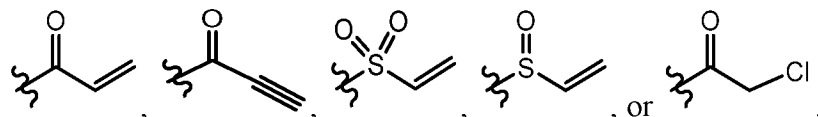
optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X^1 , X^{16} , X^{17} , X^{18} , and X^{19} is independently -F, -Cl, -Br, or -I;

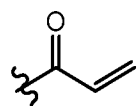
n_{16} , n_{17} , n_{18} , and n_{19} are independently an integer from 0 to 4; and

5 m_{16} , m_{17} , m_{18} , m_{19} , v_{16} , v_{17} , v_{18} , and v_{19} are independently 1 or 2.

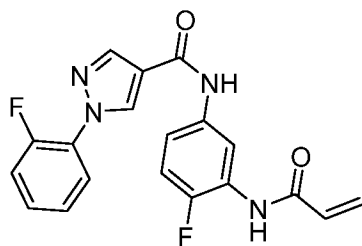
[0536] Embodiment 19. The compound of one of embodiments 1 to 17, wherein E is



[0537] Embodiment 20. The compound of one of embodiments 1 to 17, wherein E is



10 **[0538]** Embodiment 21. The compound of one of embodiments 1 to 3, wherein the



compound is not

[0539] Embodiment 22. A pharmaceutical composition comprising a compound of one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

15 **[0540]** Embodiment 23. A method for treating cancer in a subject in need thereof, said method comprising administering to the subject in need thereof a therapeutically effective amount of a compound of one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof.

[0541] Embodiment 24. The method of embodiment 23, wherein said cancer is renal
20 cell carcinoma, follicular lymphoma, glioblastoma, colorectal cancer, endometrial cancer, or lung cancer.

[0542] Embodiment 25. A method of reducing the level of activity of mTORC1 in a subject in need thereof, the method comprising administering to the subject in need thereof an

effective amount of a compound of one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof.

[0543] Embodiment 26. A method of reducing the level of activity of mTORC1 in a cell, the method comprising contacting a Vacuolar H⁺-ATPase protein complex in said cell with a compound of one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof.

[0544] Embodiment 27. A method of reducing the level of activity of mTORC1 in a cell, the method comprising contacting an ATP6V1A in said cell with a compound of one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof.

[0545] Embodiment 28. A method of reducing the level of activity of a Vacuolar H⁺-ATPase protein complex, the method comprising contacting an ATP6V1A in the Vacuolar H⁺-ATPase protein complex with a compound of one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof.

EXAMPLES

Example 1: Covalent targeting of the vacuolar H⁺-ATPase enhances cellular clearance through inhibition of lysosomal mTORC1 signaling

[0546] Autophagy is a lysosomal degradation pathway that eliminates aggregated proteins and damaged organelles to maintain cellular homeostasis. A major route for activating autophagy involves inhibition of the mTORC1 kinase, but selective and complete mTORC1 inhibition remains beyond the reach of current mTORC1-targeting compounds. Here, we have coupled screening of a covalent ligand library with activity-based protein profiling to discover EN6, a small-molecule *in vivo* activator of autophagy that covalently and selectively targets cysteine 277 in the ATP6V1A subunit of the lysosomal v-ATPase, which mediates mTORC1 activation at the lysosome. EN6-mediated ATP6V1A modification impairs mTORC1 lysosomal recruitment via the Rag guanosine triphosphatases, activates autophagy and increases lysosomal acidification. Consistently, EN6 clears TDP-43 aggregates, a causative agent in frontotemporal dementia, in an autophagy-dependent manner. Our results provide insight into how the v-ATPase regulates mTORC1, and reveal a unique approach for enhancing cellular clearance based on covalent inhibition of lysosomal mTORC1 signaling.

[0547] Autophagy is central to the maintenance of organismal homeostasis in both physiological and pathological situations. It is an essential, conserved lysosomal degradation

pathway that controls the quality of the cytoplasm by eliminating aggregated proteins and damaged organelles. Accordingly, alterations in autophagy have been linked to a wide range of diseases and conditions, including aging, cancer, metabolic disorders, and neurodegenerative diseases (1-3). Throughout the past decade, autophagy has attracted considerable attention as a target for the development of novel therapeutics (3,4).

[0548] The activity of the autophagic machinery is tightly linked to upstream signals, nutrients and stressors through mechanistic target of rapamycin complex 1 (mTORC1) protein kinase. mTORC1 phosphorylates and inhibits a master switch for autophagosome formation, the ULK1 kinase (5,6). Moreover, mTORC1 blocks the nuclear translocation and activation of the TFEB transcription factors, which functions as a ‘master regulator’ of catabolism by coordinately promoting the expression of genes required for autophagosome formation and lysosomal function (5-9). Inhibition of mTORC1 resulting from starvation or chemical inhibitors triggers autophagy by simultaneously unleashing the activity of ULK1 and TFEB. Most autophagy-modulators that have entered clinical development either target the mTOR pathway or impinge on poorly understood mTORC1-independent mechanisms, and their efficacy is predicted to be modest at best, versus their potential for significant off-target toxicological actions.

[0549] Most protein misfolding diseases are associated with intracytoplasmic deposition of aggregate-prone proteins in neurons and non-neuronal cells, which impair essential cellular pathways for transport, energy production and quality control (10,11). Over recent years, evidence has accumulated to demonstrate that upregulation of autophagy is protective against neurodegeneration. Numerous studies have demonstrated that aggregate-prone proteins at the heart of neurodegenerative disease toxicity are autophagy substrates, and that pharmacological activators of autophagy can be beneficial in both cell and animal models of these diseases, by both degrading intracytoplasmic aggregates and by preventing associated cell death (12-15).

[0550] While many agents have been discovered that either inhibit or activate autophagy, many of these compounds do not possess the required specificity to activate autophagy in a selective manner, either due to off-target effects or due to multiple functions of a specific target. The allosteric mTORC1 inhibitor, rapamycin, results in the relatively specific inhibition of mTORC1 by causing its binding to FK506-binding protein 1A (FKBP1A). However, rapamycin is an incomplete mTORC1 inhibitor; most notably it largely fails at

blocking mTORC1-dependent inhibitory phosphorylation of ULK1 and TFEB and at triggering their pro-catabolic programs. Thus, despite some early success in vitro, rapamycin-based drugs (Rapalogues) have proven ineffective in reducing neurotoxic protein aggregates (16-18). The recently developed 'ATP-competitive' compounds block the kinase activity of mTOR toward virtually all substrates. The higher potency and broader range of ATP-competitive mTOR inhibitors has led to promising results in cancer clinical trials; however, these compounds have shown considerable toxicity and the ability to cause substantial toxicity to pancreatic β -cell islets leading to β -cell death. Most relevant in the context of neurodegenerative disease, ATP competitive mTOR inhibitors strongly suppress Akt signaling, which is an essential survival signal for neuronal cells (19-22). The limitations of current mTOR inhibitors thus create an urgent need to identify new targets that could lead to selective activation of autophagy while avoiding unacceptable toxicities.

[0551] To be activated, mTORC1 needs to translocate to the lysosome membrane (5,6). Nutrients, primarily amino acids, directly regulate the lysosomal recruitment of mTORC1 by modulating the nucleotide state of the Rag GTPases. The Rags assemble as obligate heterodimers composed of RagA or RagB (which are highly similar to each other) associated with RagC or RagD, and are tethered to the lysosomal membrane by the pentameric Ragulator complex, composed of the LAMTOR1-5 proteins (23-25). Under amino acid sufficiency, the Rag GTPases become active by adopting a nucleotide state in which Rag-A/B is GTP-loaded and Rag-C/D is GDP-loaded, and mediate the lysosomal attachment of mTORC1 by directly interacting with the mTORC1 subunit Raptor (23-25).

[0552] A key but poorly understood player in Rag-mTORC1 activation is the vacuolar H⁺-ATPase (v-ATPase), an evolutionarily conserved ATP-driven rotary proton pump that couples ATP hydrolysis by its peripheral V1 domain to proton translocation through membrane integral V0 domain to acidify the lysosome and enable its degradative functions (26,27). The v-ATPase forms a physical supercomplex with Ragulator and the Rag GTPases, and its integrity and activity are essential for lysosomal mTORC1 recruitment in response to amino acids (28-31). Although its precise role in Rag-mTORC1 activation is not completely understood, the v-ATPase represents a prime target for discovery of small molecules that may simultaneously block mTORC1 activation and enhance autophagic function. In this study, through the coupling of chemoproteomics and covalent ligand screening, we have discovered a small-molecule activator of autophagy that acts through covalently targeting a unique

regulatory cysteine on ATP6V1A, resulting in the complete and selective inactivation of mTORC1 and enhanced cellular clearance of toxic protein aggregates.

[0553] To simultaneously discover new targets, druggable hotspots and small-molecule modulators for activating autophagy, we screened a library of 217 cysteine- and lysine-reactive ligands based on acrylamide, chloroacetamide, and dichlorotriazine scaffolds in a cell-based autophagic flux assay that utilizes a dual-color, cleavable LC3B reporter (32-37). By running this screen in mouse embryonic fibroblast (MEF) cells, we identified several covalent ligands that increased LC3B processing and thus potentially increased autophagy activation (FIG. 1A, Table 1). mTORC1 inhibitors rapamycin and Torin1 also demonstrated expected efficacy in this assay. Upon replication in HEK293 cells, the screen yielded the cysteine-reactive acrylamide EN6 as an inducer of LC3B degradation to a comparable degree to direct mTORC1 inhibitors, rapamycin and Torin1 (FIGS. 1B-1D). We validated these findings by showing that, in HEK293 cells, EN6 treatment increased the levels of processed LC3BII (FIG. 1E), and triggered formation of LC3 puncta to a similar degree to Torin1 treatment (FIG. 1F).

[0554] We next mapped the proteome-wide cysteine-reactivity of EN6 in MEF cells using competitive isotopic tandem orthogonal proteolysis-enabled activity-based protein profiling (isoTOP-ABPP) to discover the mechanism of action of this compound (FIG. 2A). Upon in situ treatment of cells with vehicle or EN6, we labeled the resulting cell lysates with the cysteine-reactive alkyne-functionalized iodoacetamide probe (IA-alkyne) followed by the isoTOP-ABPP chemoproteomics pipeline (35,36,38-41). The primary site of EN6 was identified as cysteine 277 (C277) of ATP6V1A, the catalytic subunit of the lysosomal v-ATPase (FIG. 2B). This site showed an isotopic light-to-heavy (control-to-EN6-treated) ratio of >50 indicating high target engagement of this site compared to other targets. We confirmed this interaction by demonstrating that EN6 displaces iodoacetamide-rhodamine (IA-rhodamine) labeling from recombinant human ATP6V1A protein with an IC₅₀ of 1.7 μM (FIG. 2C).

[0555] Previous studies showed that the lysosomal v-ATPase physically interacts with the Ragulator-Rag complex in an amino acid-regulated manner and enables Ragulator-Rags to recruit mTORC1, leading to activation of anabolic programs and inhibition of autophagy initiation (28,42). We thus asked whether, by binding to the ATP6V1A subunit of the v-ATPase, EN6 may disrupt mTORC1 recruitment to the lysosome, thus leading to its observed

autophagy-activating effect. Consistent with this premise, we found that EN6 treatment in cells led to complete inactivation of mTORC1 signaling as shown by reduced levels of phosphorylated canonical substrates, S6 kinase 1 (S6K1) and 4EBP1 (FIG. 3A). Notably, consistent with specific mTORC1 inhibition by EN6, treatment with Torin1, but not EN6, blocked mTORC2-dependent AKT phosphorylation (FIG. 3B). Confirming that mTORC1 inhibition by EN6 involves modification of C277 of ATP6V1A, phosphorylation of S6K and ULK1 were completely resistant to EN6-mediated inhibition in cells in which endogenous ATP6V1A was knocked down and replaced with the non-modifiable C277A mutant (FIG. 3C, FIG. 3D). In these cells, EN6-induced LC3BII accumulation and p62/SQSTM1 degradation were also prevented by the C277A substitution, indicating that autophagy activation by EN6 is also strictly dependent on C277 modification (FIG. 3C, FIG. 3D).

[0556] The v-ATPase interacts with Ragulator-Rags to enable amino acid-dependent recruitment of mTORC1 to the lysosome (28,42). Consistent with an inhibitory mechanism towards this pathway, EN6 treatment completely abrogated amino acid-induced mTORC1 recruitment to LAMP2-positive lysosomes (FIG. 3E).

[0557] As previously shown, amino acids modulate the interaction of FLAG-tagged Ragulator subunit p14 with the v-ATPase (FIG. 4A). Notably, EN6 decreased the overall binding between the v-ATPase and Ragulator, and rendered this interaction insensitive to amino acids (FIG. 4A). An explanation for this result is that covalent modification of C277 of ATP6V1A by EN6 causes a conformational change in the v-ATPase that partially decouples it from Ragulator-Rag and prevents activation of the latter complex by amino acids. Collectively, these data reveal that, by targeting C277 of ATP6V1A, EN6 impairs Rag GTPase-mediated recruitment of mTORC1 to the lysosome, leading to constitutive activation of autophagy.

[0558] mTORC1 inhibition leads to upregulation of the catabolic functions of the lysosome through dephosphorylation and nuclear translocation of TFEB (5,7-9). Consistently, upon EN6 treatment we observed greatly enhanced nuclear translocation of TFEB and significantly increased levels of several lysosomal gene transcripts that are direct TFEB transcriptional targets, including v-ATPase components (FIG. 4B, FIG. 4C). We also showed that transcriptional targets measured that are not regulated by TFEB are not changed (FIG. 8). Consistent with these transcriptional changes, EN6 treatment led to significantly increased

acidification of the lysosome, as shown by lysosensor staining, and this heightened acidification was blocked by the v-ATPase inhibitor bafilomycin A1 (FIG. 4D, FIG. 4E).

[0559] To determine whether EN6-mediated inhibition of mTORC1 and activation of autophagy could aid in boosting cellular clearance, we tested the effect of EN6 in clearing toxic Tar-binding protein 43 (TDP43) protein aggregates, which drive the development of amyotrophic lateral sclerosis (ALS) (43). In an IPTG-inducible GFP-TDP43 U2OS osteosarcoma cell line model, IPTG stimulation led to the rapid formation of TDP-43 aggregates, which were reduced by 75 % upon 7 hour EN6 treatment. EN6-mediated clearance of TDP-43 aggregates was lysosome- and v-ATPase-dependent, as it was prevented by co-treatment with bafilomycin A1 (FIG. 5A, FIG. 5B). Thus, our results indicate that EN6 is capable of clearing toxic protein aggregates in an autophagy-dependent manner.

[0560] We next tested whether EN6 is able to inhibit mTORC1 and activate autophagy *in vivo*. Three mice cohorts were injected intraperitoneally with vehicle, rapamycin or EN6, and analyzed after 4 hours. mTORC1 signaling was significantly impaired across the heart, kidney, and skeletal muscle, as demonstrated by reduced phosphorylation of S6, whereas autophagy was strongly activated, as shown by heightened LC3BII levels (FIGS. 6A-6C). While EN6 was somewhat less potent than rapamycin in shutting down p-S6, it was significantly more effective than rapamycin at inhibiting phosphorylation of 4EBP1, consistent with our data in cell lines (FIG. 6A). Thus, due to its unique mechanism of action, EN6 functions as a complete and selective mTORC1 inhibitor both in cells and *in vivo*.

[0561] Our study identifies a covalent ligand, EN6, which selectively targets a unique druggable hotspot—C277 within the v-ATPase subunit ATP6V1A—to activate autophagy by selectively and completely inhibiting mTORC1 signaling through disrupting mTORC1 localization to the lysosome (FIG. 7). This is a distinct mechanism from other pharmacological modulators of autophagy that mostly act through directly targeting the kinase function mTORC1, such as with rapalogues and ATP-competitive inhibitors. While both rapalogues and ATP-competitive mTORC1 inhibitors have potential therapeutic activity, their clinical utility is hampered by their incomplete mTORC1 inhibition (rapalogues) and concomitant inhibition of mTORC2 (ATP competitors) (44-47). Chronic exposure to rapalogues also inhibits mTORC2, leading to metabolic dysregulation (48, 49). While EN6 shows promising cellular and *in vivo* activity, this covalent ligand is an early hit that still requires further medicinal chemistry efforts to optimize potency, selectivity, and *in vivo*

bioavailability and efficacy. Furthermore, while isoTOP-ABPP studies here show that C277 of ATP6V1A is one of the primary and most highly engaged targets of EN6 in cells, EN6 may possess additional off-targets that either exhibit lower degree of engagement or act through reversible interactions. Development of an alkyne-functionalized EN6 probe will aid in future assessment of EN6 selectivity and provide a foundation for additional medicinal chemistry, target engagement, and screening efforts to identify improved ligands against this site. Nonetheless, our study convincingly demonstrates that the EN6 signaling impairments are driven through the targeting of C277 of ATP6V1A.

[0562] A key question is how covalent modification of C277 within ATP6V1A affects v-ATPase function and mTORC1 regulation. By inspecting the previously reported crystal structures of the v-ATPase from *Thermus Thermophilus* and *Enterococcus Hirae* (50,51), we note that the equivalent residues to human C277, C255 in *Thermus* and C259 in *Enterococcus* V1A subunits, respectively, lie in the core of the catalytic B-A interface, in close proximity to residues that are critical for catalysis, such as E279 in human (E257 in *Thermus* and E261 in *Enterococcus*, respectively). Because the side chain of C277 points away from the nucleotide, this residue is unlikely to play a direct role in catalysis, however, covalent modification of this cysteine could affect the rate of ATP hydrolysis and, therefore, proton pumping, ultimately impacting lysosomal acidification (52). Moreover, the conformational change induced by covalent modification of C277 could propagate to the Ragulator-Rag binding interface, thus interfering with their activation and ability to recruit mTORC1. Future structural biology efforts with EN6 and v-ATPase will yield additional insights into the mechanism through which the v-ATPase interacts with the Ragulator-Rag complex to enable mTORC1 recruitment to the lysosome, and into how covalent modification by EN6 disrupts this process.

[0563] A major challenge of chemical genetic screens is identifying the targets of leads that arise from screens. Oftentimes, lead compounds must be derivatized to bear biorthogonal and photoaffinity handles or conjugated to beads to facilitate chemoproteomic target identification. These approaches require additional synthetic efforts to make analogs of the lead molecule and alter the structure of the molecule, which may hinder or prevent target identification. Previous studies have highlighted the utility of covalent ligands and chemoproteomics in accessing unique ligandable sites within classically undruggable protein targets (34-36,41,53).

[0564] Our study once again highlights the utility of chemoproteomics-enabled covalent ligand screening platforms to rapidly deconvolute the mechanism of action of cellular phenotypic screening hits and uncover unique and novel ligandable sites and druggable modalities that would not be predicted *a priori*. In this study, we reveal a cell and *in vivo*-active covalent ligand EN6 that uniquely targets a novel ligandable cysteine within the ATP6V1A v-ATPase complex to inhibit mTORC1 signaling and activate autophagy to improve cellular clearance.

Example 2: Methods

[0565] Cell culture

[0566] Human embryonic kidney HEK293T and HEK293A cells, mouse embryonic fibroblasts (MEF), HEK293A cells stably expressing GFP-LC3-RFP-LC3ΔG, MEF cells stably expressing GFP-LC3-RFP-LC3ΔG and human bone osteosarcoma epithelial U2OS cells stably expressing GFP-TDP43 were maintained in DMEM supplemented with 10 vol% FBS and 1 vol% GlutaMax. All cells were incubated in 5% CO₂ humidified air, and subcultured when 80% confluence was reached.

[0567] Screening for autophagy modulators. MEF cells stably expressing GFP-LC3-RFP-LC3ΔG were plated on 96-well plates (Corning; 3904) at 30,000 cells/well and allowed to grow in complete medium overnight. The cells were then incubated with covalent ligands (50 μM or at indicated concentrations), rapamycin (100 nM), Torin 1 (250 nM) or DMSO solvent control in complete medium (100 μL) for 24 h. After that, the medium was aspirated and the cells were fixed with 4% paraformaldehyde in PBS (100 μL) for 10 min, washed with PBS (100 μL) and assayed in PBS (100 μL) by SpectraMax i3 (Molecular Devices). GFP fluorescence was measured with excitation and emission at 488±9 nm and 514±15 nm respectively, while RFP fluorescence was measured with excitation and emission at 584±9 nm and 612±15 nm respectively.

[0568] For HEK293A cells stably expressing GFP-LC3-RFP-LC3ΔG, before they were seeded, 96-well plates were coated with fibronectin in PBS (5 μg/mL, 75 μL/well) for 1 h at 37 °C. The solution was then aspirated, and cells were plated at 30,000 cells/well, allowed to grow in complete medium overnight, treated and assayed with the same protocol as described above for MEF cells.

[0569] For checking cell viability, solutions were aspirated after treatment with the compounds, and the cells were fixed and stained by Hoechst 33342 (13.3 µg/mL) in formalin (100 µL) for 15 min. After that, cells were washed with PBS (100 µL) and assayed in PBS (100 µL) by SpectraMax i3 with excitation and emission at 350±9 nm and 461±15 nm respectively.

[0570] IsoTOP-ABPP chemoproteomic studies. IsoTOP-ABPP studies were done as previously reported (35,36). Cells were lysed by probe sonication in PBS and protein concentrations were measured by BCA assay (54). For *in situ* experiments, cells were treated for 90 min with either DMSO vehicle or covalently-acting small molecule (from 1000X DMSO stock) before cell collection and lysis. For *in vitro* experiments, proteome samples diluted in PBS (4 mg of proteome per biological replicate) were treated with a DMSO vehicle or covalently-acting small-molecule for 30 min at room temperature. Proteomes were subsequently labeled with IA-alkyne labeling (100 µM) for 1 h at room temperature. CuAAC was used by sequential addition of tris(2-carboxyethyl)phosphine (1 mM, Sigma), tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (34 µM, Sigma), copper (II) sulfate (1 mM, Sigma), and biotin-linker-azide—the linker functionalized with a TEV protease recognition sequence as well as an isotopically light or heavy valine for treatment of control or treated proteome, respectively. After CuAAC, proteomes were precipitated by centrifugation at 6500 x g, washed in ice-cold methanol, combined in a 1:1 control/treated ratio, washed again, then denatured and resolubilized by heating in 1.2% SDS/PBS to 80 °C for 5 minutes. Insoluble components were precipitated by centrifugation at 6500 x g and soluble proteome was diluted in 5 mL 0.2% SDS/PBS. Labeled proteins were bound to avidin-agarose beads (170 µl resuspended beads/sample, Thermo Pierce) while rotating overnight at 4 °C. Bead-linked proteins were enriched by washing three times each in PBS and water, then resuspended in 6 M urea/PBS (Sigma) and reduced in TCEP (1 mM, Sigma), alkylated with iodoacetamide (IA) (18 mM, Sigma), then washed and resuspended in 2 M urea and trypsinized overnight with 0.5 µg/µL sequencing grade trypsin (Promega). Tryptic peptides were eluted off. Beads were washed three times each in PBS and water, washed in TEV buffer solution (water, TEV buffer, 100 µM dithiothreitol) and resuspended in buffer with Ac-TEV protease and incubated overnight. Peptides were diluted in water and acidified with formic acid (1.2 M, Spectrum) and prepared for analysis.

[0571] Mass spectrometry analysis. Peptides from all chemoproteomic experiments were pressure-loaded onto a 250 µm inner diameter fused silica capillary tubing packed with 4 cm

of Aqua C18 reverse-phase resin (Phenomenex # 04A-4299) which was previously equilibrated on an Agilent 600 series HPLC using gradient from 100% buffer A to 100% buffer B over 10 min, followed by a 5 min wash with 100% buffer B and a 5 min wash with 100% buffer A. The samples were then attached using a MicroTee PEEK 360 μ m fitting (Thermo Fisher Scientific #p-888) to a 13 cm laser pulled column packed with 10 cm Aqua C18 reverse-phase resin and 3 cm of strong-cation exchange resin for isoTOP-ABPP studies. Samples were analyzed using an Q Exactive Plus mass spectrometer (Thermo Fisher Scientific) using a 5-step Multidimensional Protein Identification Technology (MudPIT) program, using 0%, 25%, 50%, 80%, and 100% salt bumps of 500 mM aqueous ammonium acetate and using a gradient of 5-55% buffer B in buffer A (buffer A: 95:5 water:acetonitrile, 0.1% formic acid; buffer B 80:20 acetonitrile:water, 0.1% formic acid). Data were collected in data-dependent acquisition mode with dynamic exclusion enabled (60 s). One full MS (MS1) scan (400-1800 m/z) was followed by 15 MS2 scans (ITMS) of the nth most abundant ions. Heated capillary temperature was set to 200 °C and the nanospray voltage was set to 2.75 kV.

[0572] Data were extracted in the form of MS1 and MS2 files using Raw Extractor 1.9.9.2 (The Scripps Research Institute) and searched against the Uniprot human database using ProLuCID search methodology in IP2 v.3 (Integrated Proteomics Applications, Inc.) (55). Cysteine residues were searched with a static modification for carboxyamino methylation (+57.02146) and up to two differential modifications for methionine oxidation and either the light or heavy TEV tags (+464.28596 or +470.29977, respectively). Peptides were required to have at least one tryptic end and to contain the TEV modification. ProLUCID data was filtered through DTASelect to achieve a peptide false-positive rate below 5%. Only those probe-modified peptides that were evident across all two out of three biological replicates were interpreted for their isotopic light to heavy ratios. Those probe-modified peptides that showed ratios >4 were further analyzed as potential targets of the covalently-acting small-molecule. For modified peptides with ratios >4, we filtered these hits for peptides were present in all three biological replicates. For those probe-modified peptide ratios >4, only those peptides with 3 ratios >4 were interpreted, and otherwise replaced with the lowest ratio. MS1 peak shapes of any resulting probe-modified peptides with ratios >3 were then manually confirmed to be of good quality for interpreted peptides across all biological replicates.

[0573] Constructing knockdown lines. We used short-hairpin oligonucleotides to knock down the expression of ATP6V1A in Hela cells using previously described methods (56).

The pLKO.1 lentiviral vector (TRC, Broad institute) was used to express the shRNA against ATP6V1A (TRCN0000029542). ATP6V1A WT or C277A resistant to the shRNA was cloned into pLKO.1 shRNA vector under the hPGK promoter. For lentivirus production, lentiviral plasmids and packaging plasmids (pMD2.5G, Addgene #12259 and psPAX2, Addgene #12260) were transfected into HEK293T cells using PEI transfection method. Viral supernatant was collected 48 hours after transfection and filtered with 0.45 µm filter. The viruses were further concentrated using Lenti-X Concentrator (Clontech, 631231) according to the manufacturer's instructions. Target cells were plated in 6-well or 10 cm plates with 8 µg/mL polybrene (Millipore, TR-1003-G) and incubated with virus containing media. 24 hours later, the media was changed to fresh media containing 2 µg/mL puromycin (Calbiochem, 540411) and selected for over 3 days. Knockdown and protein expression were confirmed by immunoblotting.

[0574] Gel-based ABPP. Gel-based ABPP methods were performed as previously described (36,38,57,58). Recombinant pure human ATP6V1A protein was purchased from Abcam (ab132441). Pure protein (0.1 µg) was pre-treated with DMSO vehicle or covalently-acting small molecules for 1 h at 37 °C in an incubation volume of 50 µL PBS, and were subsequently treated with tetramethylrhodamine-5-iodoacetamide dihydroiodide (IA-rhodamine; 1 µM final concentration) for 1 h at room temperature. Samples were then diluted with 30 µL of 4 x reducing Laemmli SDS sample loading buffer (Alfa Aesar) and heated at 90 °C for 5 min. The samples were separated on precast 4-20% TGX gels (Bio-Rad Laboratories, Inc.) and scanned by ChemiDoc MP (Bio-Rad Laboratories, Inc.). Inhibition of target labeling was assessed by densitometry using ImageJ.

[0575] Resynthesis and characterization of EN6. The initial autophagy screen shown in FIG. 1A used EN6 from our screening plates. All subsequent uses of EN6 in this study are either from resupplied EN6 or resynthesized EN6. See Example 3 for experimental details.

[0576] Covalent ligand library. The synthesis and characterization of the covalent ligands screened here have been previously reported (33-37,59). Compounds starting with "EN" were purchased from Enamine LLC.

[0577] Antibodies and reagents for biological experiments. Antibodies to phospho-T389-S6K1 (9234), S6K1 (2708), phospho-S65-4E-BP1(9451), phospho-T37/46 4E-BP1 (2855), 4E-BP1 (9644), phospho-T308-Akt (13038), phospho-S473-Akt (4060), Akt (4691), phospho-S757-ULK1 (14202), ULK1 (8054), S6 (9202), phospho-S240/244 S6 (5364),

LC3B (3868), p62/SQSTM1 (39749), ATP6V1B2 (14488) and FLAG epitope (2368) were from Cell Signaling Technology; Antibody to ATP6V1A (ab137574) was from Abcam; Antibodies to LAMP2 (sc-18822) and ATP6V1D (sc-390164) were from Santa Cruz Biotechnology. Goat anti-rabbit IgG superclonal secondary antibody-Alexa Fluor 647 (A27040) was from Thermo Fisher Scientific. IRDye® 800CW Goat anti-Rabbit IgG (H + L; 926-32211) was from Li-Cor. Recombinant human ATP6V1A protein (ab132441) was from Abcam; Tetramethylrhodamine-5-iodoacetamide dihydroiodide (6222) was from Setareh Biotech.; Normal goat serum (10%; 50062Z), Hoechst 33342 (H3570) and LysoSensor Yellow/Blue DND-160 (L7545) were from Thermo Fisher Scientific. Amino acids, Flag-M2 affinity gel (A2220) and Bafilomycin A1 (B1793) from Sigma-Aldrich. Torin 1 (4247) from Tocris Biosciences. Rapamycin was from Selleckchem. Pierce Protease Inhibitor Tablets (A32965) from ThermoFisher Scientific. Amino acid-free RPMI (R9010-01) from US Biologicals. Dulbecco's Modified Eagle's Medium (DMEM; 10-013-CV) and fetal bovine serum (FBS; 35-015-CV) were from Corning. 0.25% Trypsin-EDTA (1×; 25200-056) and GlutMax (100×; 25030-081) were from Thermo Fisher Scientific. Sequencing grade modified trypsin (V51111) was from Promega.

[0578] Amino acid starvation and stimulation. Sub-confluent cells were rinsed and incubated with RPMI without amino acids supplemented with 2% dialyzed FBS for 50 min, as described (27). Stimulation with amino acids (concentration as in RPMI) was performed for 10 min. Where drug treatment was performed, cells were incubated during the 50 min starvation period and the 10 min stimulation period.

[0579] Western blotting and immunoprecipitation. Cells were washed twice with ice-cold phosphate-buffered saline (PBS) and lysed in lysis buffer (1% Triton X-100, 10 mM β -glycerol phosphate, 10 mM sodium pyrophosphate, 4 mM EDTA, 40 mM HEPES at pH 7.4, and 1 tablet of EDTA-free protease inhibitors per 50 mL). Cell lysates were cleared by centrifugation in a microcentrifuge at 17,000 g for 10 minutes at 4 °C. Cell lysate samples were prepared by addition of 5X sample buffer, heated at 95 °C for 5 minutes, resolved by 10% or 12% SDS-PAGE, and analyzed by immunoblotting. Antibodies were obtained from various commercial sources and dilutions were prepared per recommended manufacturers' procedures.

[0580] For FLAG immunoprecipitations, HEK293T cells stably expressing Flag-tagged proteins were lysed as above and 30 μ L of a well-mixed 50% slurry of anti-FLAG M2

Affinity Gel (Sigma A2220) was added to each lysate (1 mg/mL) and incubated at 4 °C in a shaker for 1 hour. Immunoprecipitates were washed four times, three times with lysis buffer and once with lysis buffer containing 400 mM NaCl. Immunoprecipitated proteins were denatured by addition of 50 µL of sample buffer and heating to 95 °C for 5 minutes, resolved
5 by SDS-PAGE, and analyzed by immunoblotting.

[0581] Imaging LC3B puncta in EN6-treated HEK293A cells by confocal fluorescence microscopy. HEK293A cells were plated on fibronectin-coated (5 µg/mL) 8-well Lab Tek borosilicate chambered coverglass slides (Nunc) at 40,000 cells/well and allowed to grow in complete medium overnight. The cells were then incubated with EN6 (at indicated
10 concentrations), Torin 1 (250 nM) or DMSO control for indicated time intervals. After aspiration of the solution, the cells were washed with PBS (350 µL) and fixed with methanol for 15 min at –20 °C. The cells were rinsed three times with PBS (350 µL each), and incubated with PBS containing 5% normal goat serum and 0.3% Triton X-100 (300 µL) for 1 h. The cells were washed with PBS (350 µL) and incubated with anti-LC3B (Cell Signaling
15 Technology #3868; v/v, 1:200) in PBS containing 1% BSA and 0.3% Triton X-100 at 4 °C overnight. After that, the cells were washed three times with PBS (350 µL each), and incubated with anti-rabbit superclonal secondary antibody-Alexa Fluor 647 (Thermo Fisher Scientific A27040; v/v = 1:500) in PBS containing 1% BSA and 0.3% Triton X-100 in dark at room temperature for 1 h. The cells were washed three times with PBS (350 µL each) and
20 stained with Hoechst 33342 (5 µg/mL) in PBS in dark at room temperature for 15 min. After washing with PBS three times (350 µL each), the cells were imaged in PBS by Zeiss laser scanning microscope (LSM) 710 with a 20× or 63× oil-immersion objective lens. Hoechst 33342 was excited with a 405 nm diode laser, and emission was collected on a META detector between 410 and 587 nm. Alexa Fluor 647 was excited with a 633 nm HeNe laser,
25 and emission was collected on a META detector between 638 and 755 nm.

[0582] Image analysis was performed by use of ImageJ. A threshold of 100–255 (for 8-bit images) was first set for selection of LC3B puncta, and a region of interest (ROI) was created over a single cell. The number of cellular LC3B puncta was then quantified by “Analyze Particles” using size and circularity of 0.1–infinity and 0.0–1.0 respectively. 25 individual
30 cells of each group from triplicate experiments were analyzed, and the statistical analyses were performed with a two-tailed Student’s t-test (MS Excel).

[0583] Imaging lysosomal recruitment of mTORC1 by immunofluorescence. HEK-293T or Hela cells were seeded on fibronectin-coated glass coverslips and allowed to attach overnight. On the following day, cells were subjected to either amino acid starvation and stimulation with or without drug incubation and fixed in 4% paraformaldehyde (PFA) for 15 minutes at room temperature. The coverslips were rinsed twice with PBS and cells were permeabilized with 0.1% (w/v) saponin in PBS for 10 minutes. After rinsing twice with PBS, the slides were incubated with primary antibodies in 5% normal donkey serum (Jackson ImmunoResearch, 017-000-121) for 1 hour at room temperature, rinsed four times with PBS, and incubated with fluorophore conjugated secondary antibodies derived from goat or donkey (Life Technologies, diluted 1:400 in 5% normal donkey serum) for 1 hour at room temperature in the dark. The coverslips were then washed four times with PBS, mounted on glass slides using Vectashield (Vector Laboratories) and imaged on a spinning disk confocal system built upon a Nikon Eclipse Ti microscope with Andor Zyla-4.5 sCMOS camera.

[0584] Imaging lysosomal pH by LysoSensor DND-160. HEK293A cells were plated on fibronectin-coated (5 µg/mL) 8-well Lab Tek borosilicate chambered coverglass slides (Nunc) at 40,000 cells/well and allowed to grow in complete medium overnight. The cells were then incubated with DMSO control, EN6 (50 µM), bafilomycin A1 (0.2 µM), or a mixture of EN6 and bafilomycin A1 (50 and 0.2 µM respectively) at 37 °C for 4 h. After that, LysoSensor DND-160 (2 µM final concentration) was added to the solution and the cells were stained at 37 °C for 5 min. The solution was then replaced by DPBS and the live cells were imaged by Zeiss LSM 880 with a 40× water-immersion objective lens. The blue fluorescence of DND-160, F_{blue}, was excited with a two-photon laser at 760 nm and emission was collected on a META detector between 400 and 490 nm. The yellow fluorescence of DND-160, F_{yellow}, was excited with a two-photon laser at 760 nm and emission was collected on a META detector between 514 and 649 nm.

[0585] The ratiometric images, $F_{\text{yellow}} / F_{\text{blue}}$, were generated by Ratio Plus plugin of ImageJ. For quantification, a threshold value was set as background and the average intensity of the whole image was measured by ImageJ. All experiments were performed in triplicate, and statistical analyses were performed with a two-tailed Student's t-test (MS Excel).

[0586] RNA extraction and quantitative RT-PCR (qRT-PCR). Total RNAs were extracted using Aurum™ Total RNA Mini Kit (Bio-rad) and reverse transcription was performed from 1 µg total RNAs using iScript™ Reverse Transcription for RT-qPCR (Bio-rad)

according to manufacturer's instruction. All real-time qPCR(qRT-PCR) analyses were performed using StepOnePlus machine (Applied Biosystems) with SsoAdbanced™ Universal SYBR Green supermix (Bio-rad).

[0587] The quantity of mRNA was calculated using the $\Delta\Delta C_t$ method and normalized to β -actin. All reactions were performed as triplicates.

[0588] Assessing TDP-43 aggregates. U2OS cells stably expressing GFP-TDP-43 were plated on fibronectin-coated (5 $\mu\text{g/mL}$) 8-well Lab Tek borosilicate chambered coverglass slides (Nunc) at 30,000 cells/well and allowed to grow in complete medium overnight. The cells were incubated with DMSO control, isopropylthio- β -galactoside (IPTG; 50 μM), a mixture of EN6 (25 μM) and IPTG (50 μM), or a mixture of EN6 (25 μM), IPTG (50 μM) and bafilomycin A1 (0.2 μM) at 37 °C for 7 h. The cells were washed with PBS (350 μL) and fixed with 4% paraformaldehyde (PFA) for 15 minutes at room temperature. After fixation, the cells were washed three times with PBS (350 μL each) and stained with Hoechst 33342 (0.5 $\mu\text{g/mL}$) in PBS in dark at room temperature for 15 min. After washing with PBS three times (350 μL each), the cells were imaged in PBS by Zeiss laser scanning microscope (LSM) 710 with a 20 $\times$ or 63 $\times$ oil-immersion objective lens. Hoechst 33342 was excited with a 405 nm diode laser, and emission was collected on a META detector between 410 and 483 nm. GFP was excited with a 488 nm Ar laser, and emission was collected on a META detector between 493 and 598 nm.

[0589] Image analysis was performed by use of ImageJ. A threshold was first set for selection of GFP-TDP-43 aggregate, and a region of interest (ROI) was created over a single cell. The number of cellular aggregates was then quantified by "Analyze Particles" using size and circularity of 5–infinity and 0.0–1.0 respectively. 26 individual cells of each group from triplicate experiments were analyzed, and the statistical analyses were performed with a two-tailed Student's t-test (MS Excel).

[0590] Assessing mTORC1 inhibition *in vivo* in mice. 6-week-old male C57BL/6 mice (Jackson Laboratory) were injected intraperitoneally with solvent control, EN6 (50 mg/kg) or rapamycin (10 mg/kg) in PBS/ethanol/PEG-40 (v/v/v = 18:1:1). After 6 h, mice were euthanized, and tissues were harvested and lysed in lysis buffer (1% Triton X-100, 10 mM β -glycerol phosphate, 10 mM sodium pyrophosphate, 4 mM EDTA, 40 mM HEPES at pH 7.4, and 1 tablet of EDTA-free protease inhibitors per 50 ml) at 4 °C for 30 min. The lysates were cleared by centrifugation in a microcentrifuge at 21,130 g for 10 minutes at 4°C and protein

concentration of supernatant was determined by BCA assay (Thermo Fisher Scientific). The lysates was then diluted to 1.5 mg/mL, mixed with 4× sample buffer, heated at 95 °C for 5 minutes, resolved by precast 4-20% TGX gels, and analyzed by immunoblotting. Antibodies were obtained from various commercial sources and dilutions were prepared per

recommended manufacturers' procedures. Animal experiments were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committees of the University of California, Berkeley.

Example 3: Methods for chemical syntheses

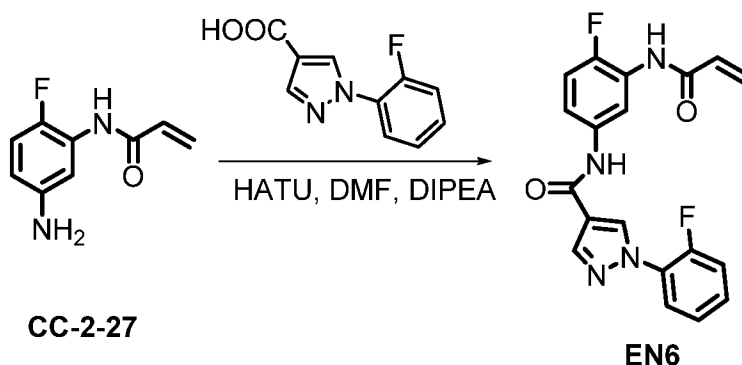
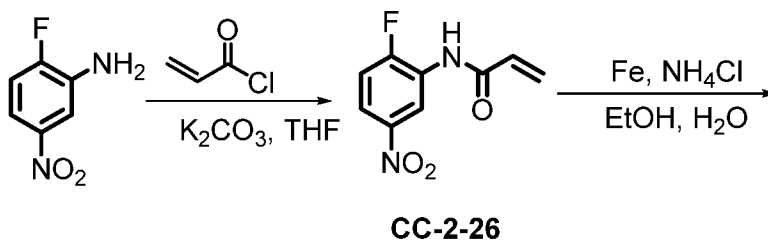
[0591] Materials and reagents for chemical syntheses. 2-Fluoro-5-nitroaniline was purchased from AK Scientific. 1-(2-Fluorophenyl)-1*H*-pyrazole-4-carboxylic acid was purchased from Enamine LLC. Acryloyl chloride, potassium carbonate, iron powder, ammonium chloride and *N,N*-diisopropylethylamine (DIPEA) were purchased from Sigma-Aldrich. All the solvents were of HPLC grade and were from Sigma-Aldrich. All other reagents were of analytical grade and were used without further purification. MilliQ water was used in all experiments unless otherwise stated.

[0592] Physical Measurements and Instrumentation. ¹H NMR and ¹³C{¹H} spectra were collected at 25 °C on Bruker AVB-400, AVQ-400 and AV-300 at the College of Chemistry NMR Facility at the University of California, Berkeley. All chemical shifts are reported in the standard δ notation of parts per million relative to residual solvent peak as an internal reference. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets. High-resolution mass spectra were collected at the QB3/Chemistry Mass Spectrometry Facility at the University of California, Berkeley.

Fluorescence from microplates were recorded on SpectraMax i3 (Molecular Devices). In-gel fluorescence images were recorded on ChemiDoc MP Gel Imaging system (Bio-Rad).

Fluorescence from western blots were imaged by Odyssey Infrared Imager (Li-Cor). Confocal microscopy images were recorded on a Zeiss laser scanning microscope (LSM) 710 with a 20× or 63× oil-immersion objective lens, and a Zeiss LSM 880 with a 40× water-immersion objective lens at the CRL Molecular Imaging Center at the University of California, Berkeley.

[0593] Synthesis of EN6.



[0594] CC-2-26. K_2CO_3 (936.6 mg, 6.8 mmol) was added to 2-fluoro-5-nitroaniline (529.4 mg, 3.4 mmol) in dry THF (20 mL). At 0 °C, acryloyl chloride (300 μ L, 3.8 mmol) in dry THF (10 mL) was added dropwise to the solution mixture with vigorous stirring. The solution mixture was further stirred at 0 °C for 1 h, and then the reaction was quenched by addition of water. Any organic volatile was removed by evaporation under reduced pressure, and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layer was then washed by saturated NaCl solution, dried by $MgSO_4$ and filtered. Volatile organic solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (4:1, v/v) as eluent, yielding CC-2-26 as yellow solid (643 mg, 90%). 1H NMR ($CDCl_3$, 400 MHz): δ 9.34-9.44 (1H, m), 7.97-8.04 (1H, m), 7.55 (1H, br), 7.26 (1H, t, J = 9.5 Hz), 6.50-6.56 (1H, m), 6.27-6.35 (1H, m), 5.89-5.92 (1H, m). $^{13}C\{^1H\}$ NMR ($[D_6]DMSO$, 100 MHz) δ 164.1, 143.7, 130.8, 128.7, 127.4, 127.3, 120.5, 120.4, 118.0, 116.8, 116.5. $^{19}F\{^1H\}$ NMR ($CDCl_3$, 376 MHz) δ = 119.0. HRMS (ESI) m/z $[M-H]^-$ calcd for $C_9H_7FN_2O_3$: 209.0363; found: 209.0371.

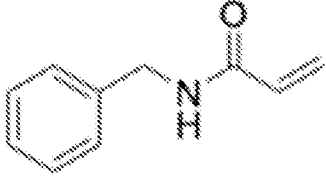
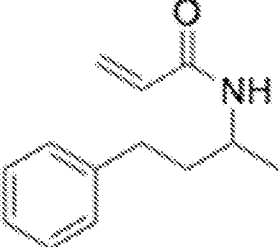
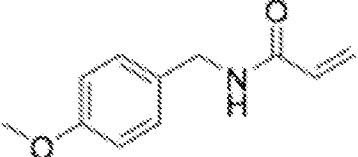
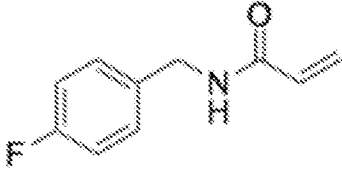
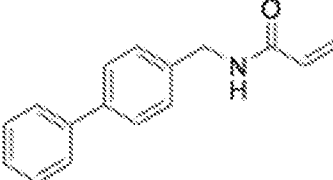
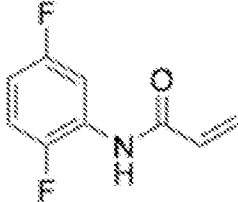
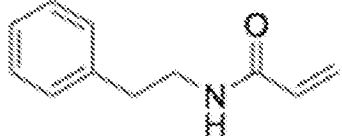
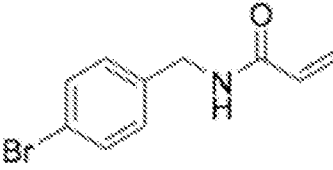
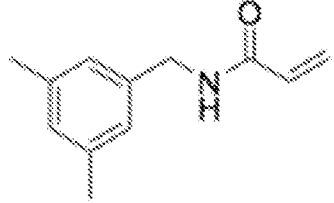
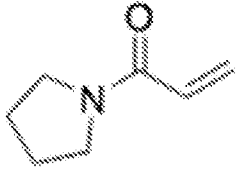
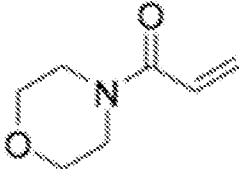
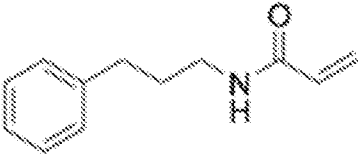
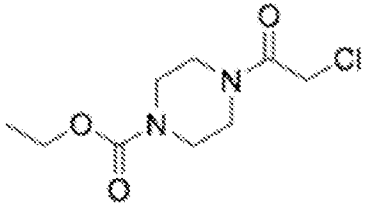
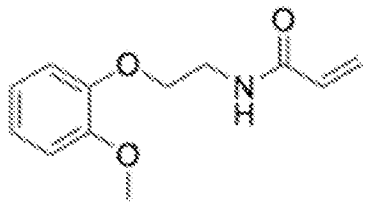
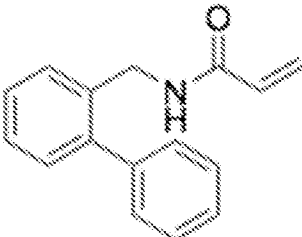
[0595] CC-2-27. CC-2-26 (343 mg, 1.63 mmol) and ammonium chloride (873 mg, 16.3 mmol) were dissolved in EtOH/ H_2O mixture (50 mL; v/v = 4:1) with heating. Iron powder (911.5 mg, 16.3 mmol) was then added and the reaction mixture was heated under reflux for 3 h. After complete consumption of CC-2-26 as indicated by TLC, the reaction mixture was cooled to room temperature and any undissolved solid was filtered off. The filtrate was evaporated under reduced pressure, and the aqueous solution was extracted with ethyl acetate

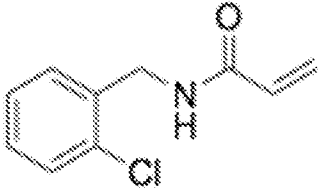
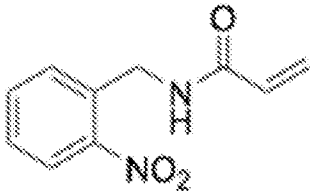
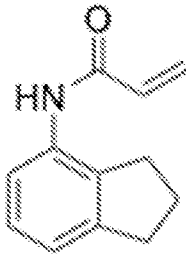
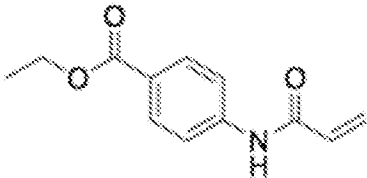
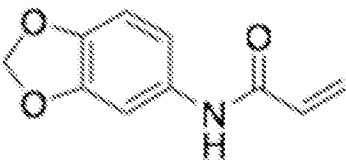
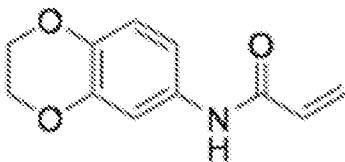
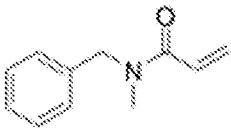
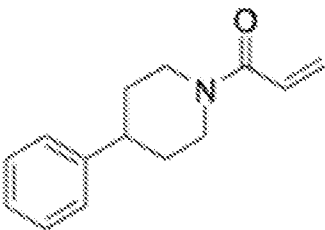
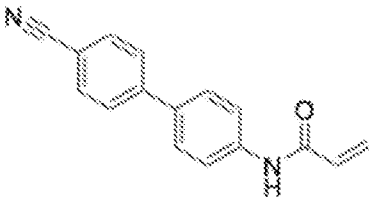
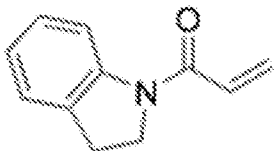
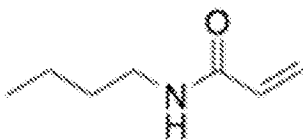
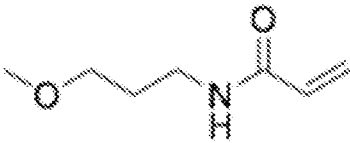
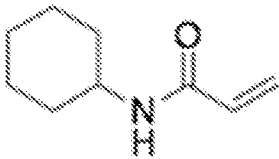
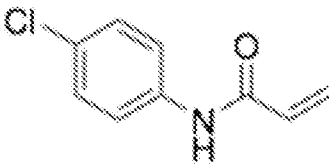
three times. The combined organic layer was dried by MgSO_4 and filtered. Volatile organic solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:2, v/v) as eluent, yielding CC-2-27 as pale yellow solid (211.5 mg, 72%). ^1H NMR ($[\text{D}_6]$ DMSO, 400 MHz): δ 9.66 (1H, s), 7.26 (1H, d, $J = 5.3$ Hz), 6.89 (1H, t, $J = 9.4$ Hz), 6.60 (1H, dd, $J = 5.1$ and 17.0 Hz), 6.27-6.33 (1H, m), 6.24 (1H, d, $J = 17.0$ Hz), 5.73 (1H, d, $J = 10.2$ Hz), 5.13 (2H, br). $^{13}\text{C}\{^1\text{H}\}$ NMR ($[\text{D}_6]$ DMSO, 100 MHz) δ 163.3, 144.8, 131.7, 127.0, 125.9, 125.8, 115.3, 115.1, 110.1, 109.1. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_9\text{H}_{10}\text{FN}_2\text{O}$: 181.0777; found: 181.07772.

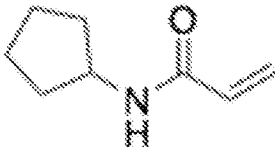
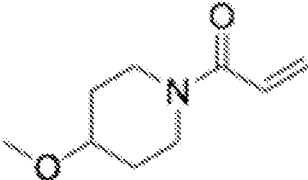
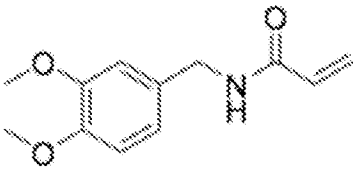
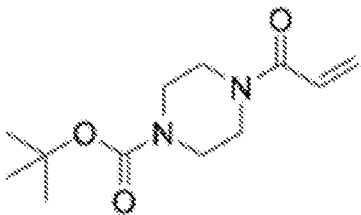
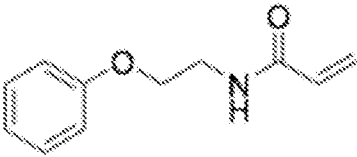
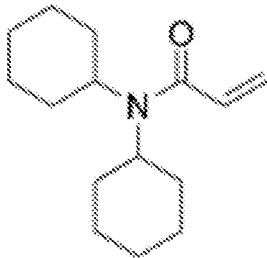
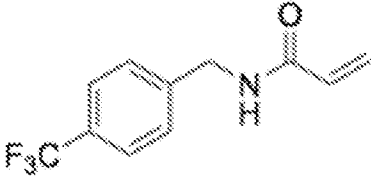
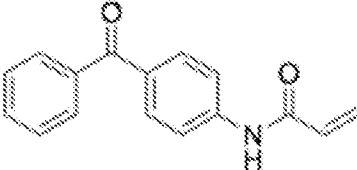
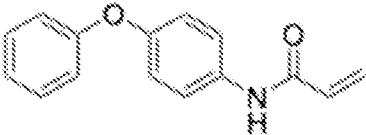
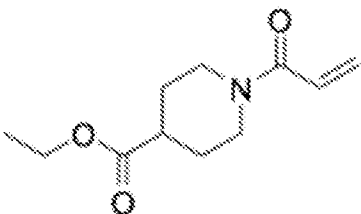
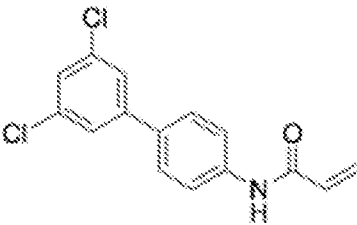
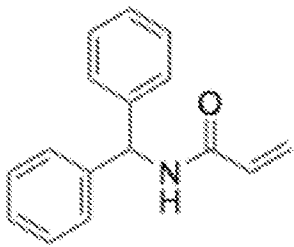
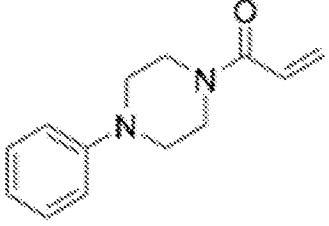
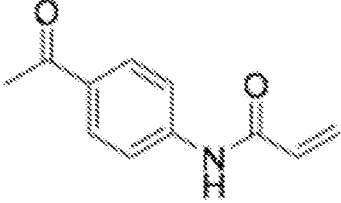
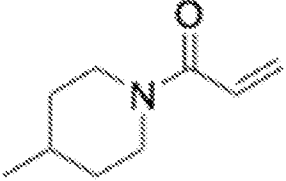
[0596] EN6. 1-(2-Fluorophenyl)-1*H*-pyrazole-4-carboxylic acid (57.2 mg, 0.28 mmol) and HATU (127.6 mg, 0.33 mmol) were dissolved in anhydrous DMF (2 mL) and the mixture was stirred at room temperature for 15 min. CC-2-27 (50 mg, 0.28 mmol) in anhydrous DMF (1 mL) was then added, followed by the addition of DIPEA (146 μL , 0.84 mmol). After reaction overnight, the solvent was evaporated under reduced pressure and the crude product was dissolved in ethyl acetate. The organic solution was washed with sat. $\text{NaHCO}_3(\text{aq})$ solution and sat. $\text{NaCl}(\text{aq})$ solution, dried by MgSO_4 and filtered. Volatile organic solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel using dichloromethane/methanol (24:1, v/v) as eluent, yielding the desired product as an off-white solid (38 mg, 37%). ^1H NMR ($[\text{D}_6]$ DMSO, 400 MHz): δ 10.13 (1H, s), 9.98 (1H, s), 8.88 (1H, s), 8.37 (1H, d, $J = 6.2$ Hz), 8.34 (1H, s), 7.87 (1H, t, $J = 7.6$ Hz), 7.61-7.68 (1H, m), 7.45-7.57 (2H, m), 7.40 (1H, t, $J = 7.6$ Hz), 7.26 (1H, t, $J = 9.6$ Hz), 6.60-6.71 (1H, m), 6.30 (1H, d, $J = 17.0$ Hz), 5.79 (1H, d, $J = 10.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR ($[\text{D}_6]$ DMSO, 100 MHz) δ 163.5, 159.9, 154.7, 152.2, 150.9, 148.5, 141.0, 135.2, 135.1, 132.9, 132.9, 131.4, 129.6, 129.5, 127.5, 127.4, 127.3, 125.9, 125.8, 125.5, 125.5, 125.0, 120.4, 117.3, 117.1, 117.0, 116.9, 115.8, 115.4, 115.2. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{14}\text{F}_2\text{N}_4\text{O}_2\text{Na}$: 391.0983; found: 391.0977.

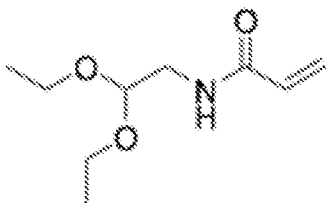
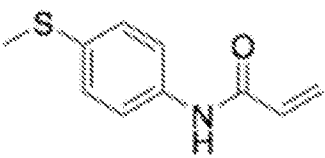
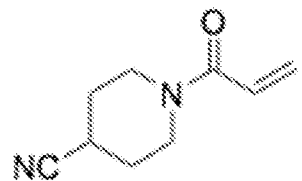
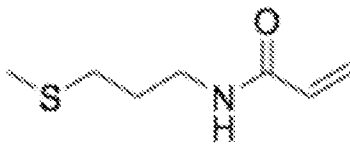
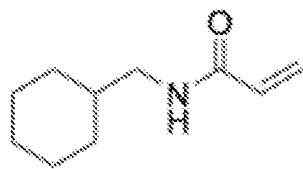
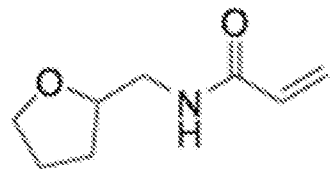
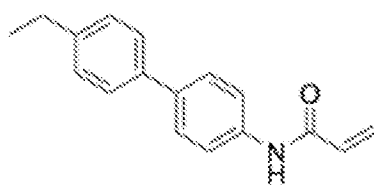
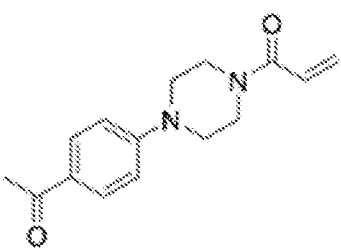
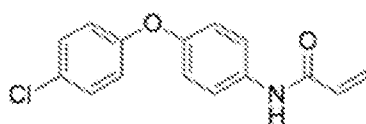
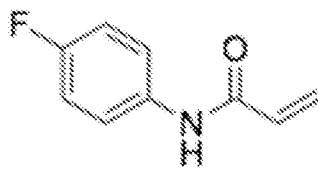
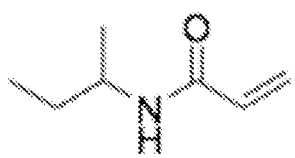
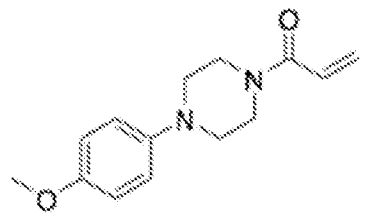
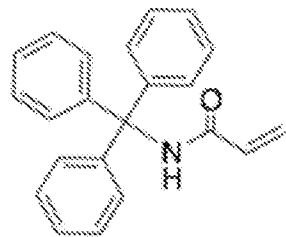
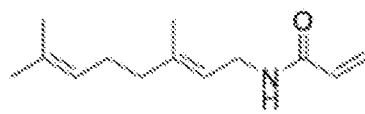
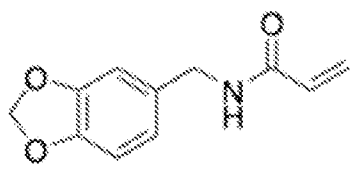
Table 1: Structures of covalent ligands screened for autophagy activation

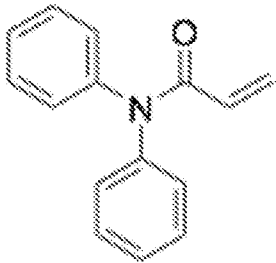
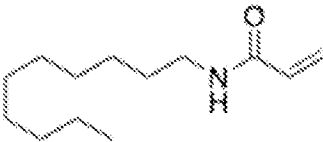
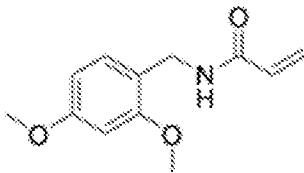
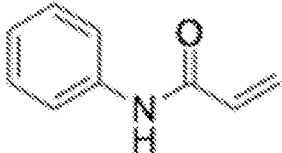
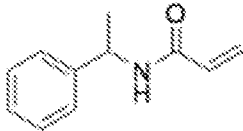
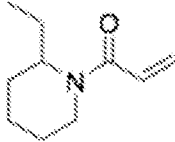
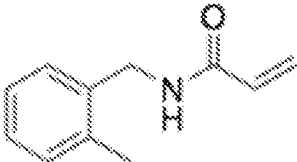
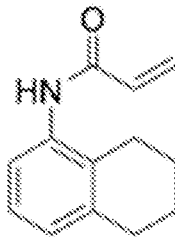
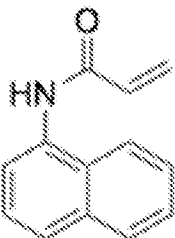
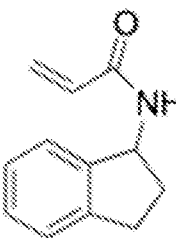
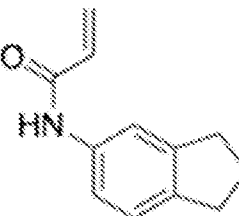
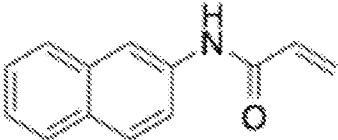
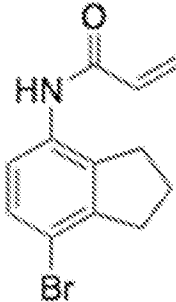
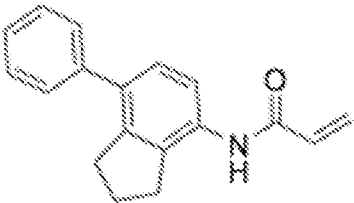
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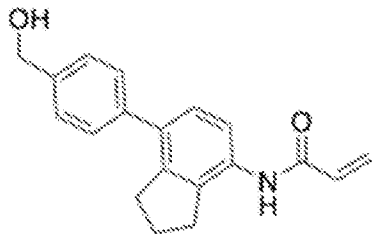
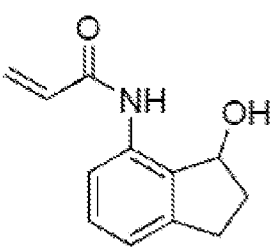
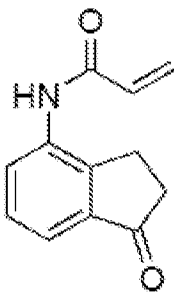
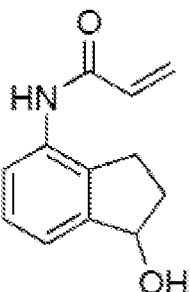
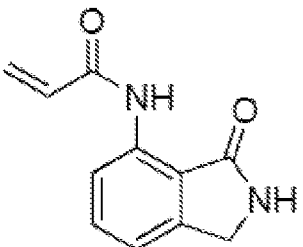
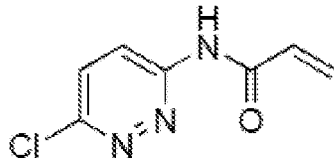
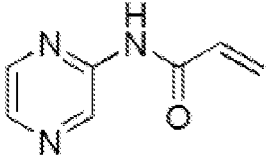
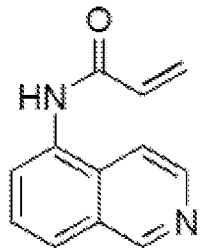
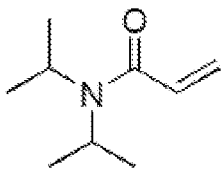
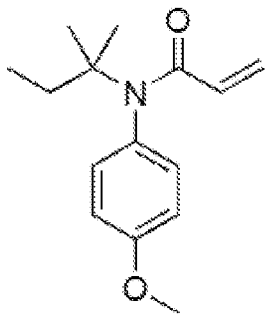
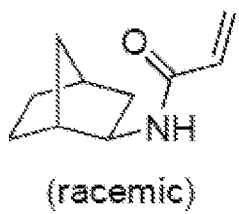
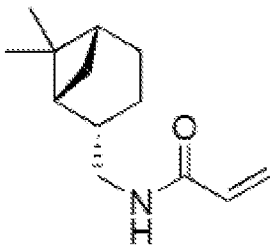
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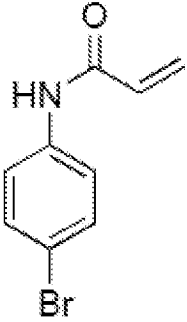
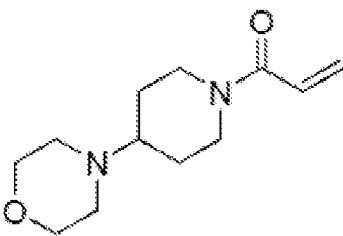
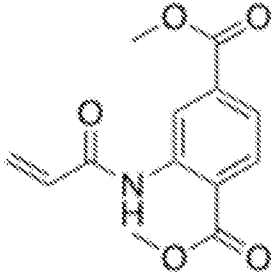
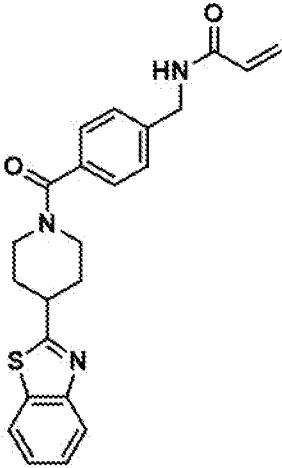
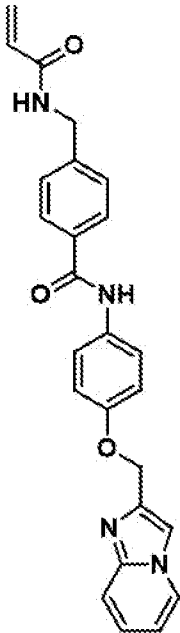
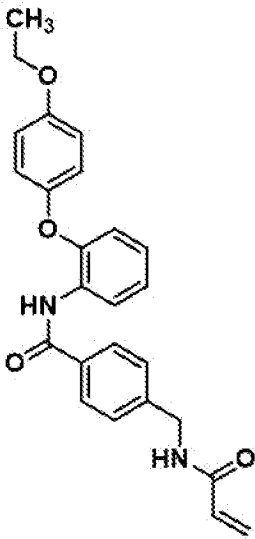
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DKM 2-95  (Two rotamers in equal amounts)	DKM 2-97 	DKM 2-98 
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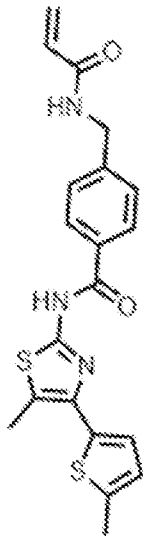
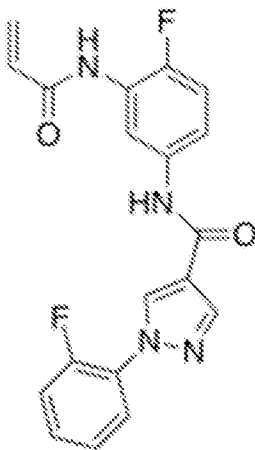
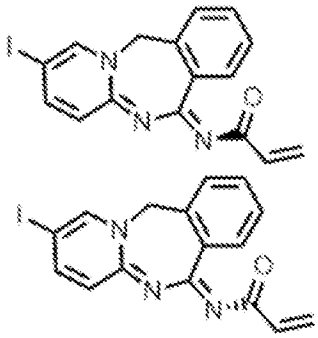
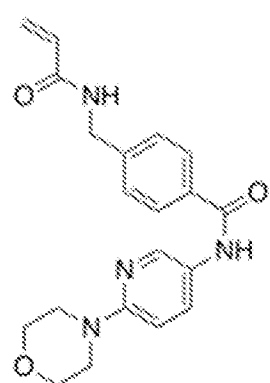
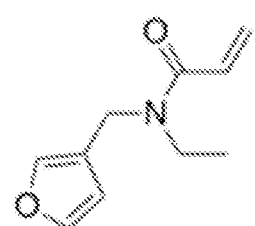
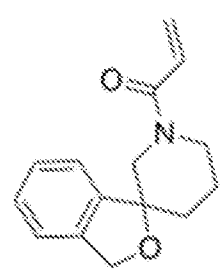
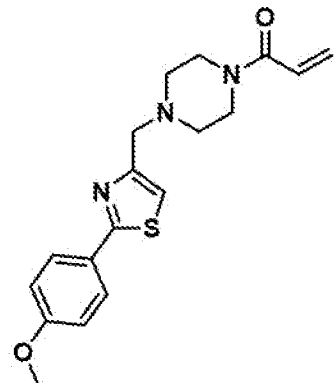
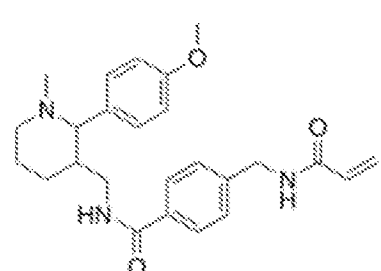
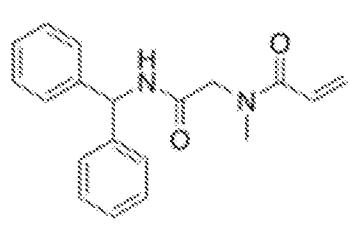
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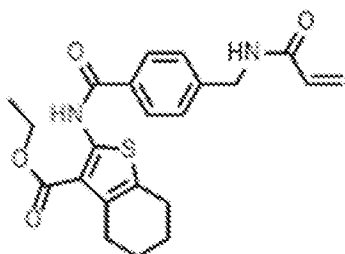
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TRH 1-60 	TRH 1-65 	TRH 1-68 

TRH 1-70 	TRH 1-133 	TRH 1-134 
TRH 1-135 	TRH 1-152 	TRH 1-155 
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TRH 1-170 	TRH 1-176  (racemic)	TRH 1-178 

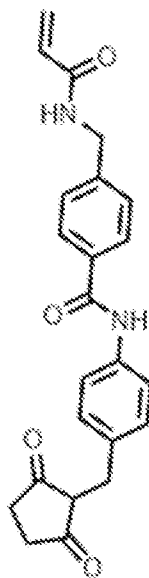
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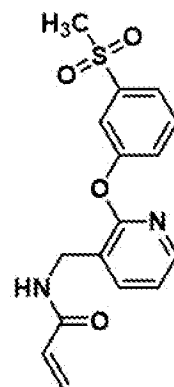
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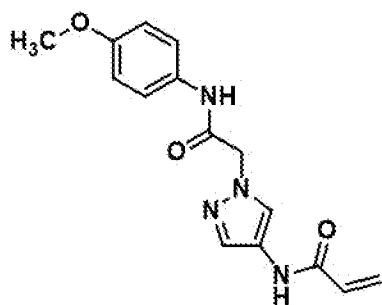
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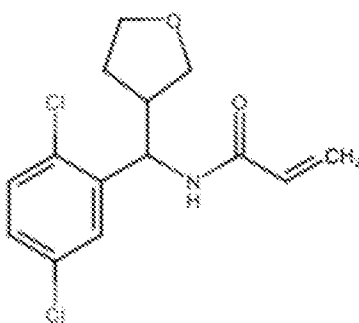
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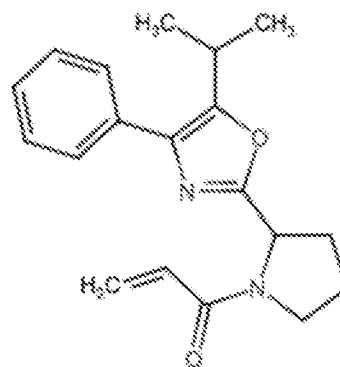
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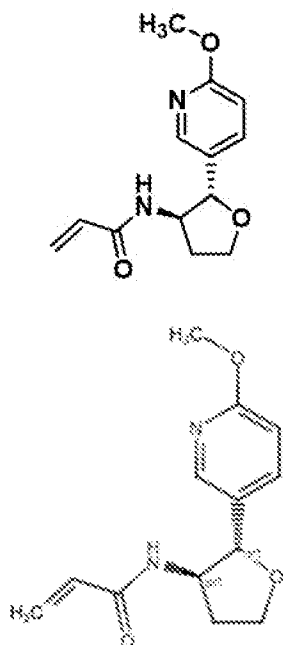
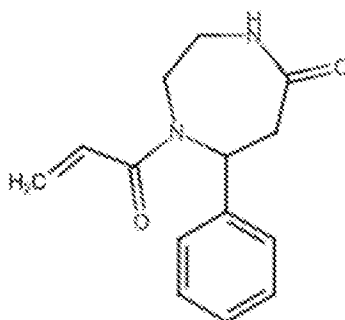
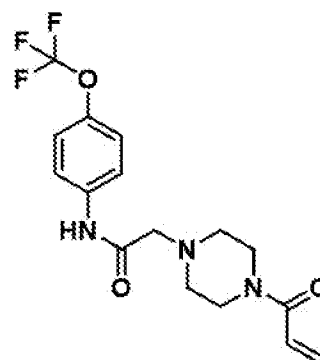
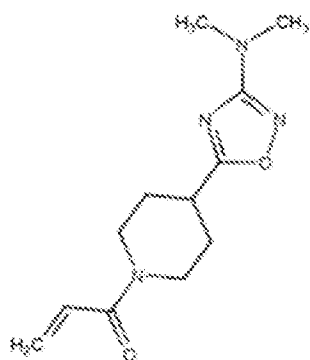
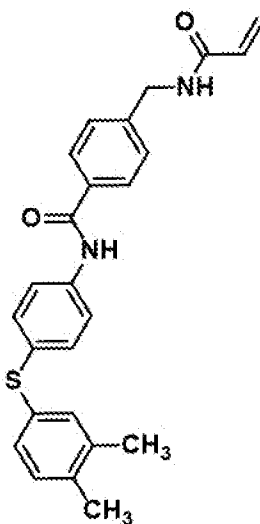
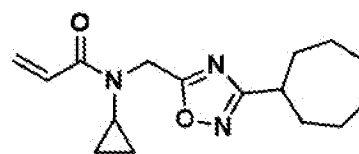


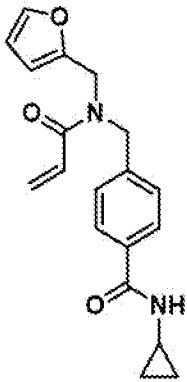
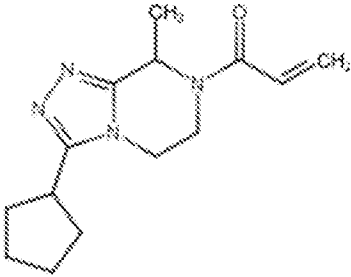
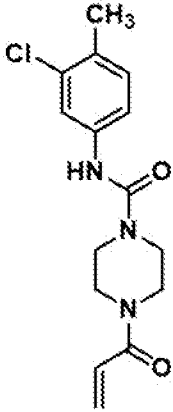
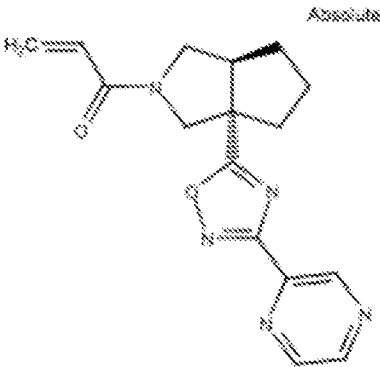
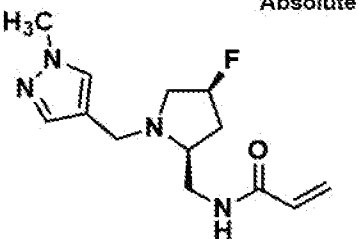
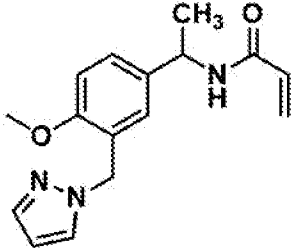
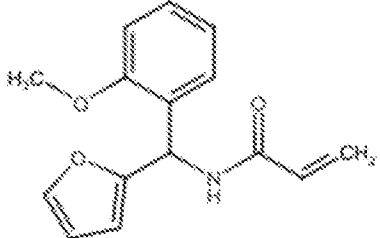
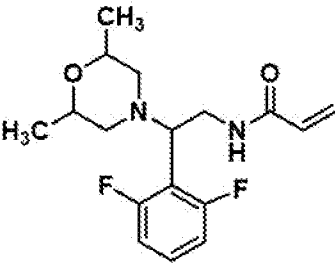
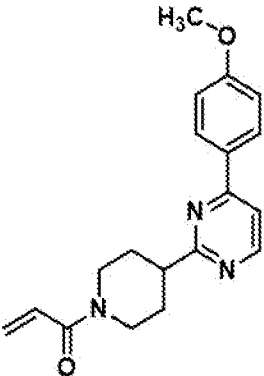
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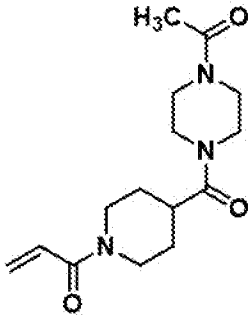
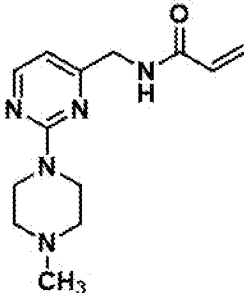
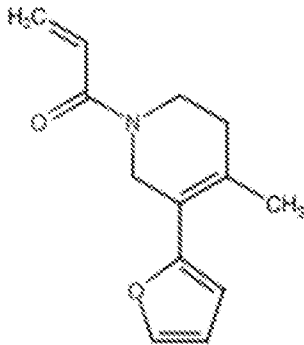
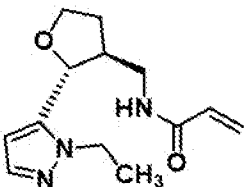
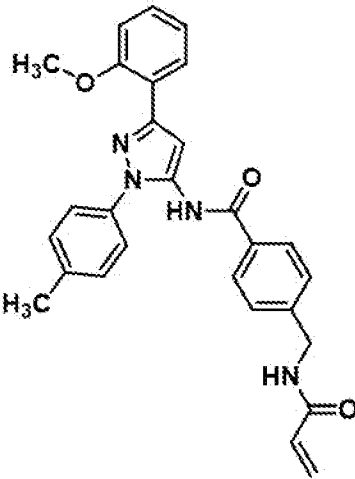
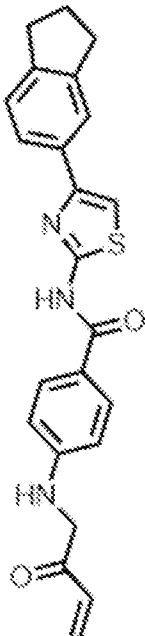
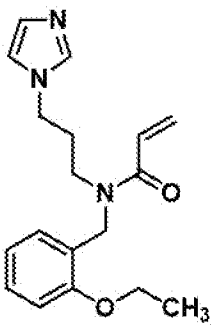
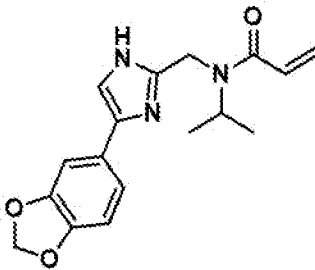
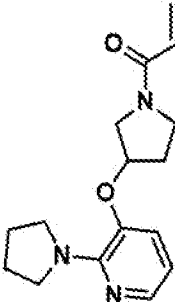


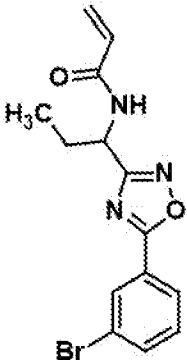
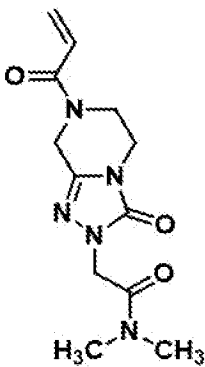
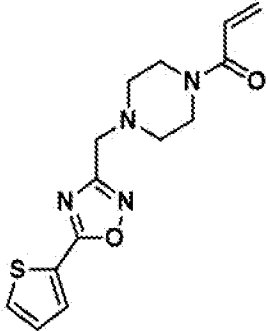
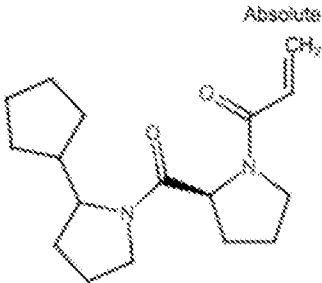
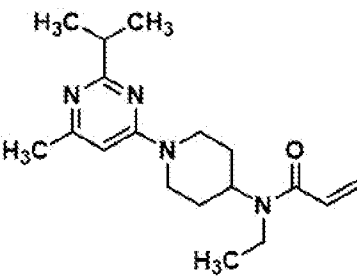
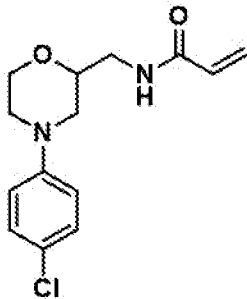
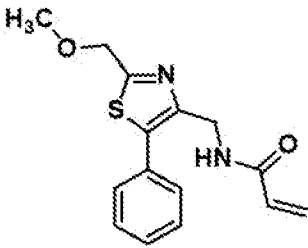
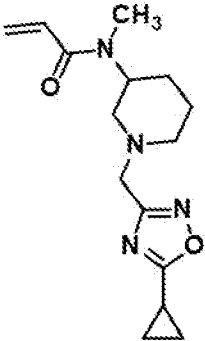
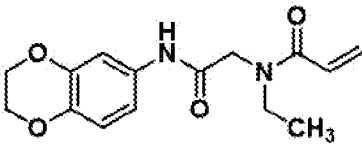
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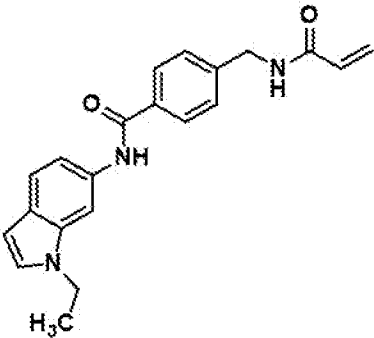
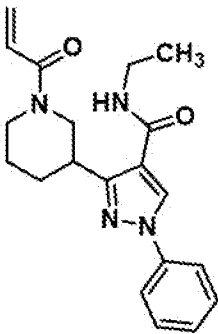
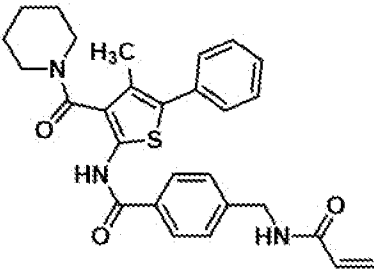
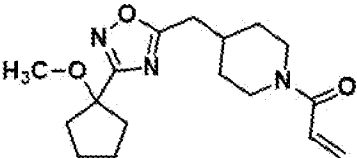
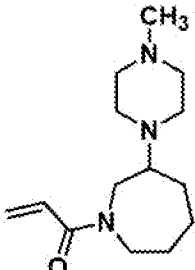
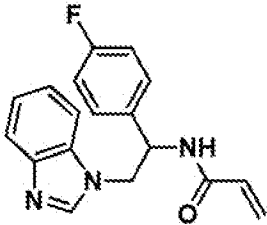
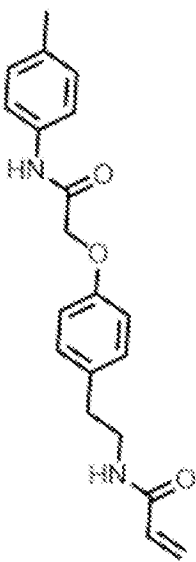
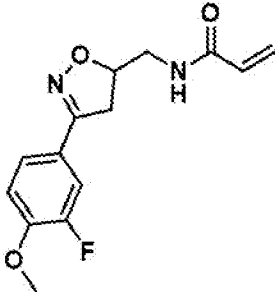


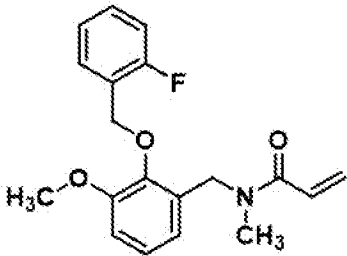
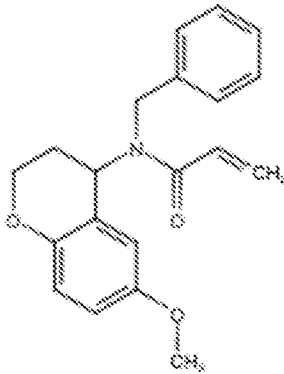
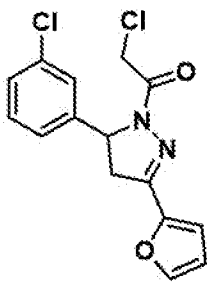
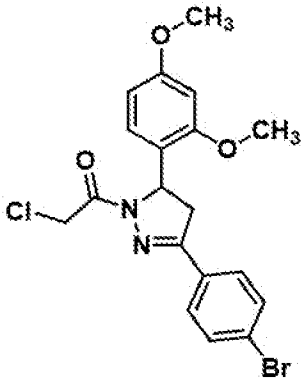
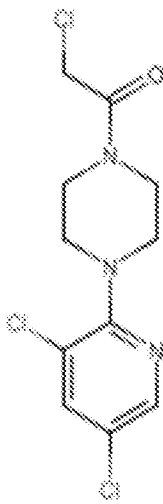
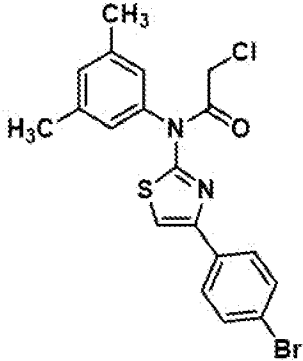
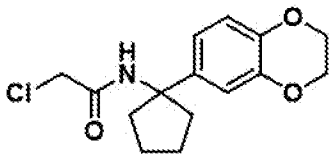
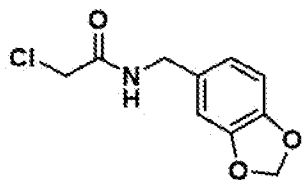
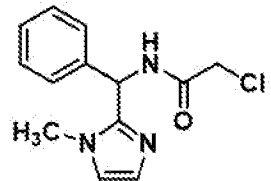
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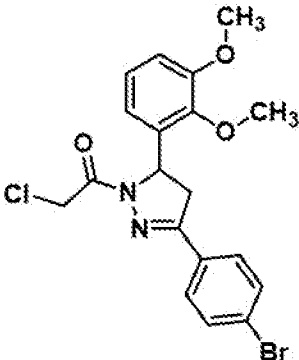
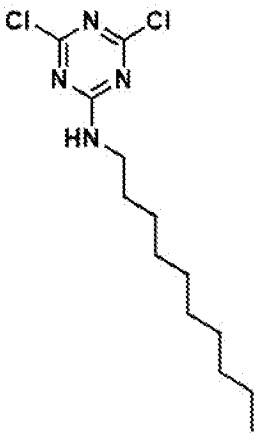
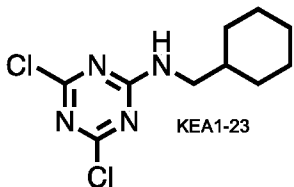
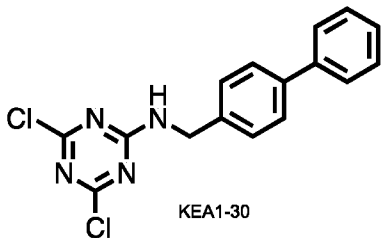
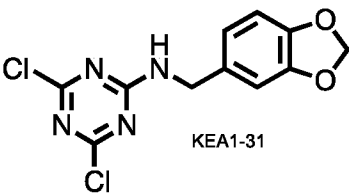
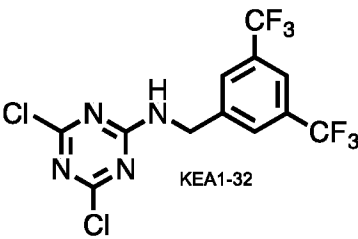
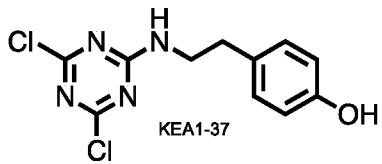
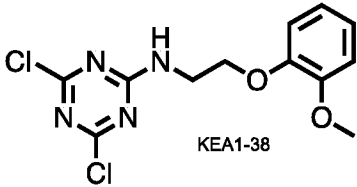
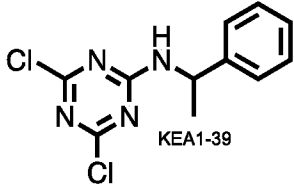
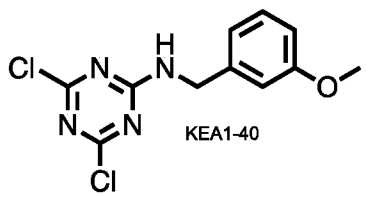
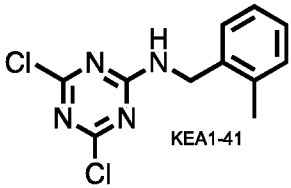
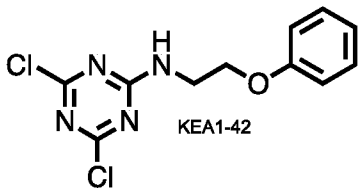
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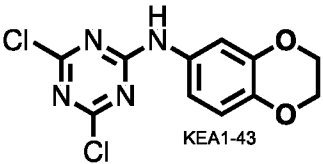
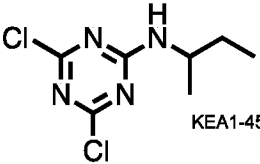
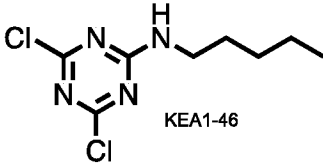
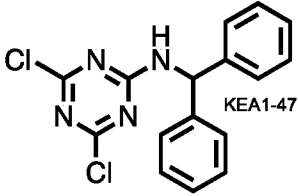
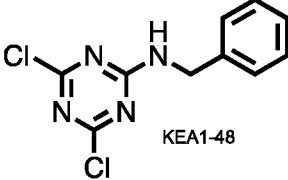
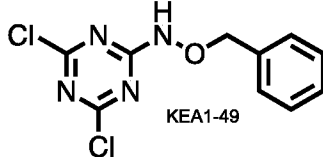
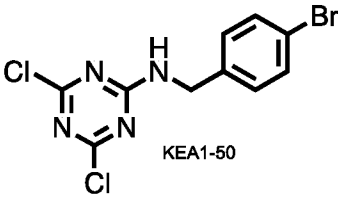
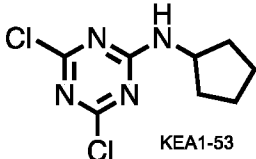
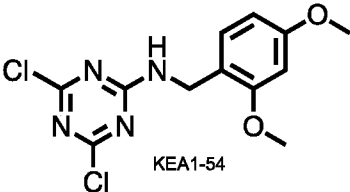
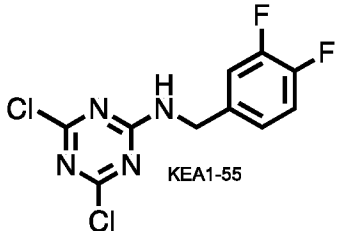
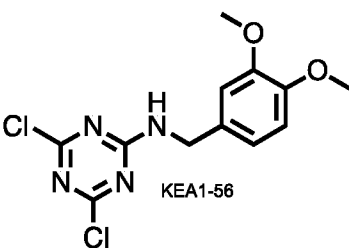
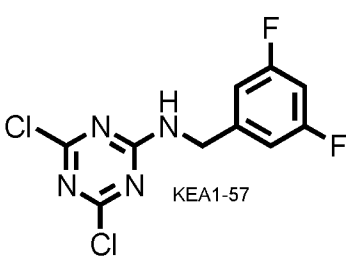
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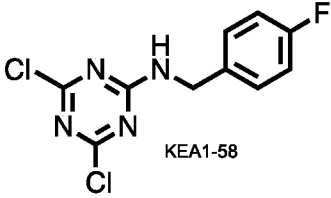
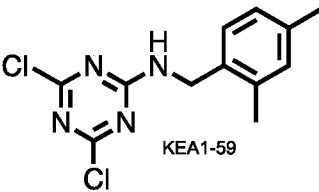
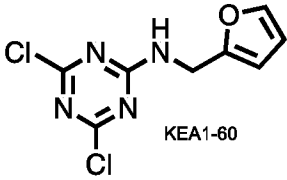
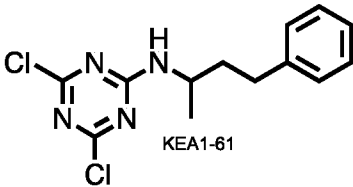
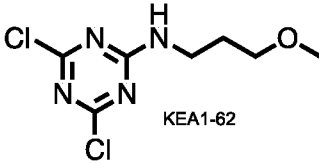
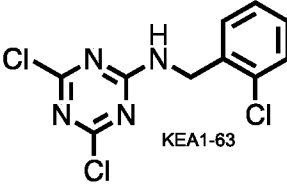
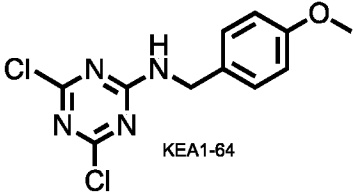
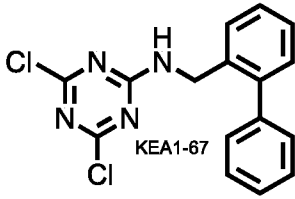
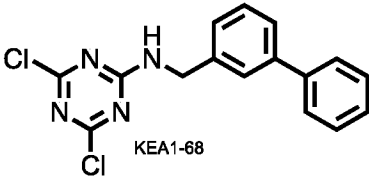
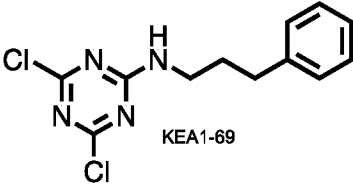
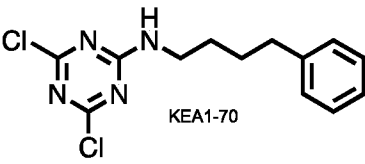
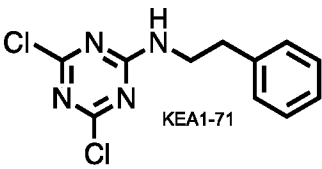
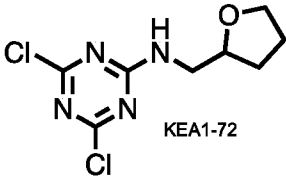
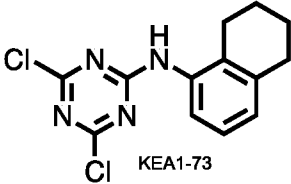
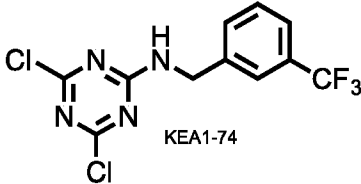
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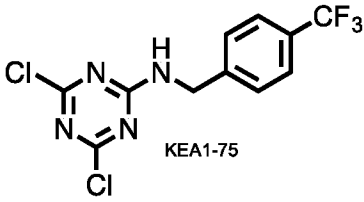
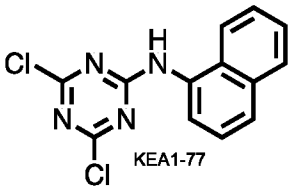
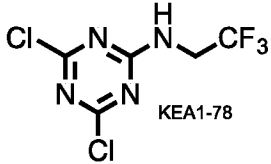
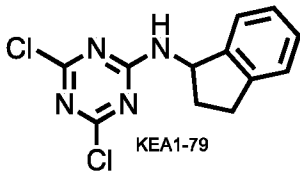
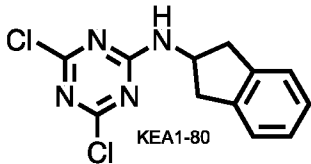
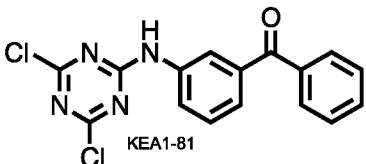
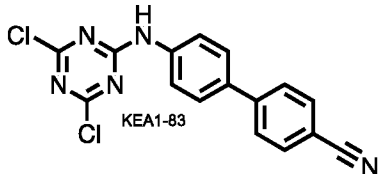
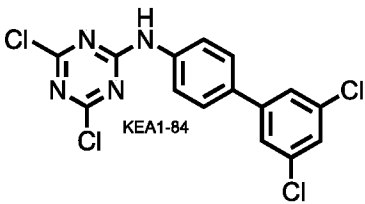
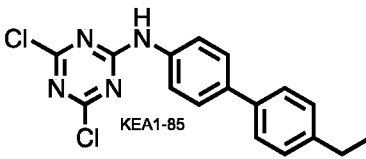
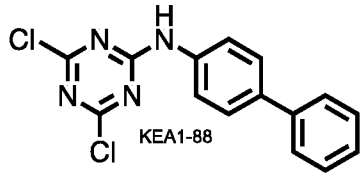
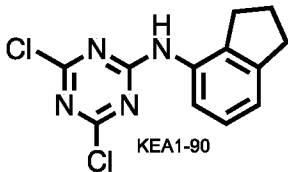
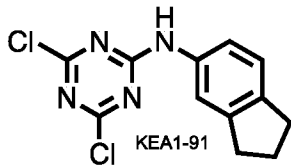
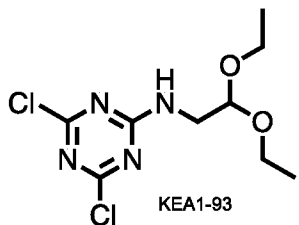
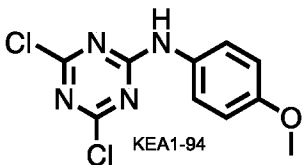
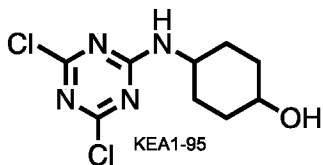
EN59 	EN60 	EN61 
EN62 	EN63 	EN64 
EN65 	EN66 	EN67 

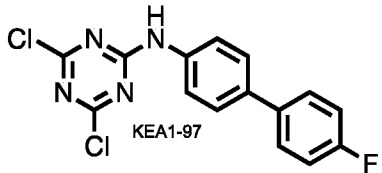
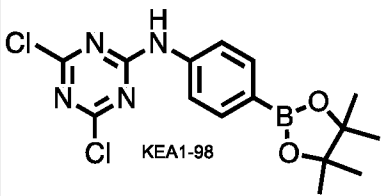
EN68 	EN69 	EN70 
EN71 	EN75 	EN80 
EN84 	EN85 	EN86 

EN103 	KEA1-22 	KEA1-23 
KEA1-30 	KEA1-31 	KEA1-32 
KEA1-37 	KEA1-38 	KEA1-39 
KEA1-40 	KEA1-41 	KEA1-42 

KEA1-43  KEA1-43	KEA1-45  KEA1-45	KEA1-46  KEA1-46
KEA1-47  KEA1-47	KEA1-48  KEA1-48	KEA1-49  KEA1-49
KEA1-50  KEA1-50	KEA1-53  KEA1-53	KEA1-54  KEA1-54
KEA1-55  KEA1-55	KEA1-56  KEA1-56	KEA1-57  KEA1-57

KEA1-58  KEA1-58	KEA1-59  KEA1-59	KEA1-60  KEA1-60
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KEA1-88  KEA1-88	KEA1-90  KEA1-90	KEA1-91  KEA1-91
KEA1-93  KEA1-93	KEA1-94  KEA1-94	KEA1-95  KEA1-95

KEA1-97  KEA1-97	KEA1-98  KEA1-98	
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Example 4: Additional analogs

[0598] Liquid Chromatography-Mass Spectrometry (LCMS)

[0599] The following instrumentation and conditions were used for LCMS analysis:

Pump	Waters AcQuity UPLC Binary Solvent Manager
Sample Manager	Waters AcQuity UPLC Sample Manager
Column Compartment	Waters AcQuity UPLC Column Manager
Detector	Waters AcQuity UPLC PDA
ELSD	Waters ELSD
Mass Spec	Waters SQD
Eluent A1	0.1% Formic Acid in Water
Eluent B1	0.1% Formic Acid in Acetonitrile
Column	AcQuity UPLC BEH C18 1.7 μ m 2.1x30mm.
Column Temperature	50 °C

5

[0600] LCMS condition A:

Flow	1.0mL/min
Stop Time	5.20 min
pH	2.6

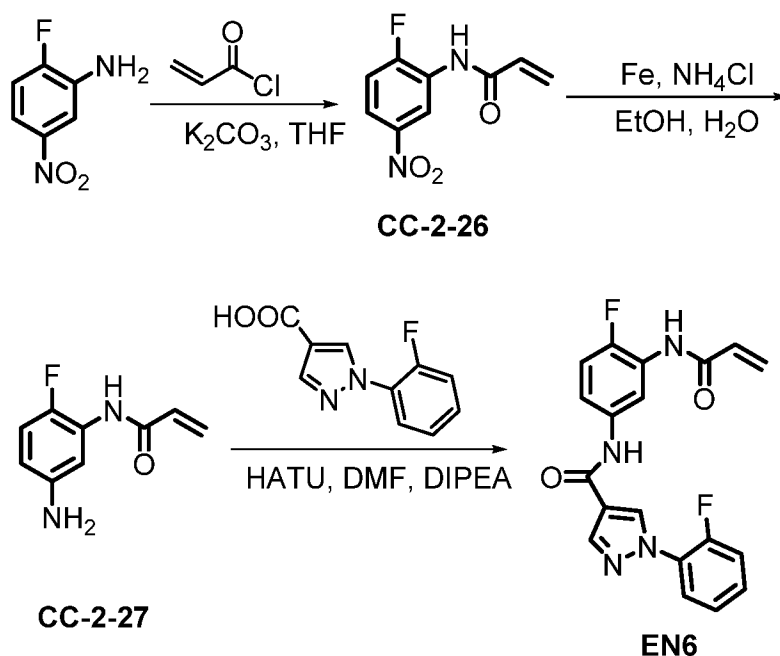
Gradient	Time (min)	%A (Eluent A1)	%B (Eluent B1)
	0.00	98	2
	4.40	2	98
	5.15	2	98
	5.19	98	2
Column	AcQuity UPLC BEH C18 1.7 μ m 2.1x50mm		
Column Temperature	50 °C		
UV	210-400 nm		
Mass Range	120-1600 m/z SQD; 120-1250 m/z QDa		
Scan Time	0.3 sec		

[0601] NMR spectra were run on Bruker AVANCE 300MHz, 400MHz or 600MHz NMR spectrometers using ICON-NMR, under TopSpin program control. Spectra were measured at 298K, unless indicated otherwise, and were referenced relative to the solvent resonance.

- 5 **[0602]** Cell culture. Huh7 cells were cultured and analyzed in phenol red-free DMEM medium, supplemented with 10 vol% FCS, 1x MEM minimum essential amino acids, Penicillin Streptomycin and Glutamine.

- [0603]** Antibodies and reagents for biological experiments. Primary antibodies include rabbit monoclonal anti-human TFE3 (Abcam ab179804). Secondary antibodies include
10 Alexa488-conjugated donkey anti-rabbit (Thermo Fischer A21206).

[0604] Synthesis of EN6.

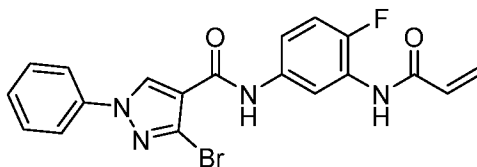


[0605] CC-2-26. K_2CO_3 (936.6 mg, 6.8 mmol) was added to 2-fluoro-5-nitroaniline (529.4 mg, 3.4 mmol) in dry THF (20 mL). At 0 °C, acryloyl chloride (300 μ L, 3.8 mmol) in dry THF (10 mL) was added dropwise to the solution mixture with vigorous stirring. The solution mixture was further stirred at 0 °C for 1 h, and then the reaction was quenched by addition of water. Any organic volatile was removed by evaporation under reduced pressure, and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layer was then washed by saturated NaCl solution, dried by $MgSO_4$ and filtered. Volatile organic solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (4:1, v/v) as eluent, yielding CC-2-26 as yellow solid (643 mg, 90%). 1H NMR ($CDCl_3$, 400 MHz): δ 9.34-9.44 (1H, m), 7.97-8.04 (1H, m), 7.55 (1H, br), 7.26 (1H, t, J = 9.5 Hz), 6.50-6.56 (1H, m), 6.27-6.35 (1H, m), 5.89-5.92 (1H, m). $^{13}C\{^1H\}$ NMR ($[D_6]DMSO$, 100 MHz) δ 164.1, 143.7, 130.8, 128.7, 127.4, 127.3, 120.5, 120.4, 118.0, 116.8, 116.5. $^{19}F\{^1H\}$ NMR ($CDCl_3$, 376 MHz) δ = 119.0. HRMS (ESI) m/z $[M-H]^-$ calcd for $C_9H_7FN_2O_3$: 209.0363; found: 209.0371.

[0606] CC-2-27. CC-2-26 (343 mg, 1.63 mmol) and ammonium chloride (873 mg, 16.3 mmol) were dissolved in EtOH/ H_2O mixture (50 mL; v/v = 4:1) with heating. Iron powder (911.5 mg, 16.3 mmol) was then added and the reaction mixture was heated under reflux for 3 h. After complete consumption of CC-2-26 as indicated by TLC, the reaction mixture was cooled to room temperature and any undissolved solid was filtered off. The filtrate was evaporated under reduced pressure, and the aqueous solution was extracted with ethyl acetate

three times. The combined organic layer was dried by MgSO_4 and filtered. Volatile organic solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (3:2, v/v) as eluent, yielding CC-2-27 as pale yellow solid (211.5 mg, 72%). ^1H NMR ($[\text{D}_6]$ DMSO, 400 MHz): δ 9.66 (1H, s), 7.26 (1H, d, $J = 5.3$ Hz), 6.89 (1H, t, $J = 9.4$ Hz), 6.60 (1H, dd, $J = 5.1$ and 17.0 Hz), 6.27-6.33 (1H, m), 6.24 (1H, d, $J = 17.0$ Hz), 5.73 (1H, d, $J = 10.2$ Hz), 5.13 (2H, br). $^{13}\text{C}\{^1\text{H}\}$ NMR ($[\text{D}_6]$ DMSO, 100 MHz) δ 163.3, 144.8, 131.7, 127.0, 125.9, 125.8, 115.3, 115.1, 110.1, 109.1. HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_9\text{H}_{10}\text{FN}_2\text{O}$: 181.0777; found: 181.07772.

[0607] EN6. 1-(2-Fluorophenyl)-1*H*-pyrazole-4-carboxylic acid (57.2 mg, 0.28 mmol) and HATU (127.6 mg, 0.33 mmol) were dissolved in anhydrous DMF (2 mL) and the mixture was stirred at room temperature for 15 min. CC-2-27 (50 mg, 0.28 mmol) in anhydrous DMF (1 mL) was then added, followed by the addition of DIPEA (146 μL , 0.84 mmol). After reaction overnight, the solvent was evaporated under reduced pressure and the crude product was dissolved in ethyl acetate. The organic solution was washed with sat. NaHCO_3 (aq) solution and sat. NaCl (aq) solution, dried by MgSO_4 and filtered. Volatile organic solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel using dichloromethane/methanol (24:1, v/v) as eluent, yielding the desired product as an off-white solid (38 mg, 37%). ^1H NMR ($[\text{D}_6]$ DMSO, 400 MHz): δ 10.13 (1H, s), 9.98 (1H, s), 8.88 (1H, s), 8.37 (1H, d, $J = 6.2$ Hz), 8.34 (1H, s), 7.87 (1H, t, $J = 7.6$ Hz), 7.61-7.68 (1H, m), 7.45-7.57 (2H, m), 7.40 (1H, t, $J = 7.6$ Hz), 7.26 (1H, t, $J = 9.6$ Hz), 6.60-6.71 (1H, m), 6.30 (1H, d, $J = 17.0$ Hz), 5.79 (1H, d, $J = 10.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR ($[\text{D}_6]$ DMSO, 100 MHz) δ 163.5, 159.9, 154.7, 152.2, 150.9, 148.5, 141.0, 135.2, 135.1, 132.9, 132.9, 131.4, 129.6, 129.5, 127.5, 127.4, 127.3, 125.9, 125.8, 125.5, 125.5, 125.0, 120.4, 117.3, 117.1, 117.0, 116.9, 115.8, 115.4, 115.2. HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{14}\text{F}_2\text{N}_4\text{O}_2\text{Na}$: 391.0983; found: 391.0977.

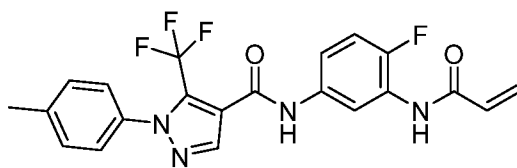
[0608]

[0609] *N*-(3-acrylamido-4-fluorophenyl)-3-bromo-1-phenyl-1*H*-pyrazole-4-carboxamide (1-1).

[0610] *Step 1: 3-bromo-1-phenyl-1H-pyrazole-4-carboxylic acid.* To a solution of ethyl 3-bromo-1-phenyl-1H-pyrazole-4-carboxylate (prepared as described in WO2017/7756, **2017**, A1) (10.0 g, 33.9 mmol) in a 160 mL mixture of MeOH and THF (1:1) was added the solution of sodium hydroxide (6.78 g, 169.4 mmol) in 40 mL of water and the reaction mixture was stirred at rt for 16 h. The reaction was monitored by TLC. After completion of the reaction, the reaction solution was concentrated under reduced pressure, the residue was diluted with water, extracted with Et₂O. The aqueous layer was collected, acidified with 4N HCl and extracted with EtOAc. The combined EtOAc layer was washed with brine, anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to afford a white residue. The residue was triturated with 5% CHCl₃-hexane to get the product as white solid (8.2 g, 91%).

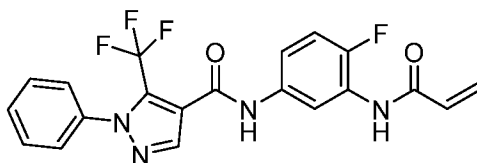
[0611] *Step 2: N-(3-acrylamido-4-fluorophenyl)-3-bromo-1-phenyl-1H-pyrazole-4-carboxamide (1-2).* To a stirred solution of 3-bromo-1-phenyl-1H-pyrazole-4-carboxylic acid (0.15 g, 0.561 mmol) in 5.0 mL DMF was added CC-2-27 (0.165 mg, 0.561 mmol) and DIPEA (0.4 mL, 2.25 mmol). The reaction was stirred at rt for 15 min. Next, HATU (0.32 g, 0.842 mmol) and reaction mixture was stirred at rt for 16 h. The reaction was monitored by TLC. The reaction was concentrated under reduced pressure added NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with brine solution, dried over Na₂SO₄, filtered, concentrated and purified by combi-flash column chromatography eluting with 20-30% EtOAc in DCM to afford the desired product as a light brown solid. The material further purified by preparative HPLC to afford a white solid, (28 mg, 26%). ¹H NMR (CDCl₃, 600 MHz): δ 8.38 (1H, s), 8.24 (1H, s), 8.01 (1H, s), 7.88 (1H, d), 7.56-7.47 (7H, m), 7.13-7.12 (2H, m), 6.49-6.46 (1H, d), 6.31-6.27 (1H, m).

[0612]

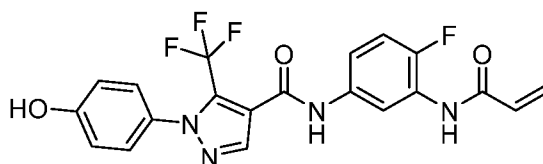


[0613] *N-(3-acrylamido-4-fluorophenyl)-1-(p-tolyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (1-2).* CC-2-27 (60.0 mg, 0.204 mmol), 1-(p-tolyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (66.1 mg, 0.245 mmol), DIPEA (89 µl, 0.510 mmol) and 2.0 mL DMF were combined and stirred at rt for 10 min. HATU (116 mg, 0.306 mmol) was added and stirred at rt for 16 h. Reaction mixture was filtered and purified by preparative HPLC.

Desired fractions were concentrated and lyophilized to afford a white solid (12 mg, 13%).
 LCMS Rt = 2.30 min (Condition A), MS (M+H) = 433.0. ¹H NMR (400 MHz, DMSO-d₆): δ
 10.60 (s, 1H), 9.98 (s, 1H), 8.39 (dd, J = 7.2, 2.6 Hz, 1H), 8.29 (s, 1H), 7.54 (ddd, J = 8.9,
 4.4, 2.7 Hz, 1H), 7.41 (s, 5H), 7.28 (dd, J = 10.7, 8.9 Hz, 1H), 6.64 (dd, J = 17.0, 10.2 Hz,
 5 1H), 6.30 (dd, J = 17.0, 2.0 Hz, 1H), 5.80 (dd, J = 10.2, 2.0 Hz, 1H), 2.43 (s, 3H). HRMS
 (ESI) m/z [M+H]⁺ calcd for C₁₉H₁₇F₄N₄O₂: 433.1288; found: 433.1323.

[0614]

[0615] *N*-(3-acrylamido-4-fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole-4-
 10 carboxamide (**1-3**). CC-2-27 (60.0 mg, 0.204 mmol), 1-phenyl-5-(trifluoromethyl)-1H-
 pyrazole-4-carboxylic acid (62.7 mg, 0.245 mmol), DIPEA (89 μl, 0.510 mmol) were
 combined in 2.5 mL DMF and stirred for 10 min. HATU (116 mg, 0.306 mmol) was added
 and stirred at rt for 16 h. The reaction mixture was filtered and purified by preparative HPLC
 to afford a white solid (14 mg, 16%). LCMS Rt = 2.18 min (Condition A), MS (M+H) =
 15 417.3. ¹H NMR (400 MHz, DMSO-d₆): δ 10.61 (s, 1H), 9.99 (s, 1H), 8.40 (dd, J = 7.5, 2.6
 Hz, 1H), 8.32 (s, 1H), 7.66-7.59 (m, 3H), 7.55 (dd, J = 6.8, 3.2 Hz, 3H), 7.28 (dd, J = 10.7,
 8.9 Hz, 1H), 6.64 (dd, J = 17.0, 10.2 Hz, 1H), 6.30 (dd, J = 17.0, 2.0 Hz, 1H), 5.80 (dd, J =
 10.2, 2.0 Hz, 1H). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₀H₁₅F₄N₄O₂: 419.3532; found:
 419.1156.

[0616]

[0617] *N*-(3-acrylamido-4-fluorophenyl)-1-(4-hydroxyphenyl)-5-(trifluoromethyl)-1H-
 pyrazole-4-carboxamide (**1-4**).

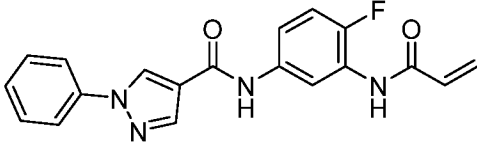
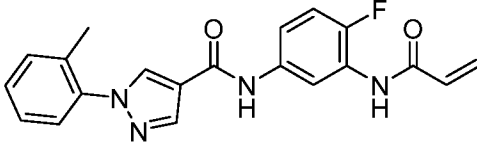
[0618] *Step 1: 1-(4-hydroxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid.*

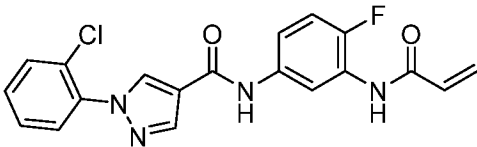
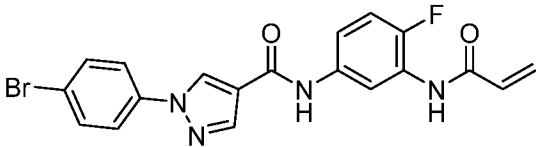
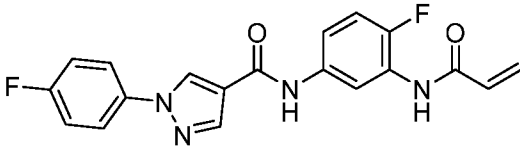
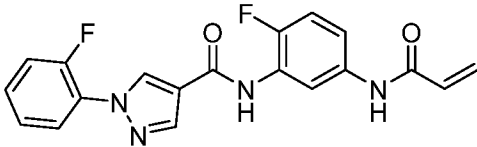
25 Ethyl 1-(4-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (prepared as
 described in: Gentile, D.; Rathinaswamy, M.; Jenkins, M.; Moss, S.; Siempelkamp, B.;

Renslo, A.; Burke, J.; Shokat, K. *Cell Chem. Bio.* **2017**, *24*, 1455-1466) (113 g, 359 mmol, 1 eq) in pyridine hydrochloride (291 g, 2.52 mol, 7 eq) was stirred at 180 °C for 8 h. LCMS showed desired MS was observed as major peak. The reaction mixture was cooled down, quenched with water 1000 mL, the solid was collected by filter and the solid was dissolved in 10% MeOH/EtOAc (2000 mL) and passed through a short silica gel column, the column was washed with EtOAc (1000 mL). The filtrate was concentrated and the residue was triturated with EtOAc (200 mL) to give c 1-(4-hydroxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (65.0 g, 65%) as a gray solid.

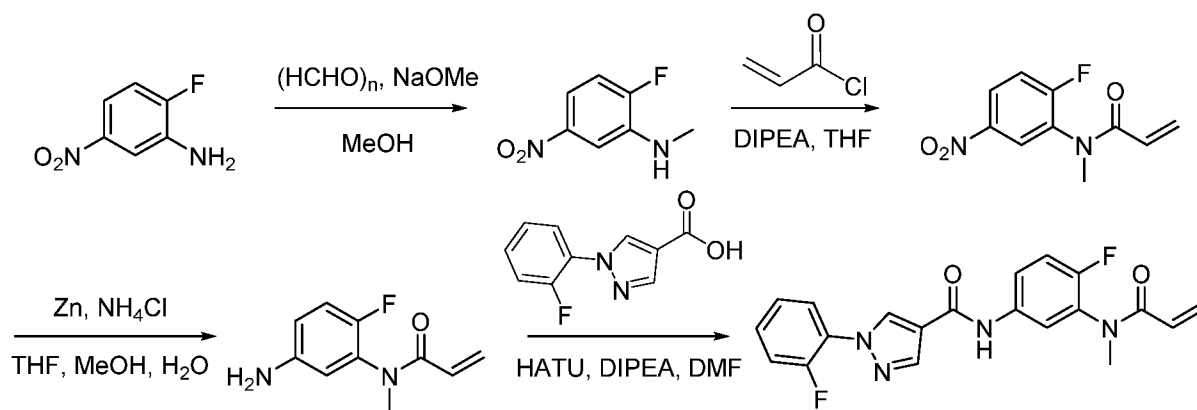
[0619] *Step 2:* CC-2-27 (60.0 mg, 0.204 mmol), 1-(4-hydroxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (66.6 mg, 0.245 mmol), DIPEA (89 µl, 0.510 mmol) and 1.0 mL DMF were combined and stirred at rt for 10 min. HATU (116 mg, 0.306 mmol) was added and stirred at rt for 16 h. Reaction mixture was filtered and purified by preparative HPLC to afford a white solid (4.5 mg, 5%). LCMS Rt = 1.77 min (Condition A), MS (M+H) = 435.1. ¹H NMR (400 MHz, DMSO-d₆): δ 10.57 (s, 1H), 10.10 (s, 1H), 9.98 (s, 1H), 8.38 (d, J = 7.3 Hz, 1H), 8.24 (s, 1H), 7.60-7.45 (m, 1H), 7.31 (dd, J = 7.6, 5.5 Hz, 2H), 7.28-7.23 (m, 1H), 6.96-6.89 (m, 2H), 6.63 (dd, J = 17.0, 10.1 Hz, 1H), 6.30 (dd, J = 17.0, 2.0 Hz, 1H), 5.80 (dd, J = 10.2, 2.0 Hz, 1H). HRMS (ESI) m/z [M+H]⁺ calcd for C₂₀H₁₅F₄N₄O₃: 435.3526; found: 435.1093.

[0620] The following compounds were prepared in a similar procedure as EN-6.

Example	Compound	LCMS M+1, Rt, conditions	HRMS (ESI) m/z
1-5	N-(3-acrylamido-4-fluorophenyl)-1-phenyl-1H-pyrazole-4-carboxamide 	351.4, 1.81min, A	[M+H] ⁺ calcd for C ₁₉ H ₁₆ FN ₄ O ₂ : 351.3552; found: 351.1266
1-6	N-(3-acrylamido-4-fluorophenyl)-1-(o-tolyl)-1H-pyrazole-4-carboxamide 	365.0, 1.87min, A	[M+H] ⁺ calcd for C ₂₀ H ₁₈ FN ₄ O ₂ : 365.3818; found: 365.1439.

1-7	N-(3-acrylamido-4-fluorophenyl)-1-(2-chlorophenyl)-1H-pyrazole-4-carboxamide. 	385.3, 1.90min, A	[M+H] ⁺ calcd for C ₁₉ H ₁₅ ClFN ₄ O ₂ : 385.7998; found: 385.0884.
1-8	N-(3-acrylamido-4-fluorophenyl)-1-(4-bromophenyl)-1H-pyrazole-4-carboxamide. 	429.0, 2.20min, A	[M] ⁺ calcd for C ₁₉ H ₁₄ BrFN ₄ O ₂ : 429.24286; found: 429.0391.
1-9	N-(3-acrylamido-4-fluorophenyl)-1-(4-fluorophenyl)-1H-pyrazole-4-carboxamide. 	369.2, 1.89min, A	[M+H] ⁺ calcd for C ₁₉ H ₁₅ F ₂ N ₄ O ₂ : 369.3456; found: 369.1187.
1-10	N-(5-acrylamido-2-fluorophenyl)-1-(2-fluorophenyl)-1H-pyrazole-4-carboxamide. 	369.1, 0.76min, A	[M+H] ⁺ calcd for C ₁₉ H ₁₅ F ₂ N ₄ O ₂ : 369.3456; found: 369.1174.

[0621] Synthesis of N-(4-fluoro-3-(N-methylacrylamido)phenyl)-1-(2-fluorophenyl)-1Hpyrazole-4-carboxamide (**1-11**).



[0622] *N*-(4-fluoro-3-(*N*-methylacrylamido)phenyl)-1-(2-fluorophenyl)-1Hpyrazole-4-carboxamide (**1-11**).

[0623] *Step 1: 2-fluoro-N-methyl-5-nitroaniline.* To a stirred solution of 2-fluoro-5-nitroaniline (1.0 g, 6.41 mmol) in MeOH (20 mL), paraformaldehyde (0.769 g, 25.62 mmol) dissolved in MeOH (20 mL) was added slowly, the reaction was stirred at rt, then NaOMe (0.173 g, 3.02 mmol) in MeOH (10 mL) was added dropwise and the reaction was stirred at rt for 16 h. Completion of the reaction was monitored by TLC. After completion of reaction, the mixture was poured into 1M KOH aqueous solution and stirred to precipitate a yellow solid, the precipitate was filtered. Crude precipitate was purified by combi-flash column chromatography using EtOAc in Hexane. Product eluted 18% EtOAc in Hexane and 2-fluoro-N-methyl-5-nitroaniline was isolated as yellow solid (0.80 g, 73%).

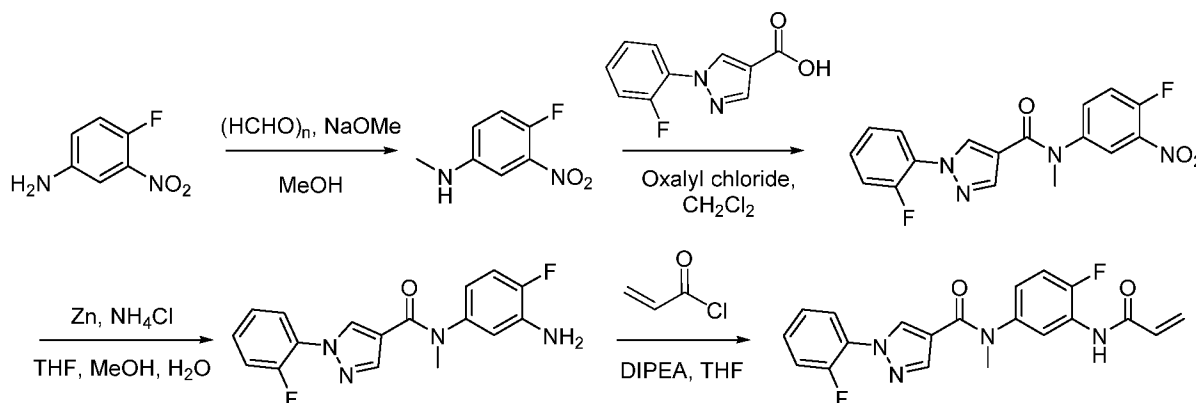
[0624] *Step 2: N-(2-fluoro-5-nitrophenyl)-N-methylacrylamide.* To a stirred solution of 2-fluoro-N-methyl-5-nitroaniline (0.60 g, 3.53 mmol) in THF (10 mL), DIPEA (1.3 mL, 7.05 mmol) was added then the reaction was stirred at rt for 10 min, then cooled to 0 °C, acryloyl chloride (0.317 g, 3.53 mmol) in THF (5 mL) added dropwise to the reaction mixture, then the reaction mixture was stirred at rt for 2 h. The reaction was monitored by TLC and after completion the reaction was quenched with water, extracted using EtOAc, then washed with brine solution, dried over Na₂SO₄ and concentrated. The residue product was purified by combi-flash column chromatography using EtOAc in Hexane. N-(2-fluoro-5-nitrophenyl)-N-methylacrylamide eluted 15% EtOAc in Hexane as a yellow oil (0.60 g, 75%).

[0625] *Step 3: N-(5-amino-2-fluorophenyl)-N-methylacrylamide.* To a stirred solution of N-(2-fluoro-5-nitrophenyl)-N-methylacrylamide (0.60 g, 2.68 mmol) in 10 mL of THF at 0 °C, was added NH₄Cl (1.14 g, 21.5 mmol) dissolved in 3.0 mL MeOH and 1.0 mL H₂O and stirred the reaction for 10 min. Followed by addition of zinc dust (1.4 g, 21.5 mmol) was

added to the reaction and it was stirred for 3 h at rt. The reaction was monitored by TLC and upon completion the reaction mixture was filtered through pad of cellite and washed with ethyl acetate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, washed with brine solution, and then dried over anhydrous sodium sulphate, filtered and concentrated to afford product as yellow solid (0.45 g, 86%).

[0626] *Step 4: N-(4-fluoro-3-(N-methylacrylamido)phenyl)-1-(2-fluorophenyl)-1H-pyrazole-4-carboxamide (1-11).* To a solution of N-(5-amino-2-fluorophenyl)-N-methylacrylamide (0.10 g, 0.514 mmol) in 3.0 mL DMF, was added 1-(2-fluorophenyl)-1H-pyrazole-4-carboxylic acid (0.106 g, 0.514 mmol) followed by DIPEA (0.9 mL, 2.57 mmol). Then reaction was stirred for 10 min and HATU (0.293 g, 0.771 mmol) was added. The reaction mixture was stirred at rt for 16 h. Completion of the reaction monitored by TLC. The reaction mixture was diluted with water and a solid was formed, and it was filtered and dried. Crude product was purified by combi-flash column chromatography using EtOAc in Hexane; compound eluted 30% EtOAc in Hexane. N-(4-fluoro-3-(N-methylacrylamido)phenyl)-1-(2-fluorophenyl)-1H-pyrazole-4-carboxamide (**1-13**) was isolated as pale pink solid (0.08 g, 40%) ¹H NMR (DMSO-d₆, 300 MHz): δ 10.22 (1H, s), 8.861 (1H, d), 8.33 (1H, s), 7.87 (1H, t), 7.79–7.77 (2H, d), 7.51 (2H, m), 7.43–7.40 (2H, d), 6.199–6.19 (1H, d), 6.15 (1H, m), 5.65 (1H, d), 3.22 (1H, t).

[0627] Synthesis of N-(3-acrylamido-4-fluorophenyl)-1-(2-fluorophenyl)-N-methyl-1H-pyrazole-4-carboxamide (**1-12**).



[0628] *N-(3-acrylamido-4-fluorophenyl)-1-(2-fluorophenyl)-N-methyl-1H-pyrazole-4-carboxamide (1-12).*

[0629] *Step 1: 4-fluoro-N-methyl-3-nitroaniline.* To a stirred solution of 4-fluoro-3-nitroaniline (1.0 g, 6.41 mmol) in MeOH (20 mL), was slowly added paraformaldehyde

(0.769 g, 25.6 mmol) dissolved in MeOH (20 mL). Upon completion of the addition, the reaction mixture was stirred at rt, while NaOMe (0.173 g, 3.02 mmol) in MeOH (10 mL) was slowly added dropwise. Upon completion of the addition, the reaction mixture was stirred at rt for 16 h. Completion of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into 1M KOH aqueous solution and stirred to precipitate a yellow solid. The precipitate was filtered and was dried. The precipitate was purified by combi-flash column chromatography using EtOAc in Hexane. Product eluted with 22% EtOAc in Hexane and was isolated as yellow solid (0.6 g, 55%).

[0630] *Step 2: N-(4-fluoro-3-nitrophenyl)-1-(2-fluorophenyl)-N-methyl-1H-pyrazole-4-*

carboxamide. To a stirred solution of 1-(2-fluorophenyl)-1H-pyrazole-4-carboxylic acid (0.20 g, 0.97 mmol) in 5.0 mL dichloromethane, thionyl chloride (0.1 mL) was added slowly at 0 °C, then catalytic amount DMF (5 drops) was added and stirred for 1 h. Then reaction mixture was concentrated under N₂ atmosphere, then crude was dissolved in THF (5 mL), cooled to 0 °C, then DIPEA (0.35 mL, 1.94 mmol) was added to the reaction at 0 °C, followed by 4-fluoro-N-methyl-3-nitroaniline (0.165 g, 0.97 mmol) dissolved in THF (5 mL). The reaction was stirred for 3 h at rt and was monitored by TLC. Upon completion, the reaction was quenched with water and extracted using EtOAc (3x). The organic layer was washed with water, washed with brine solution, and dried over anhydrous Na₂SO₄, filtered and concentrated to afford a yellow solid. The solid residue was purified by combi-flash column on eluting with 20% EtOAc in Hexane as eluent to isolate the product as a yellow solid (0.16 g, 46%).

[0631] *Step 3: N-(3-amino-4-fluorophenyl)-1-(2-fluorophenyl)-N-methyl-1H-pyrazole-4-*

carboxamide. To the stirred solution of N-(4-fluoro-3-nitrophenyl)-1-(2-fluorophenyl)-N-methyl-1H-pyrazole-4-carboxamide (0.16 g, 0.446 mmol) in THF:MeOH (7 mL : 3 mL) at 0 °C, was added ammonium chloride (0.191 g, 3.57 mmol) dissolved in 2.0 mL water and stirred the reaction for 10 min. Zinc dust (0.233 g, 3.57 mmol) was added to the resulting reaction mixture and it was stirred for 3 h at rt. The reaction was monitored by TLC. Upon completion of the reaction, the mixture was filtered through pad of cellite and washed with EtOAc. The combined washes were washed with water, washed with brine solution, and dried over anhydrous sodium sulphate, filtered and concentrated to obtain product as yellow solid (0.12 g, 92%).

[0632] *Step 4: N-(3-acrylamido-4-fluorophenyl)-1-(2-fluorophenyl)-N-methyl-1H-pyrazole-4-carboxamide (1-12).* To a solution of N-(3-amino-4-fluorophenyl)-1-(2-fluorophenyl)-N-methyl-1H-pyrazole-4-carboxamide (0.12 g, 0.365 mmol) in methylene chloride (9 mL) was added triethylamine (0.15 mL, 1.1 mmol). To the reaction mixture was added acryloyl chloride (0.033 g, 0.365 mmol) in methylene chloride (1 mL) at rt. The reaction mixture was stirred at rt for 2 h. The reaction was monitored by TLC and upon completion, the reaction mixture was concentrated. The residue was redissolved in EtOAc and washed with water and brine solution. The EtOAc layer was concentrated and the residue was purified by combi-
flash column on eluting with 20% EtOAc in Hexane as eluent to afford N-(3-acrylamido-4-fluorophenyl)-1-(2-fluorophenyl)-N-methyl-1H-pyrazole-4-carboxamide as an off-white solid (0.10 g, 71%). ¹H NMR (CDCl₃, 300 MHz): δ 8.50 (1H, dd), 7.78–7.77 (2H, t), 7.52 (1H, s), 7.27–7.23 (1H, m), 7.22–7.12 (1H, m), 6.96–6.95 (1H, m), 6.49–6.43 (1H, d), 6.32–6.23 (1H, m), 5.86–5.82 (1H, d), 3.43 (1H, s).

[0633] Activity of Compounds

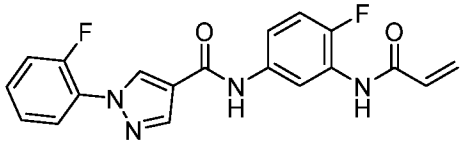
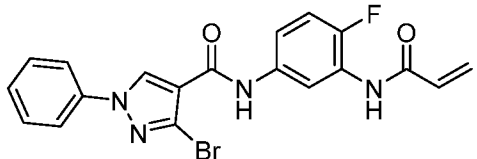
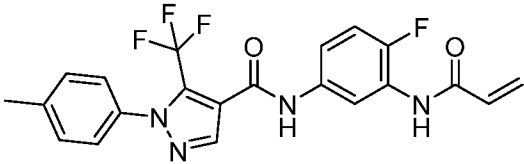
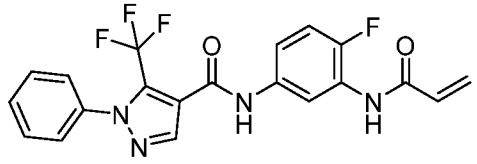
[0634] TFE3 assay. For the TFE3 nuclear translocation assay, 3000 Huh7 cells were seeded in a volume of 50 µl medium into wells of black clear bottom 384-well plates (Greiner). One day post plating, cells were treated for 4 h with a compound dose response, ranging from 80 to 0.63 µM. Compounds were added with the Echo instrument (LabCyte) using acoustic compound transfer. After 4 h, cells were fixed for 10 min at room temperature in 4% paraformaldehyde, washed 3 times with PBS, permeabilized by incubating four times 5 min in PBS containing 0.1% Triton X-100, and blocked for 1 h in blocking buffer (PBS containing 0.1% Triton X-100 and 2% BSA). TFE3 was stained overnight at 4 °C with rabbit monoclonal anti-human TFE3 antibody (Abcam ab179804) diluted 1:400 in blocking buffer. Cells were then washed 3 times with PBS and incubated in blocking buffer containing Alexa 488-conjugated donkey anti-rabbit secondary antibody (Thermo Fischer A21206, 1:2000) and Hoechst dye (Thermo Fisher H3570, 1:5000). After 3 washing steps in PBS, plates were imaged with an automated IN Cell Analyzer 2000 (GE Healthcare). Hoechst and Alexa488 fluorescence images were captured in 4 fields per well using a 20x objective. Image analysis was performed using CellProfiler (reference: PMID 17076895). Nuclei were first detected in the Hoechst image using Adaptive Otsu thresholding. The cell area was then defined by extending 10 pixels around the nuclear area. The cytoplasmic area was defined as cell area excluding the nuclear area. The mean intensity of the TFE3 staining in the nuclear versus

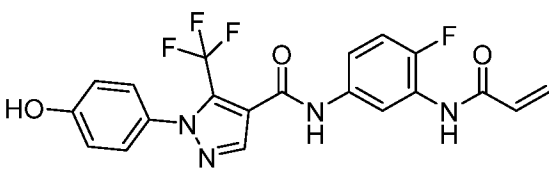
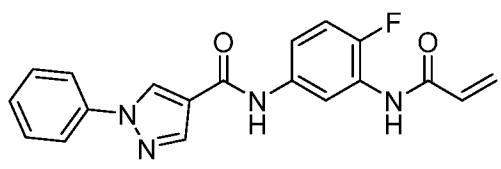
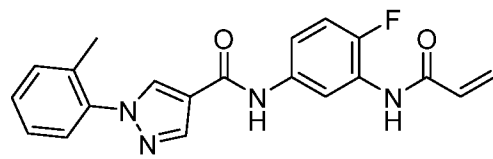
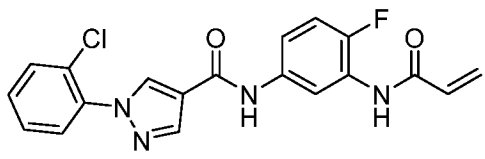
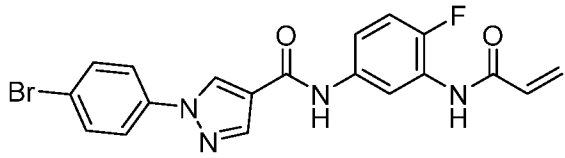
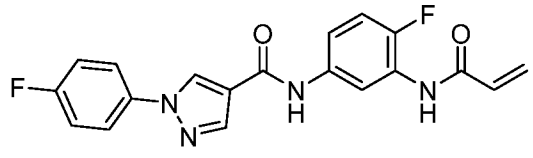
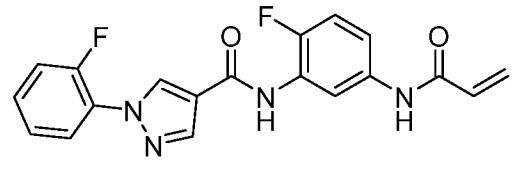
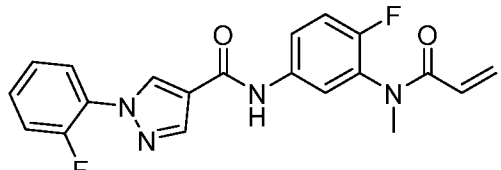
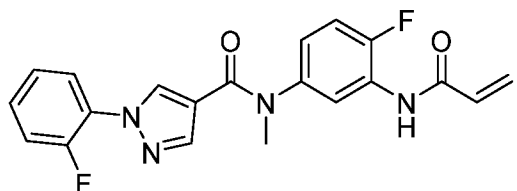
cytoplasmic area was determined in the Alexa488 image and represented as ratio relative to DMSO-treated control cells.

[0635] Table 2. The measured TFE3 translocation activity.

Example #	TFE3 AC ₅₀ (uM)	AMax
EN-6	>80.0	1.50
1-1	34.8	1.47
1-2	16.7	1.55
1-3	29.3	1.59
1-4	33.3	1.55
1-5	57.4	1.46
1-6	47.0	1.52
1-7	39.7	1.53
1-8	21.0	1.26
1-9	31.2	1.29
1-10	>80.0	1.03
1-11	34.1	1.49
1-12	48.5	1.70

5 [0636] Table 3. Compounds from TFE3 Translocation assay.

EN6 	1-1 
1-2 	1-3 

1-4 	1-5 
1-6 	1-7 
1-8 	1-9 
1-10 	1-11 
1-12 	

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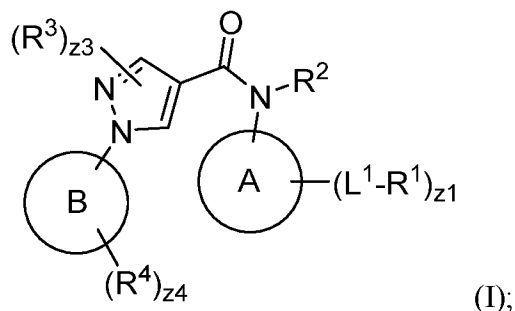
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WHAT IS CLAIMED IS:

1 1. A compound, or a pharmaceutically acceptable salt thereof, having the
2 formula:



3 wherein

4 Ring A is a phenyl or 5 to 6 membered heteroaryl;

5 Ring B is a phenyl or 5 to 6 membered heteroaryl;

6 L^1 is independently a bond, $-S(O)_2-$, $-N(R^5)-$, $-O-$, $-S-$, $-C(O)-$, $-C(O)N(R^5)-$,
7 $-N(R^5)C(O)-$, $-N(R^5)C(O)NH-$, $-NHC(O)N(R^5)-$, $-C(O)O-$, $-OC(O)-$, substituted or
8 unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or
9 unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or
10 unsubstituted arylene, or substituted or unsubstituted heteroarylene;

11 R^5 is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$,
12 $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$,
13 $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$,
14 $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$,
15 $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, unsubstituted alkyl,
16 unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl,
17 unsubstituted aryl, or unsubstituted heteroaryl;

18 R^1 is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$,
19 $-OCHX^1_2$, $-CN$, $-SO_{n1}R^{1D}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-C(O)R^{1C}$,
20 $-C(O)-OR^{1C}$, $-C(O)NR^{1A}R^{1B}$, $-OR^{1D}$, $-NR^{1A}SO_2R^{1D}$, $-NR^{1A}C(O)R^{1C}$, $-NR^{1A}C(O)OR^{1C}$,
21 $-NR^{1A}OR^{1C}$, $-N_3$, E, substituted or unsubstituted alkyl, substituted or unsubstituted
22 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
23 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
24 two adjacent $-L^1-R^1$ substituents may optionally be joined to form a substituted or
25 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
26 unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- 28 E is an electrophilic moiety;
- 29 R^2 is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$,
 30 $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$,
 31 $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$,
 32 $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$,
 33 $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, unsubstituted alkyl,
 34 unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl,
 35 unsubstituted aryl, or unsubstituted heteroaryl;
- 36 R^3 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$,
 37 $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$,
 38 $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$,
 39 $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$,
 40 $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, substituted or
 41 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 42 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 43 substituted or unsubstituted heteroaryl;
- 44 R^4 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$,
 45 $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$,
 46 $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$,
 47 $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$,
 48 $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, substituted or
 49 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 50 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 51 substituted or unsubstituted heteroaryl; two adjacent R^4 substituents may optionally be joined
 52 to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 53 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- 54 R^{1A} , R^{1B} , R^{1C} , and R^{1D} are independently hydrogen, halogen, $-CCl_3$, $-CBr_3$,
 55 $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$,
 56 $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$,
 57 $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$,
 58 $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$,
 59 $-OCHI_2$, 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;

X^1 is independently -F, -Cl, -Br, or -I;

n_1 is independently an integer from 0 to 4;

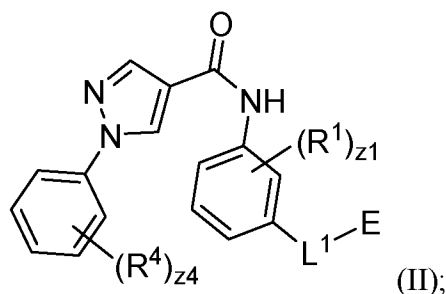
m_1 and v_1 are independently 1 or 2;

z_1 is independently an integer from 0 to 5;

z_3 is independently an integer from 0 to 2; and

z_4 is independently an integer from 0 to 5.

2. The compound of claim 1, having the formula:



wherein

L^1 is independently a bond, -S(O)₂-, -NH-, -O-, -S-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene;

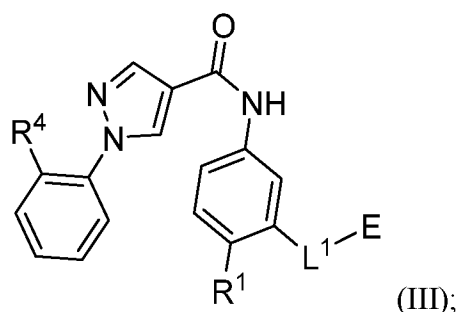
R^1 is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R^1 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

R^4 is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R⁴ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; z₁ is independently an integer from 0 to 4; and z₄ is independently an integer from 0 to 5.

3. The compound of claim 1, having the formula:



wherein

L¹ is independently a bond, -S(O)₂-, -NH-, -O-, -S-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene;

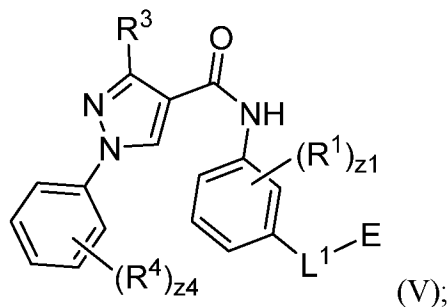
R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety; and

R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -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, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl,

-OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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.

4. The compound of claim 1, having the formula:



wherein

L¹ is independently a bond, -S(O)₂-, -NH-, -O-, -S-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heterocycloalkylene, or substituted or unsubstituted heteroarylene;

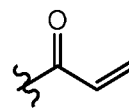
R¹ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

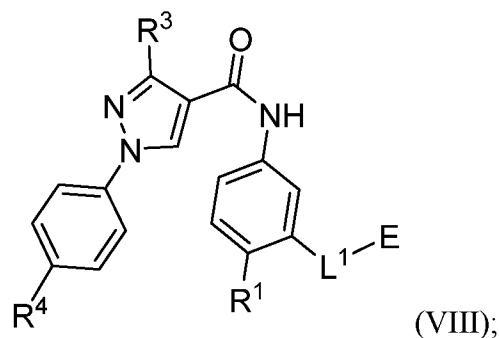
R³ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, 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 independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$,
 $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$,
 $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$,
 $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$,
 $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, 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; two adjacent R^4 substituents may optionally be joined
 to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 z_1 is independently an integer from 0 to 4; and
 z_4 is independently an integer from 0 to 5.

5. The compound of claim 4, wherein E is



6. The compound of claim 1, having the formula:

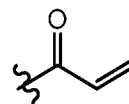


wherein

L^1 is independently a bond, $-S(O)_2-$, $-NH-$, $-O-$, $-S-$, $-C(O)NH-$, $-NHC(O)-$,
 $-NHC(O)NH-$, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
 heterocycloalkylene, or substituted or unsubstituted heteroarylene;

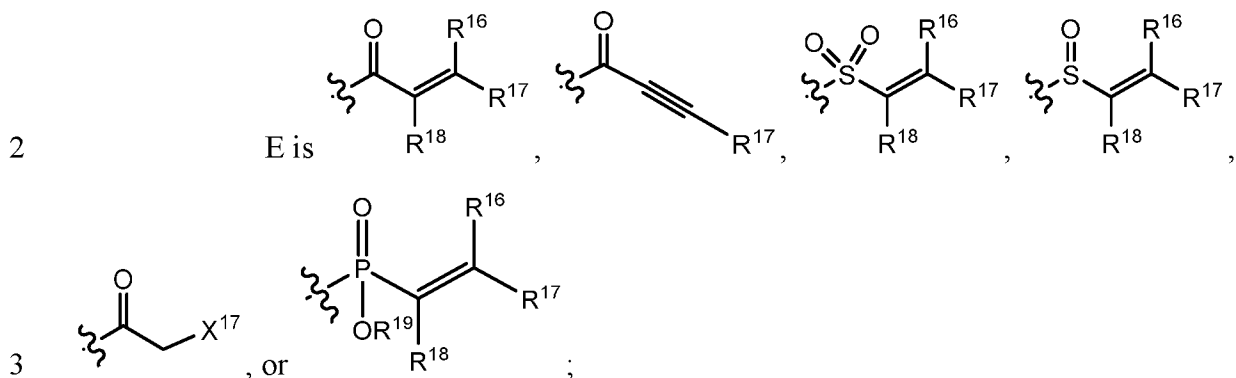
R^1 is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$,
 $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$,
 $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$,
 $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCBr_3$, $-OCF_3$, $-OCl_3$, $-OCH_2Cl$,
 $-OCH_2Br$, $-OCH_2F$, $-OCH_2I$, $-OCHCl_2$, $-OCHBr_2$, $-OCHF_2$, $-OCHI_2$, $-N_3$, substituted or
 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

13 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 14 substituted or unsubstituted heteroaryl;
 15 E is an electrophilic moiety;
 16 R³ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br,
 17 -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂,
 18 -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂,
 19 -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl,
 20 -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or
 21 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 22 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 23 substituted or unsubstituted heteroaryl; and
 24 R⁴ is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br,
 25 -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂,
 26 -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂,
 27 -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl,
 28 -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂, -OCHI₂, substituted or
 29 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 30 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 31 substituted or unsubstituted heteroaryl.



- 1 7. The compound of claim 6, wherein E is
- 1 8. The compound of claim 1, wherein R³ is independently halogen, -CCl₃,
 2 -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN,
 3 -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,
 4 -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃,
 5 -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂,
 6 -OCHI₂, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4
 7 membered heteroalkyl.
- 1 9. The compound of claim 1, wherein R³ is independently halogen, -CCl₃,
 2 -CBr₃, -CF₃, or -Cl₃.

- 1 10. The compound of claim 1, wherein R³ is independently -Br or -CF₃.
- 1 11. The compound of claim 1, wherein R¹ is independently halogen, -CCl₃,
2 -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN,
3 -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,
4 -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃,
5 -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂,
6 -OCHI₂, -N₃, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4
7 membered heteroalkyl.
- 1 12. The compound of claim 1, wherein R¹ is independently halogen.
- 1 13. The compound of claim 1, wherein R¹ is independently -F.
- 1 14. The compound of claim 1, wherein R⁴ is independently halogen, -CCl₃,
2 -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN,
3 -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,
4 -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃,
5 -OCBr₃, -OCF₃, -OCl₃, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -OCHCl₂, -OCHBr₂, -OCHF₂,
6 -OCHI₂, substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4
7 membered heteroalkyl.
- 1 15. The compound of claim 1, wherein R⁴ is independently halogen.
- 1 16. The compound of claim 1, wherein R⁴ is independently -F.
- 1 17. The compound of claim 1, wherein L¹ is independently -S(O)₂-, -NH-,
2 or substituted or unsubstituted 5 to 6 membered heterocycloalkylene.
- 1 18. The compound of claim 1, wherein L¹ is independently -S(O)₂-, -NH-,
2 unsubstituted pyrrolidinylene, unsubstituted piperidinylene, or unsubstituted piperazinylene.
- 1 19. The compound of claim 1, wherein L¹ is independently -NH-.
- 1 20. The compound of claim 1, wherein



4 wherein R¹⁶ is independently hydrogen, halogen, -CX¹⁶₃, -CHX¹⁶₂, -CH₂X¹⁶,
5 -CN, -SO_{n16}R^{16A}, -SO_{v16}NR^{16A}R^{16B}, -NHN^{16A}R^{16B}, -ONR^{16A}R^{16B}, -NHC(O)NHN^{16A}R^{16B},
6 -NHC(O)NR^{16A}R^{16B}, -N(O)_{m16}, -NR^{16A}R^{16B}, -C(O)R^{16A}, -C(O)-OR^{16A}, -C(O)NR^{16A}R^{16B},
7 -OR^{16A}, -NR^{16A}SO₂R^{16B}, -NR^{16A}C(O)R^{16B}, -NR^{16A}C(O)OR^{16B}, -NR^{16A}OR^{16B}, -OCX¹⁶₃,
8 -OCHX¹⁶₂, -OCH₂X¹⁶, substituted or unsubstituted alkyl, substituted or unsubstituted
9 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
10 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

11 R¹⁷ is independently hydrogen, halogen, -CX¹⁷₃, -CHX¹⁷₂, -CH₂X¹⁷, -CN,
12 -SO_{n17}R^{17A}, -SO_{v17}NR^{17A}R^{17B}, -NHN^{17A}R^{17B}, -ONR^{17A}R^{17B}, -NHC(O)NHN^{17A}R^{17B},
13 -NHC(O)NR^{17A}R^{17B}, -N(O)_{m17}, -NR^{17A}R^{17B}, -C(O)R^{17A}, -C(O)-OR^{17A}, -C(O)NR^{17A}R^{17B},
14 -OR^{17A}, -NR^{17A}SO₂R^{17B}, -NR^{17A}C(O)R^{17B}, -NR^{17A}C(O)OR^{17B}, -NR^{17A}OR^{17B}, -OCX¹⁷₃,
15 -OCHX¹⁷₂, -OCH₂X¹⁷, substituted or unsubstituted alkyl, substituted or unsubstituted
16 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
17 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

18 R¹⁸ is independently hydrogen, halogen, -CX¹⁸₃, -CHX¹⁸₂, -CH₂X¹⁸, -CN,
19 -SO_{n18}R^{18A}, -SO_{v18}NR^{18A}R^{18B}, -NHN^{18A}R^{18B}, -ONR^{18A}R^{18B}, -NHC(O)NHN^{18A}R^{18B},
20 -NHC(O)NR^{18A}R^{18B}, -N(O)_{m18}, -NR^{18A}R^{18B}, -C(O)R^{18A}, -C(O)-OR^{18A}, -C(O)NR^{18A}R^{18B},
21 -OR^{18A}, -NR^{18A}SO₂R^{18B}, -NR^{18A}C(O)R^{18B}, -NR^{18A}C(O)OR^{18B}, -NR^{18A}OR^{18B}, -OCX¹⁸₃,
22 -OCHX¹⁸₂, -OCH₂X¹⁸, substituted or unsubstituted alkyl, substituted or unsubstituted
23 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
24 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

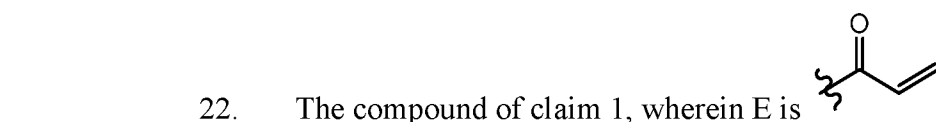
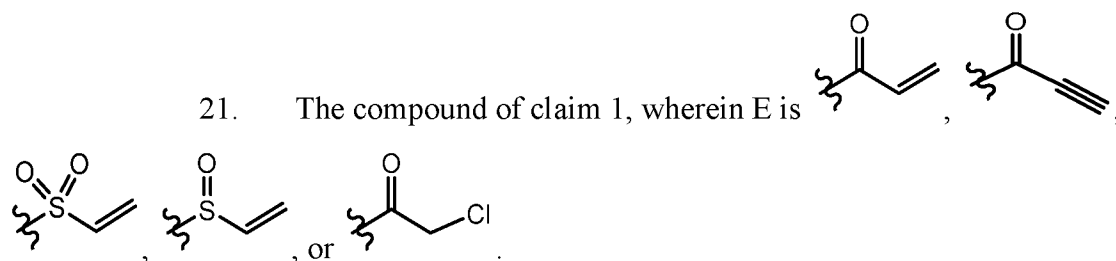
25 R¹⁹ is independently hydrogen, halogen, -CX¹⁹₃, -CHX¹⁹₂, -CH₂X¹⁹, -CN,
26 -SO_{n19}R^{19A}, -SO_{v19}NR^{19A}R^{19B}, -NHN^{19A}R^{19B}, -ONR^{19A}R^{19B}, -NHC(O)NHN^{19A}R^{19B},
27 -NHC(O)NR^{19A}R^{19B}, -N(O)_{m19}, -NR^{19A}R^{19B}, -C(O)R^{19A}, -C(O)-OR^{19A}, -C(O)NR^{19A}R^{19B},
28 -OR^{19A}, -NR^{19A}SO₂R^{19B}, -NR^{19A}C(O)R^{19B}, -NR^{19A}C(O)OR^{19B}, -NR^{19A}OR^{19B}, -OCX¹⁹₃,
29 -OCHX¹⁹₂, -OCH₂X¹⁹, substituted or unsubstituted alkyl, substituted or unsubstituted

heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{16A} , R^{16B} , R^{17A} , R^{17B} , R^{18A} , R^{18B} , R^{19A} , and R^{19B} are independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-COOH$, $-CONH_2$, 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^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

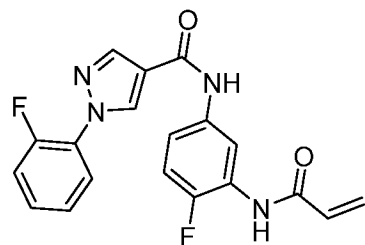
each X^1 , X^{16} , X^{17} , X^{18} , and X^{19} is independently $-F$, $-Cl$, $-Br$, or $-I$;

n_{16} , n_{17} , n_{18} , and n_{19} are independently an integer from 0 to 4; and

m_{16} , m_{17} , m_{18} , m_{19} , v_{16} , v_{17} , v_{18} , and v_{19} are independently 1 or 2.



23. The compound of claim 1, wherein the compound is not



1 24. A pharmaceutical composition comprising a compound of one of
2 claims 1 to 23, or a pharmaceutically acceptable salt thereof, and a pharmaceutically
3 acceptable excipient.

1 25. A method for treating cancer in a subject in need thereof, said method
2 comprising administering to the subject in need thereof a therapeutically effective amount of
3 a compound of one of claims 1 to 23, or a pharmaceutically acceptable salt thereof.

1 26. The method of claim 25, wherein said cancer is renal cell carcinoma,
2 follicular lymphoma, glioblastoma, colorectal cancer, endometrial cancer, or lung cancer.

1 27. A method of reducing the level of activity of mTORC1 in a subject in
2 need thereof, the method comprising administering to the subject in need thereof an effective
3 amount of a compound of one of claims 1 to 23, or a pharmaceutically acceptable salt thereof.

1 28. A method of reducing the level of activity of mTORC1 in a cell, the
2 method comprising contacting a Vacuolar H⁺-ATPase protein complex in said cell with a
3 compound of one of claims 1 to 23, or a pharmaceutically acceptable salt thereof.

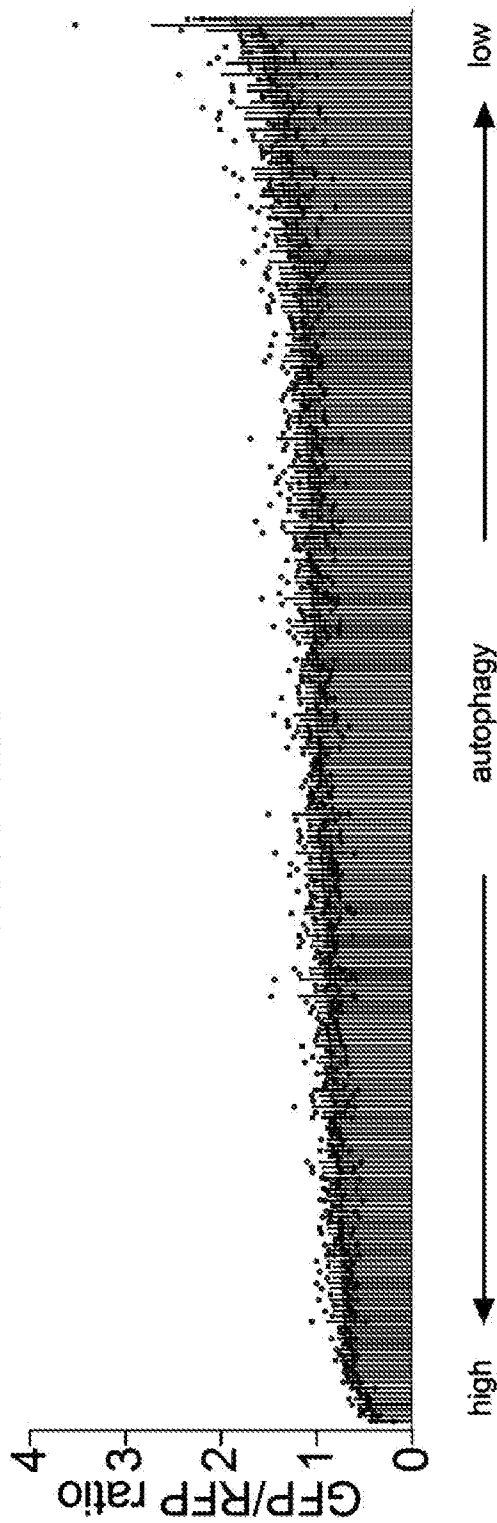
1 29. A method of reducing the level of activity of mTORC1 in a cell, the
2 method comprising contacting an ATP6V1A in said cell with a compound of one of claims 1
3 to 23, or a pharmaceutically acceptable salt thereof.

1 30. A method of reducing the level of activity of a Vacuolar H⁺-ATPase
2 protein complex, the method comprising contacting an ATP6V1A in the Vacuolar H⁺-
3 ATPase protein complex with a compound of one of claims 1 to 23, or a pharmaceutically
4 acceptable salt thereof.

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FIG. 1A

covalent ligand screen for autophagy modulators
in MEF cells



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FIG. 1B

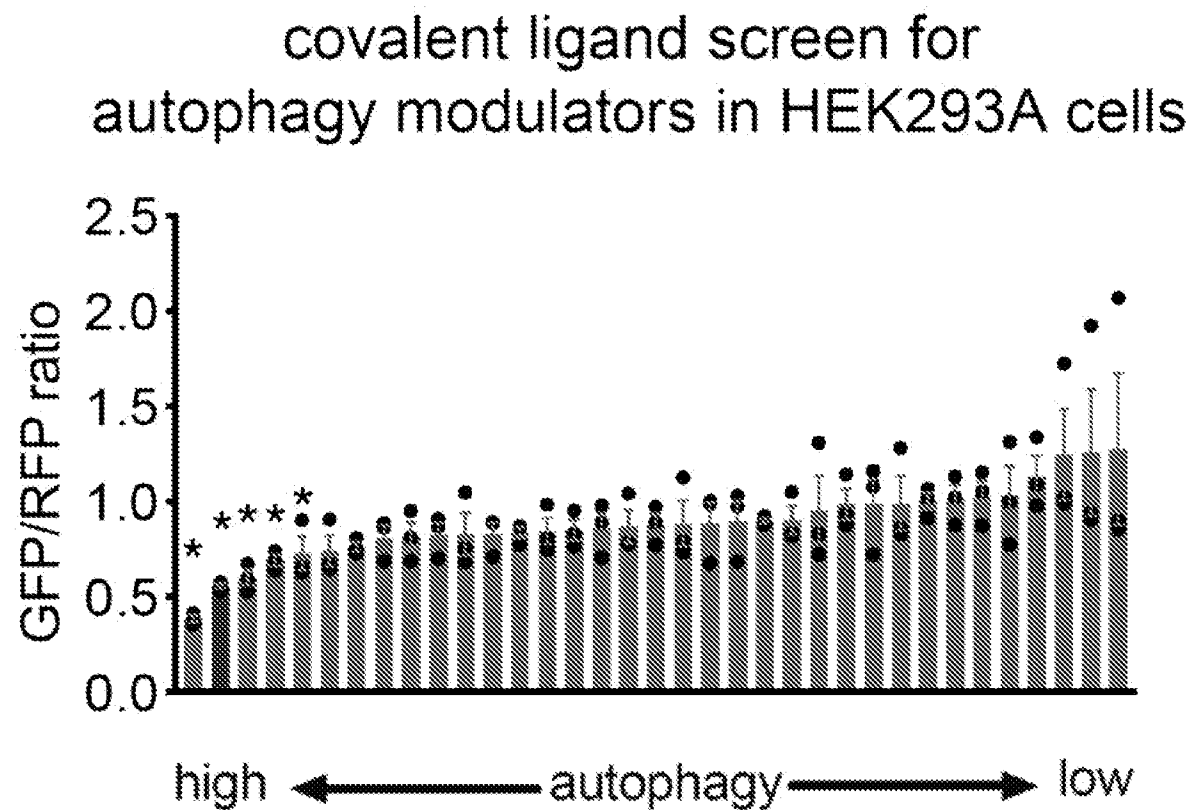
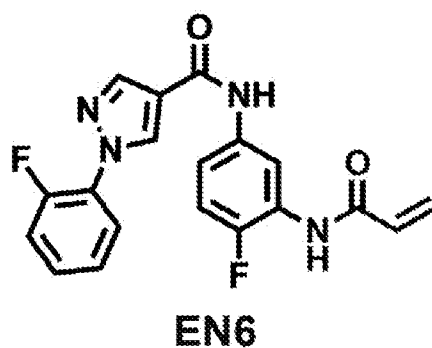
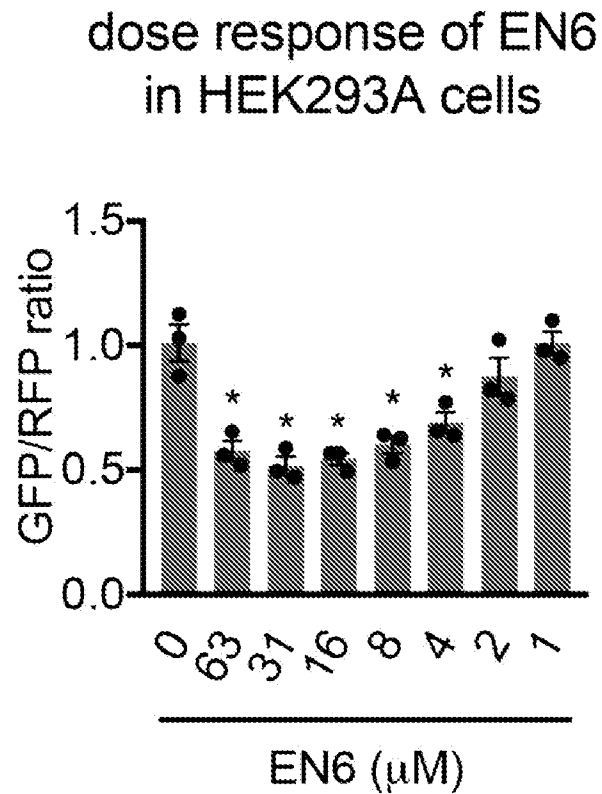


FIG. 1C

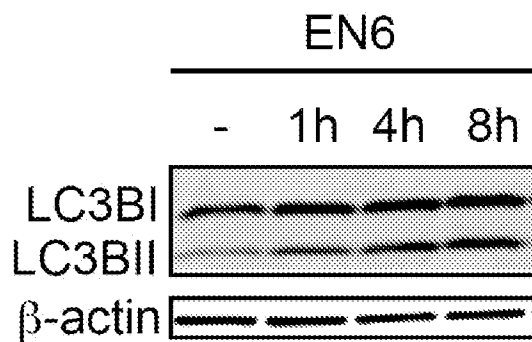
autophagy
activator hit



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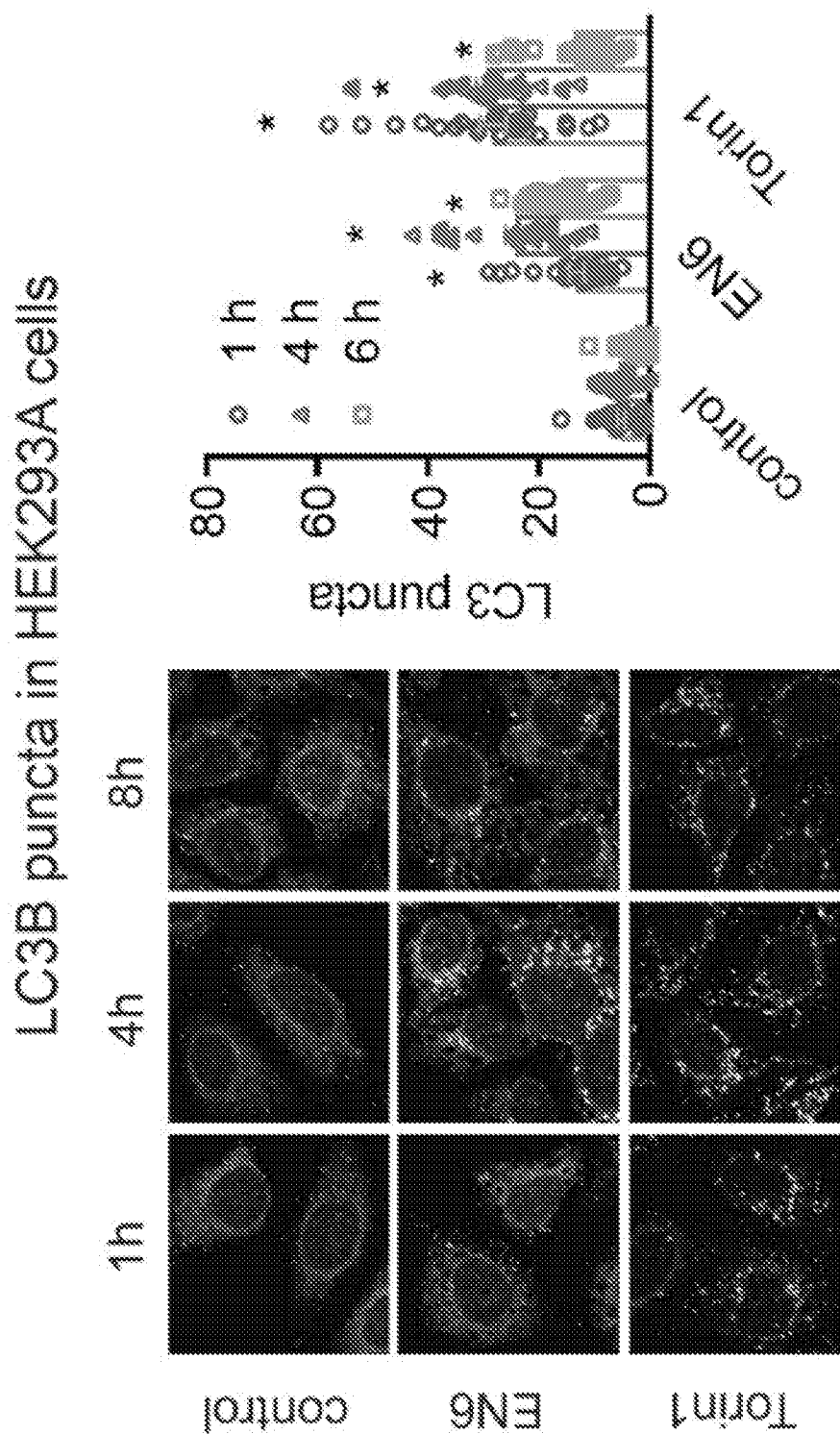
FIG. 1D**FIG. 1E**

LC3B levels
in HEK293A cells



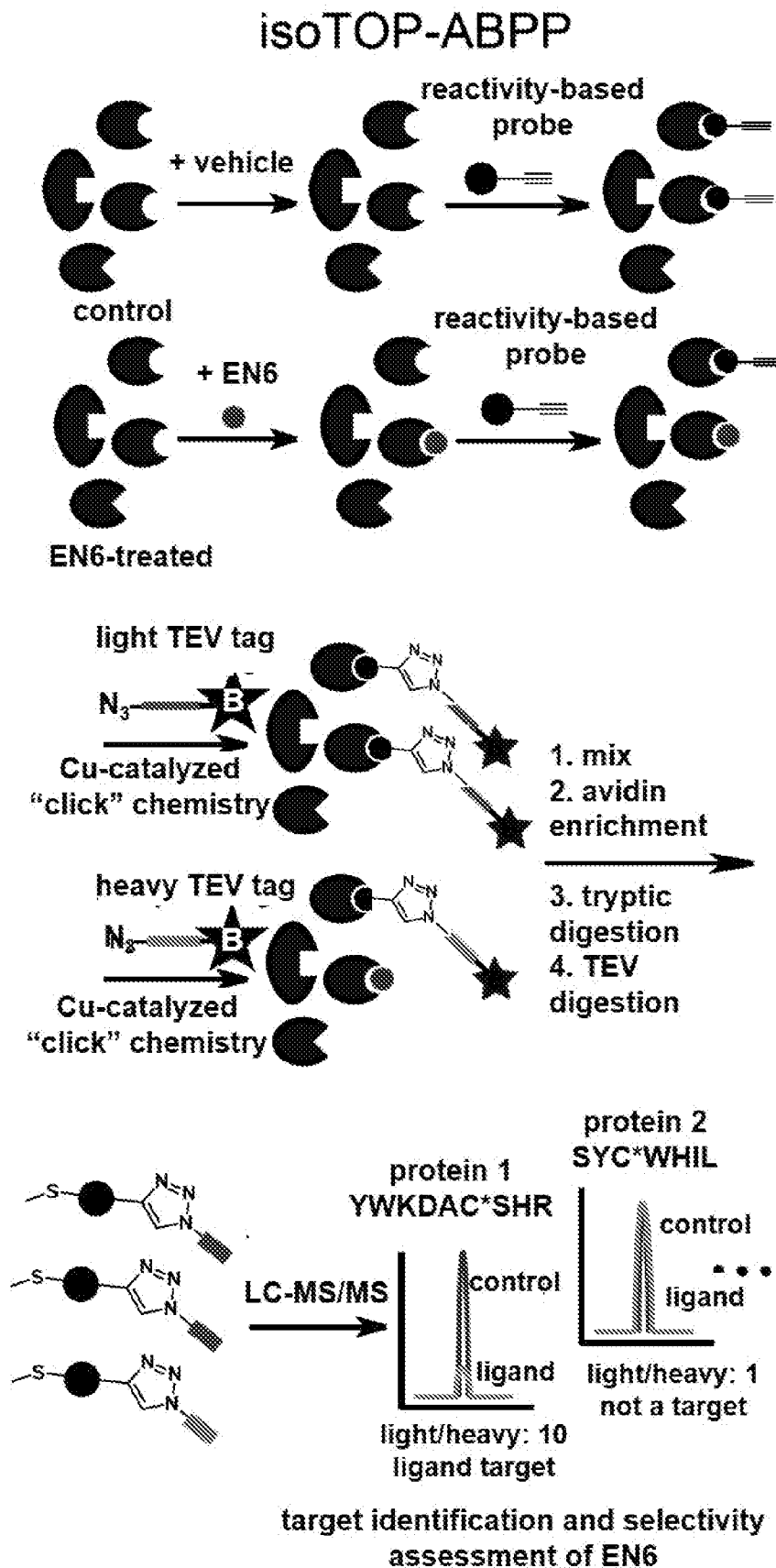
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FIG. 1F

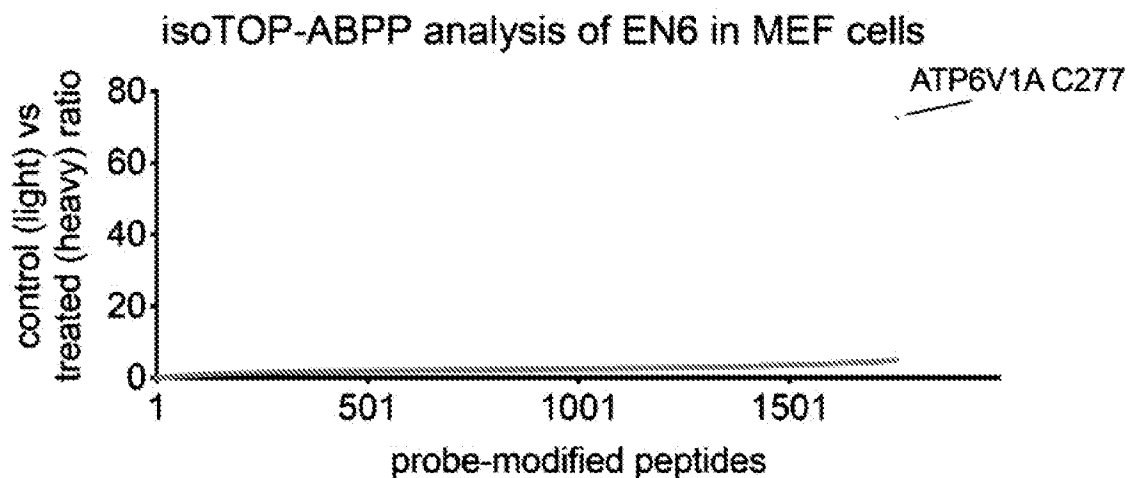


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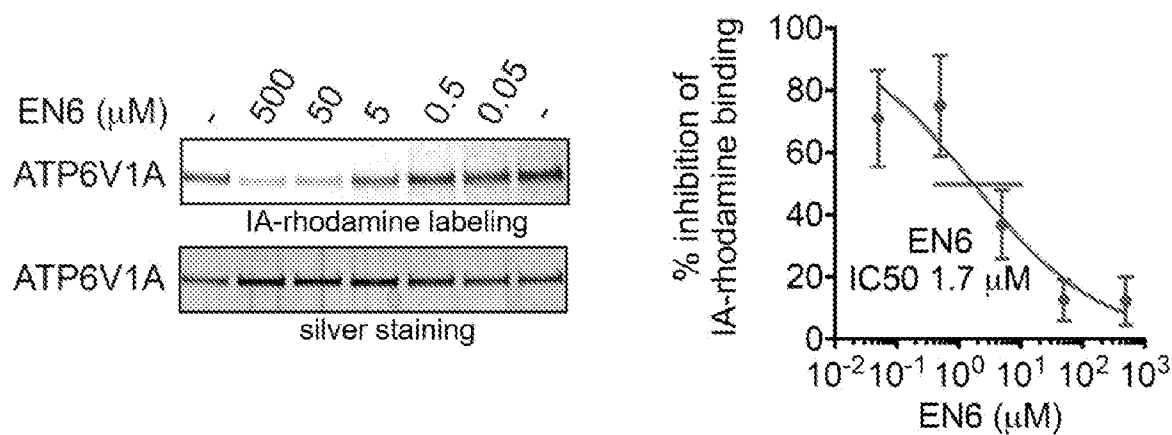
FIG. 2A



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

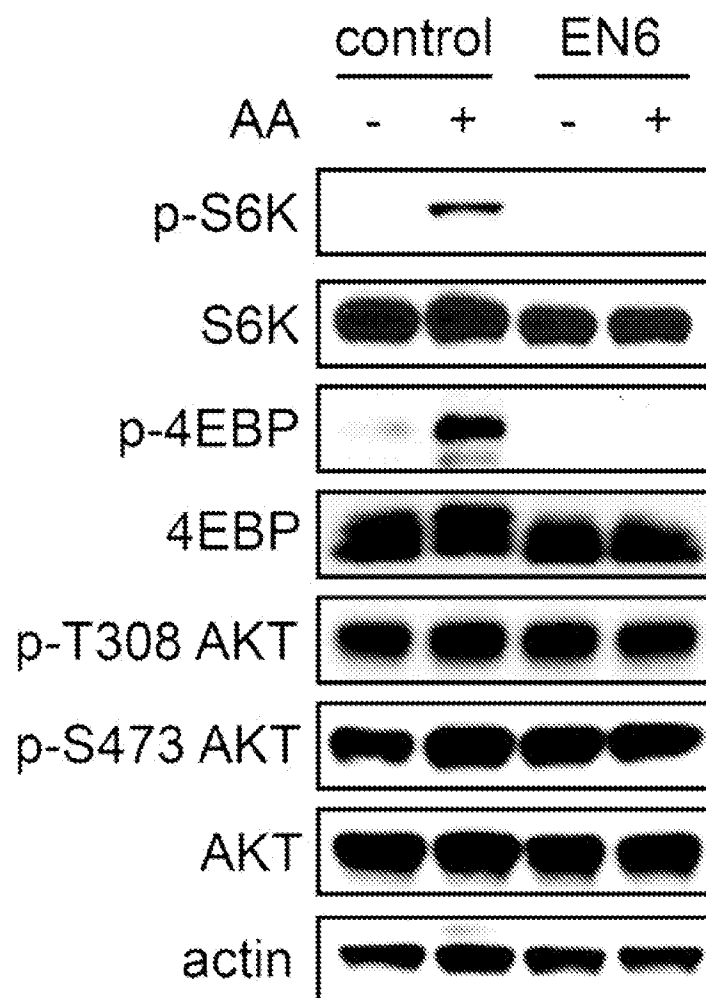
gel-based ABPP confirmation of EN6 interactions with ATP6V1A



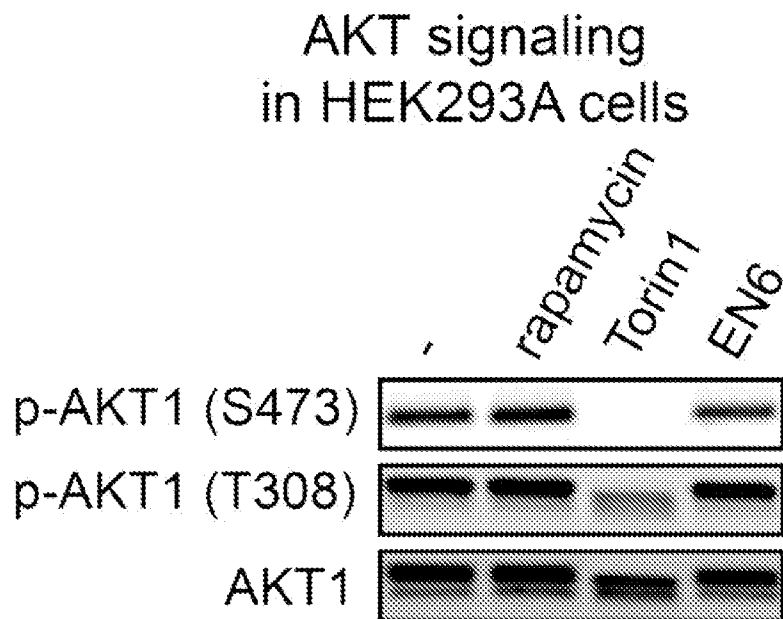
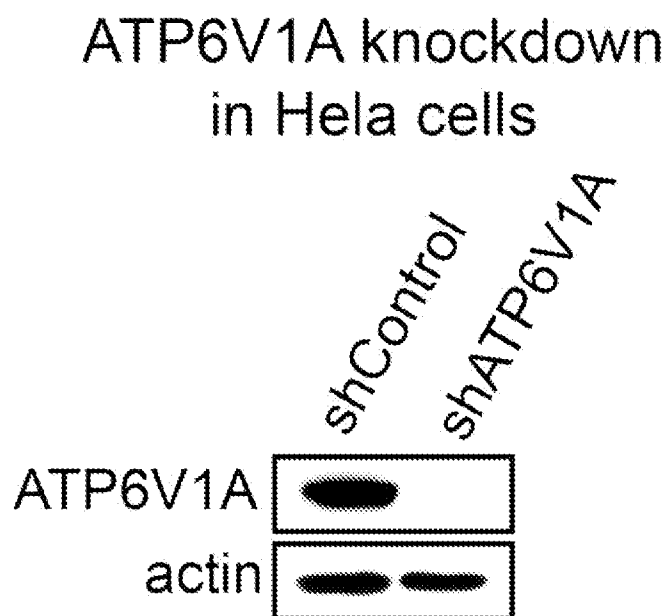
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FIG. 3A

mTORC1 signaling
in MEF cells



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FIG. 3B**FIG. 3C**

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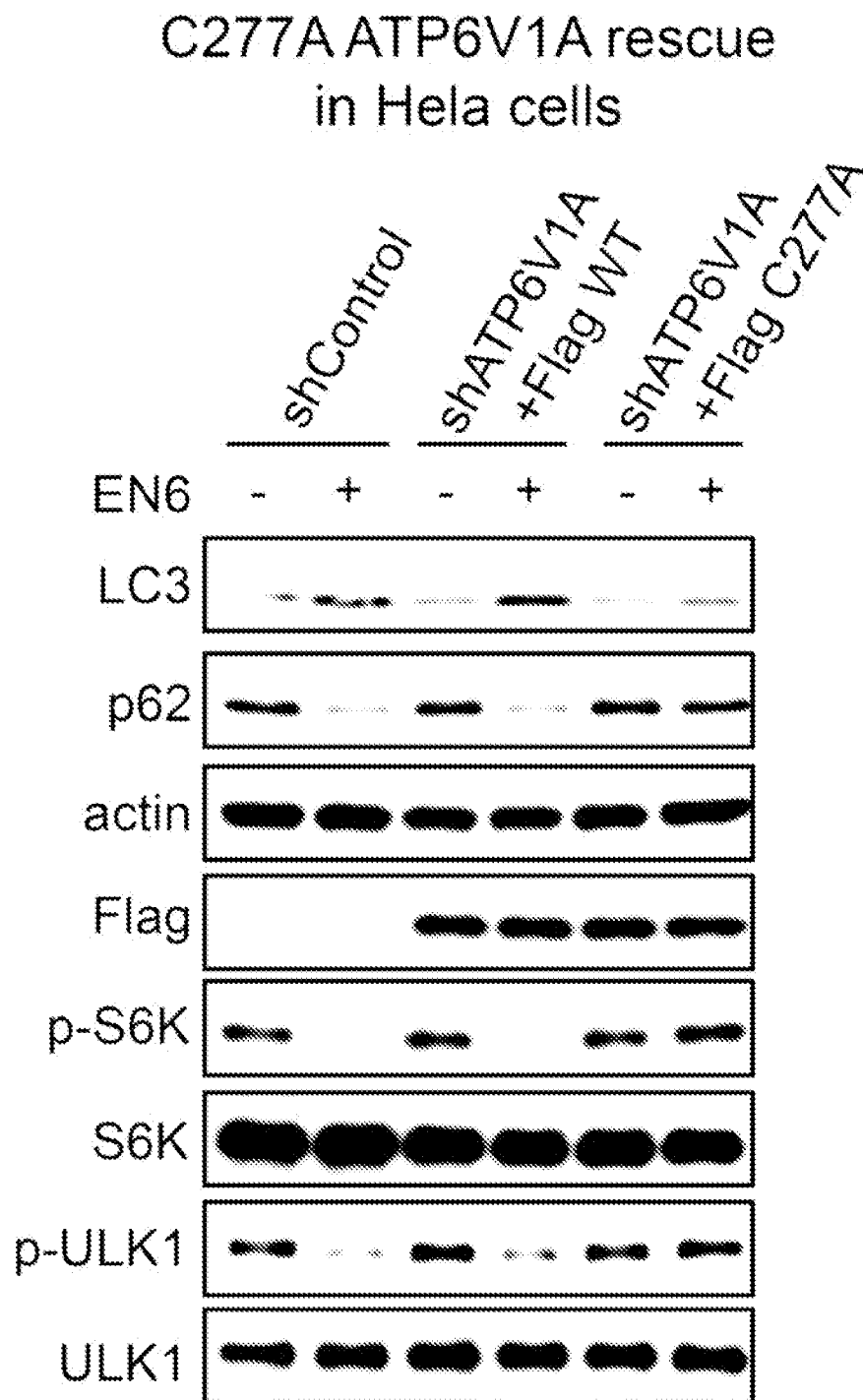
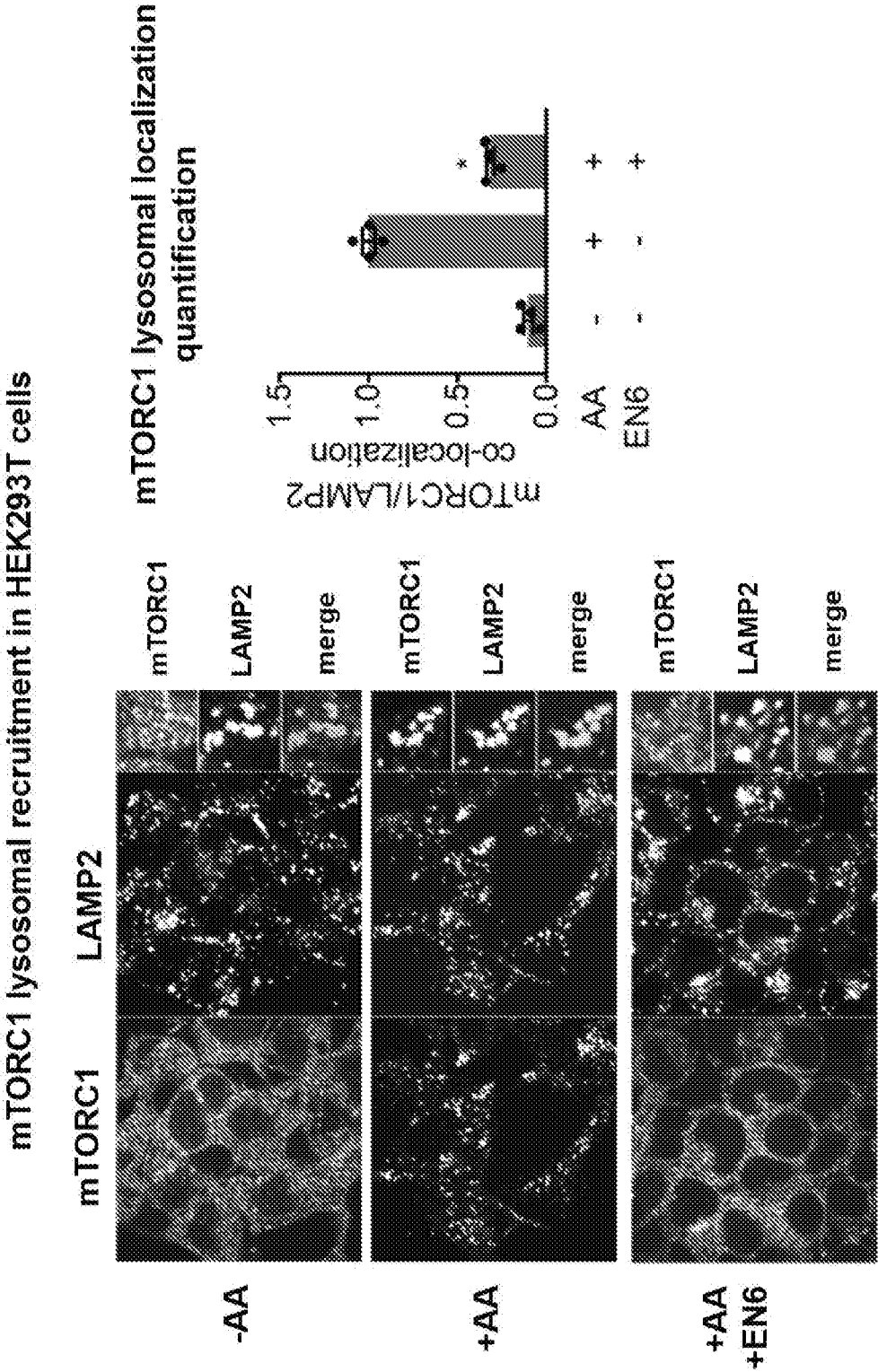
FIG. 3D

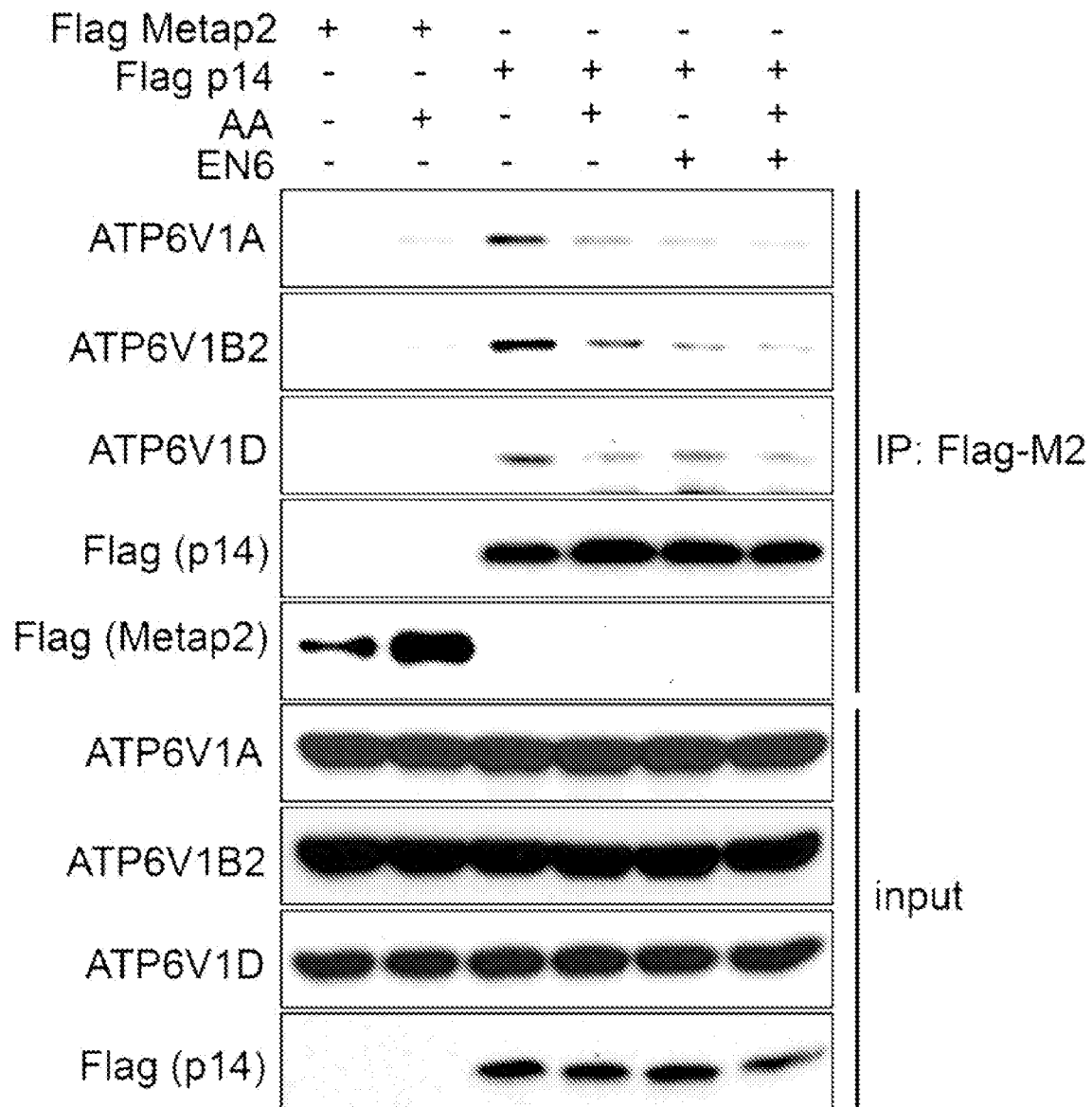
FIG. 3E



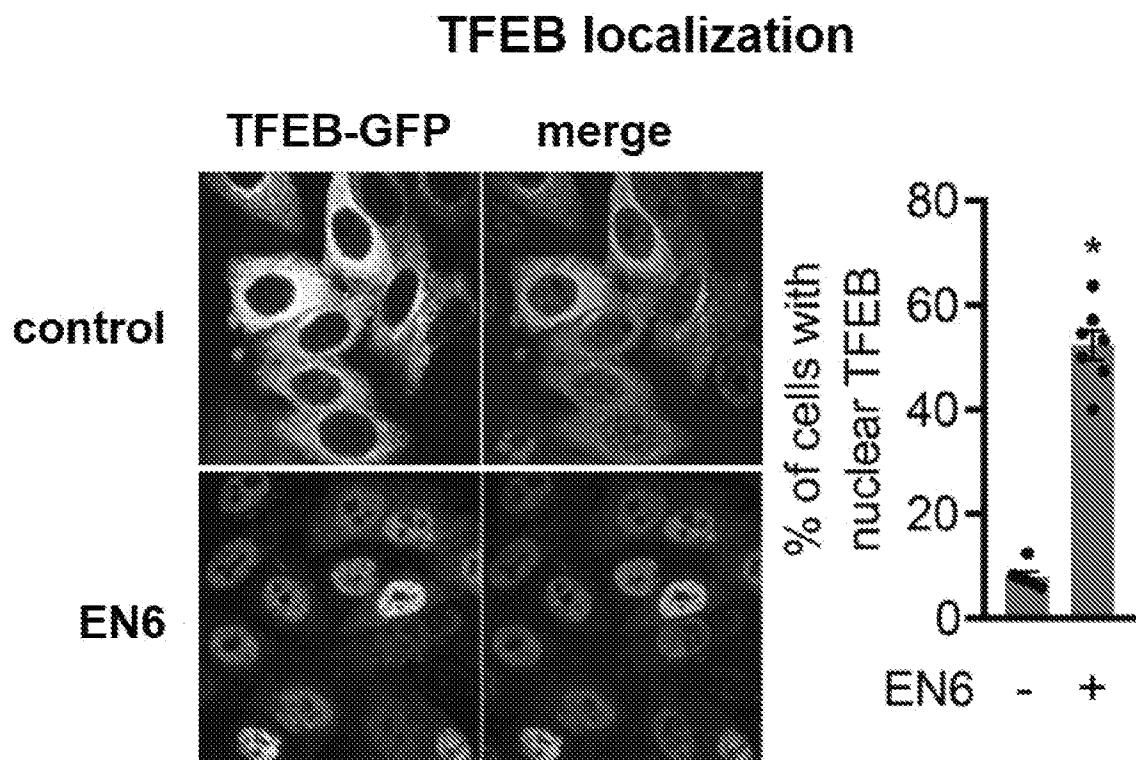
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FIG. 4A

v-ATPase subunit/Ragulator interactions

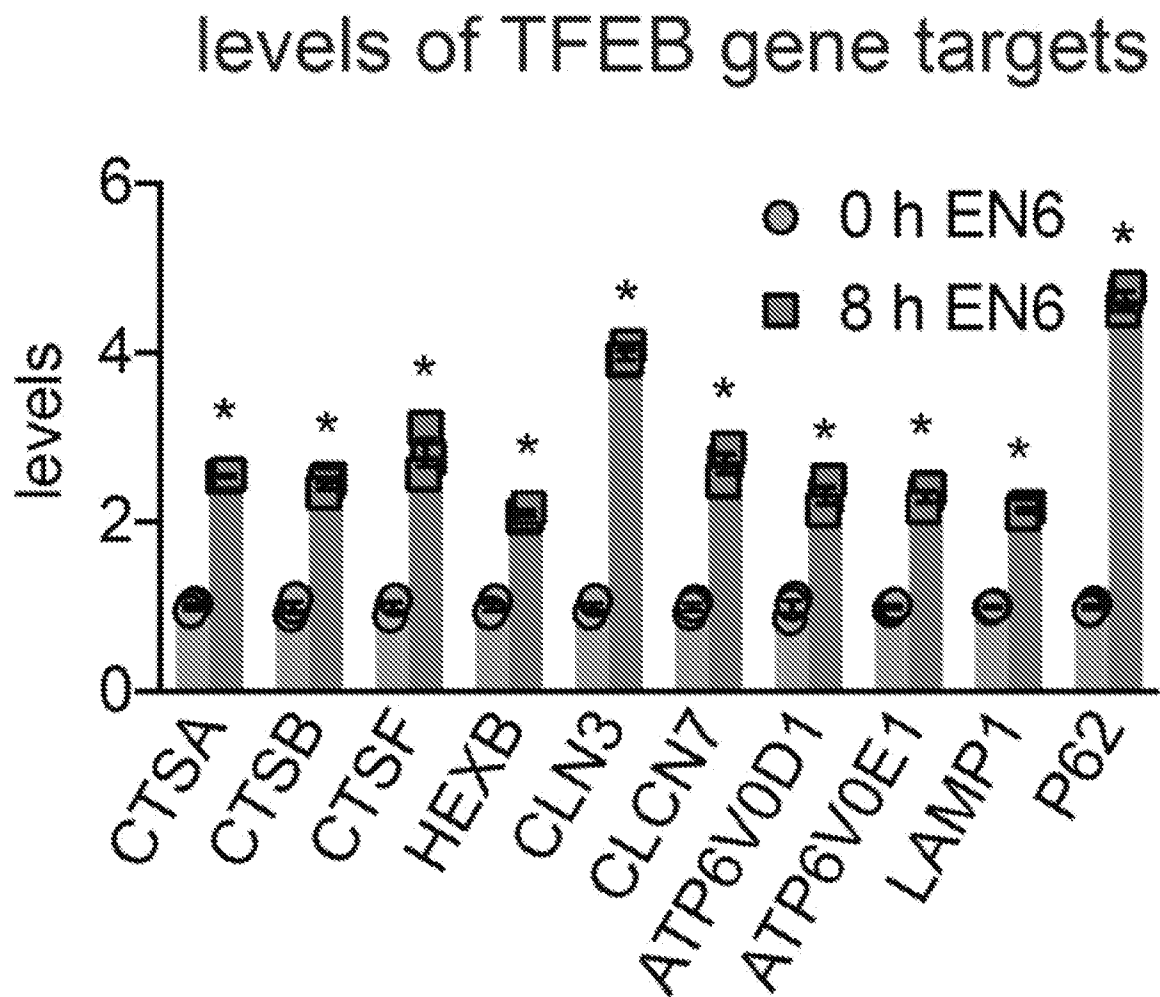


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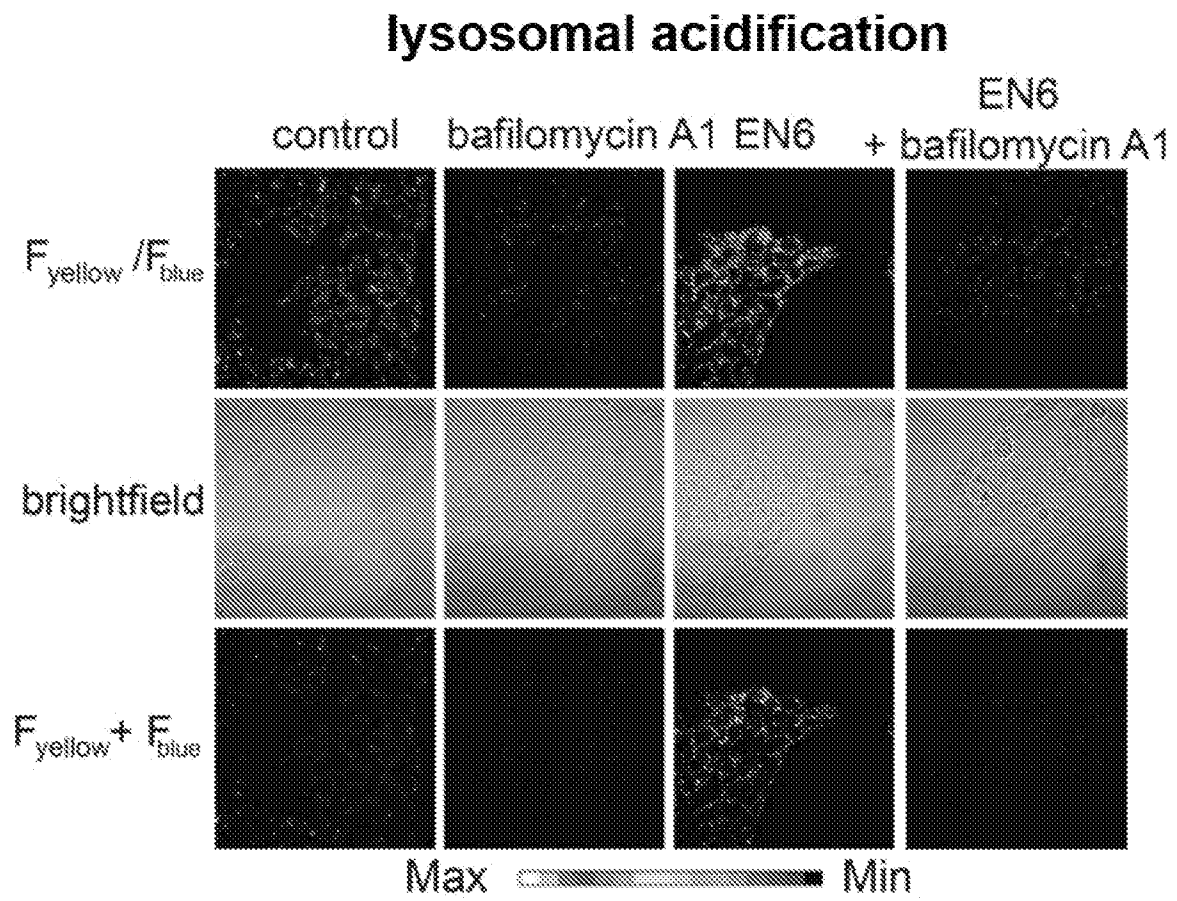
FIG. 4B

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FIG. 4C



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FIG. 4D

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FIG. 4E

quantification of lysosomal acidification

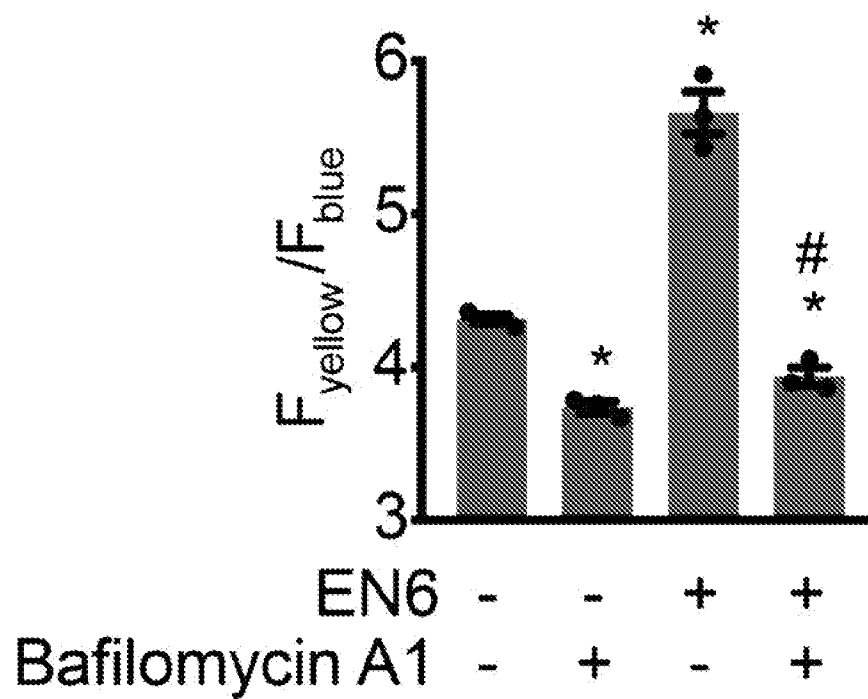


FIG. 5A

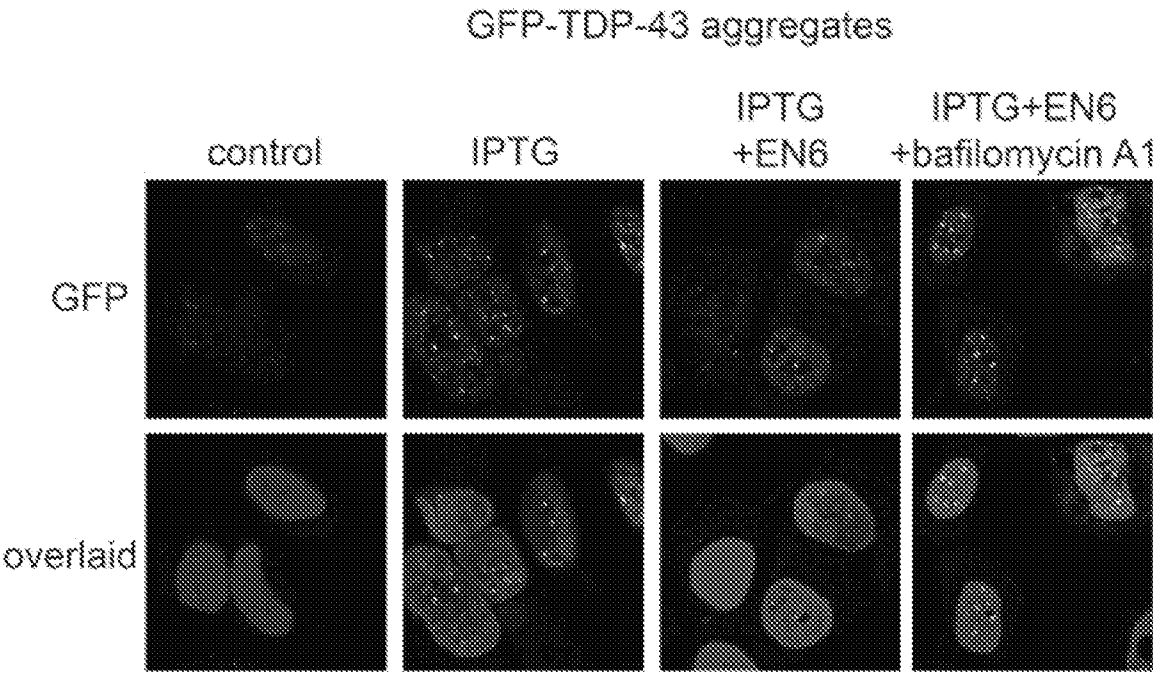
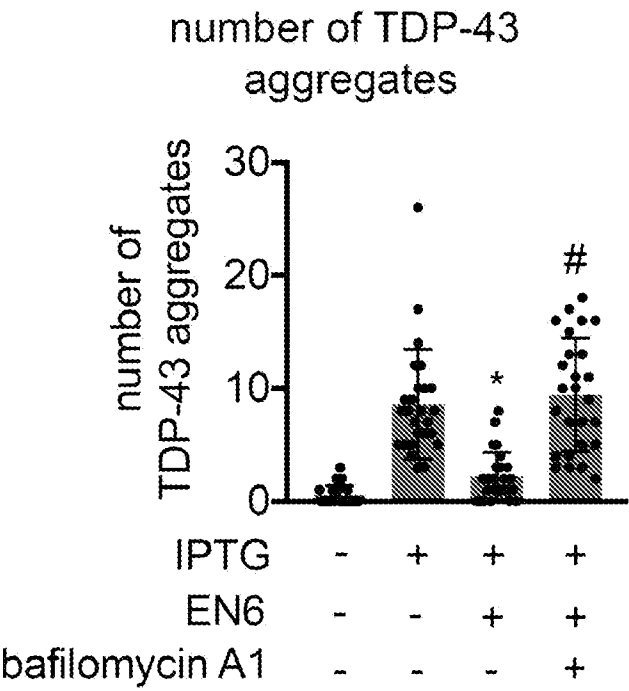
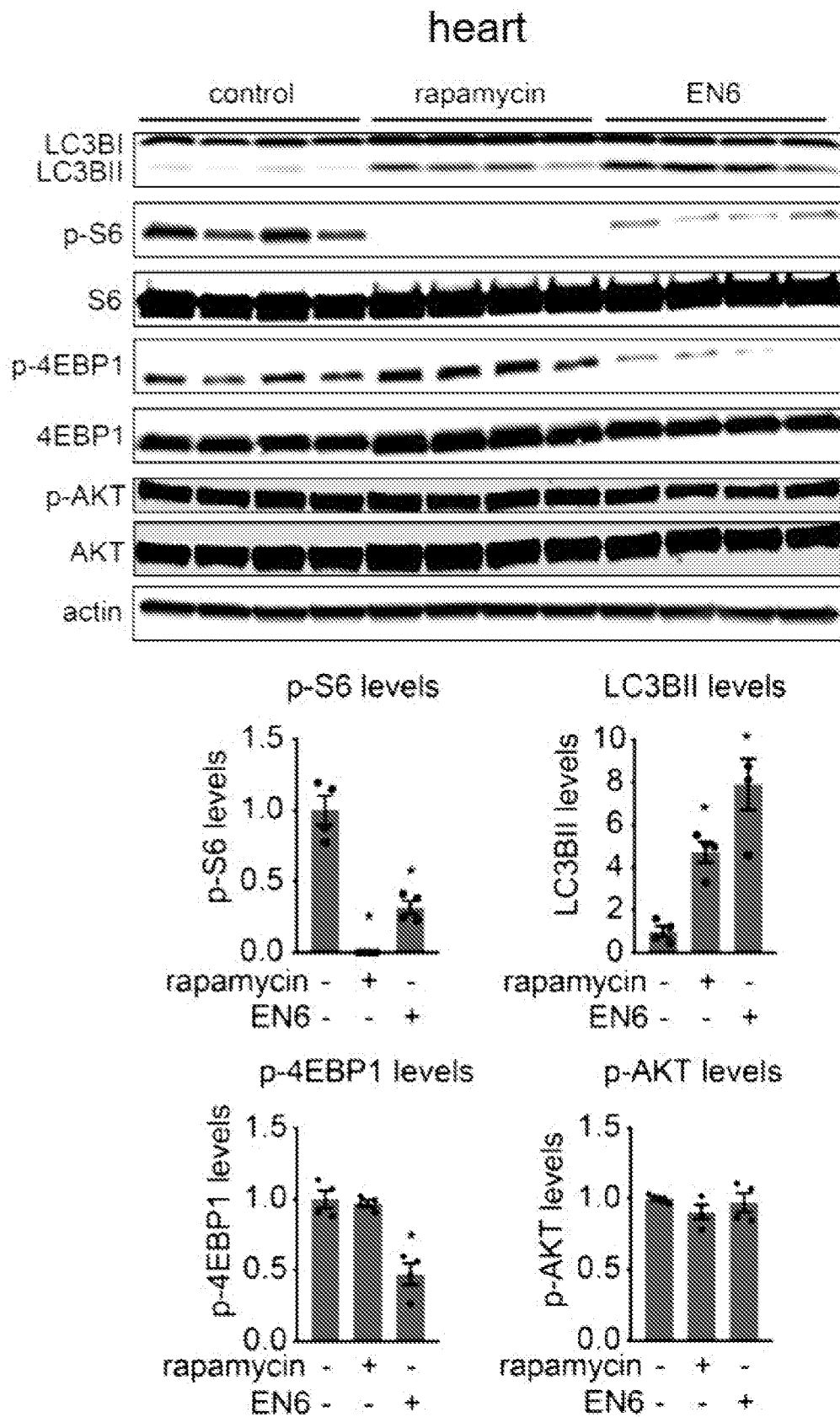


FIG. 5B

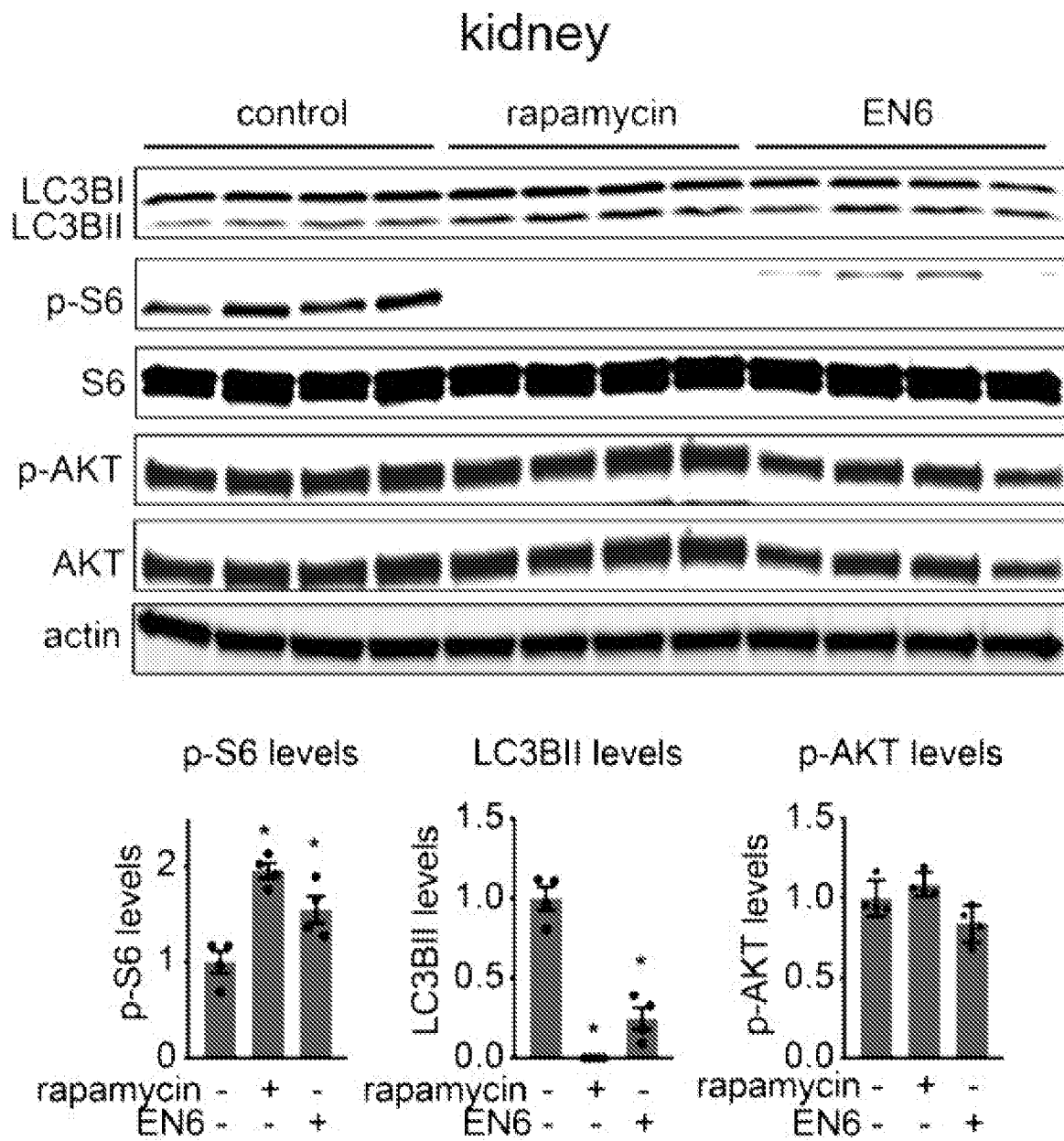


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FIG. 6A

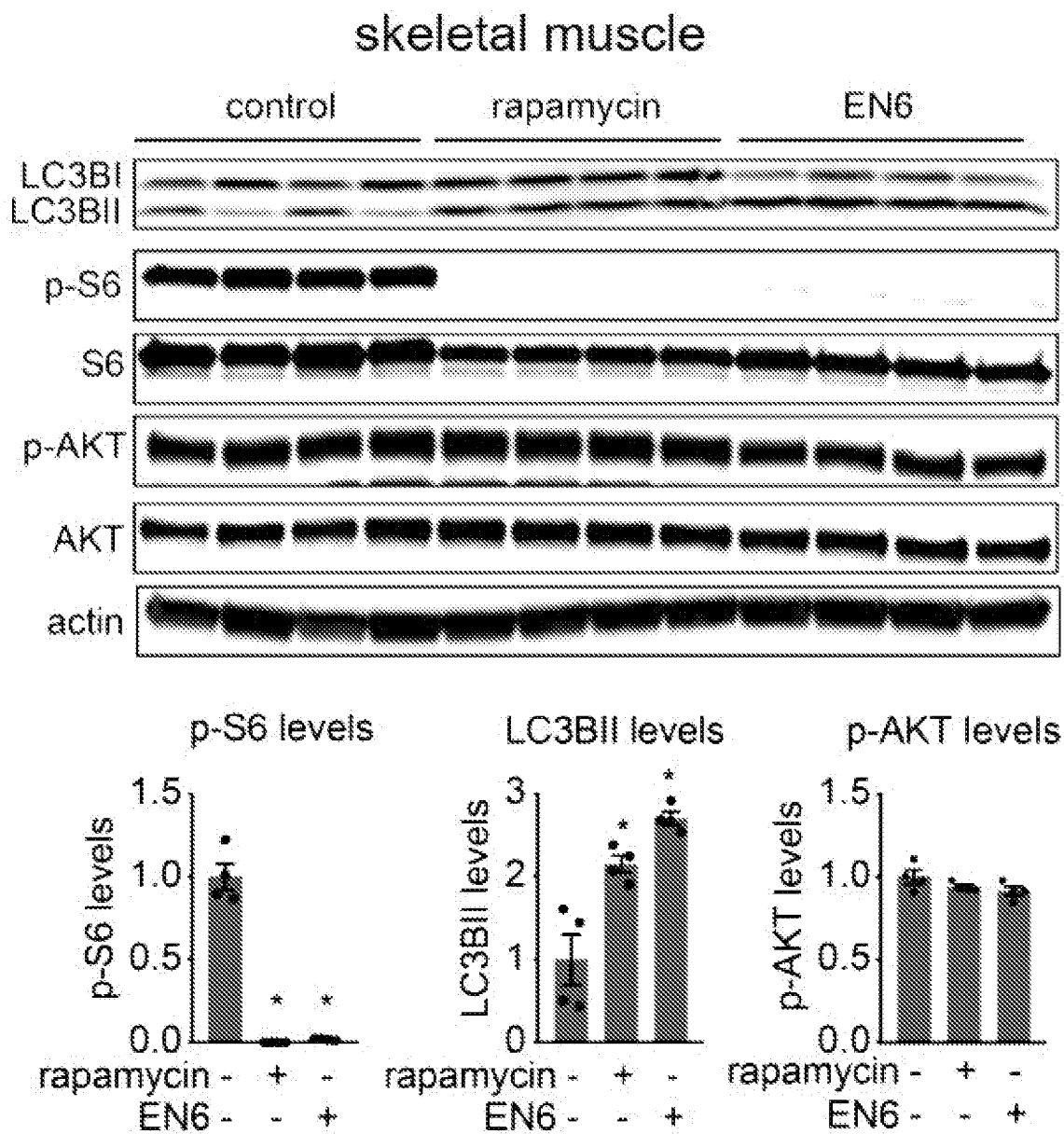


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FIG. 6B

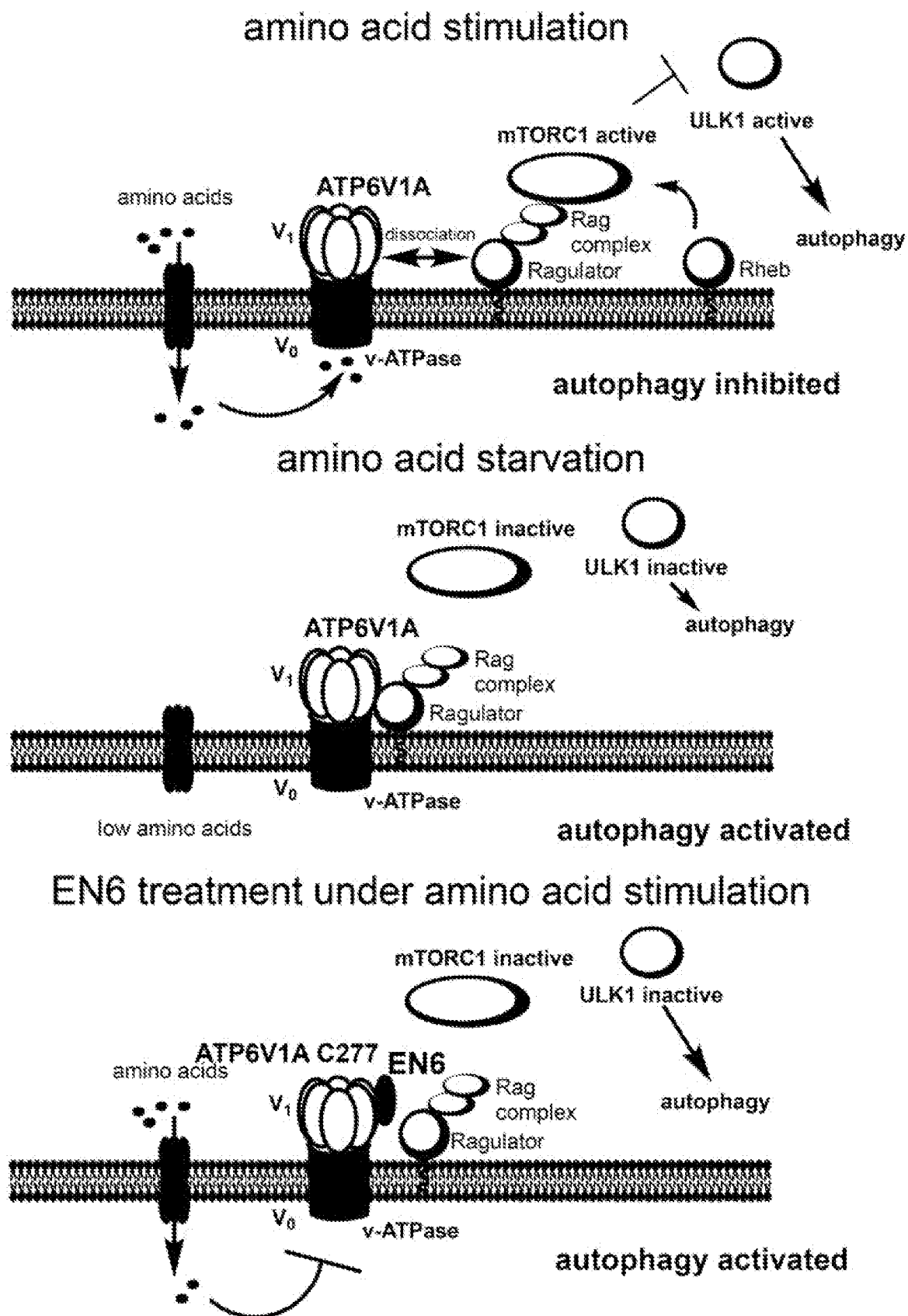
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FIG. 6C



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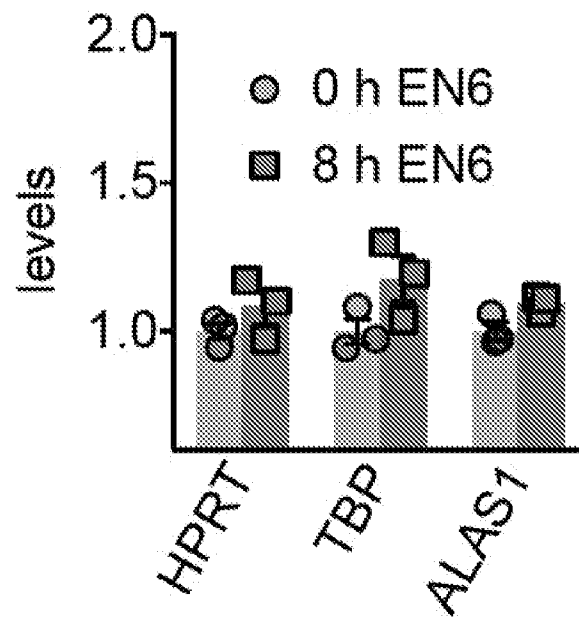
FIG. 7



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FIG. 8

transcript levels of unrelated genes



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/13158

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/4164; A61P 35/00 (2020.01)

CPC - C07D 233/64; A61K 31/4164

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y --- A	PUBCHEM 99640033 deposited on 11 December 2015 (11.12.2015) pg. 1-12, pg. 2	1-3; 11-22 ----- 4-10; 23-26;(27-30)/(1-3; 11-22) ----- (27-30)/(4-10;23)
Y ---- A	WO 2018/112420 A1 (The REGENTS of the UNIVERSITY OF CALIFORNIA) 21 June 2018 (21.06.2018) para [0128];[0131]; [0165];[0524]; Claim 22	4-10; 23-26; 27/(1-3;11- 22) ----- (27-30)/(4-10; 23)
Y --- A	McGUIRE et al. 'Glucose starvation increases V-ATPase assembly and activity in mammalian cells through AMP kinase and phosphatidylinositolide 3-kinase/Akt signaling', J. Biol. Chem. , 2018, Vol. 293(23), pp. 9113-9123; [published online March 14, 2018] pg. 9113, Col 1, para 1 to Col 2, para 3; Pg. 9118, Col 1, para 2	(28-30)/(1-3;11-22) ----- (27-30)/(4-10;23)
A	US 9,724,354 B2 (MILLENIUM PHARMACEUTICALS, Inc.) 08 August 2017 (08.08.2017) Col 81, Table 1	(27-30)/(4-10;23)
A	WO 2010/126895 A1 (AMGEN, INC.) 04 November 2010 (04.11.2010) ENTIRE DOCUMENT	1-30
A	US 2012/0213791 A1 (BERDINI et al.) 23 August 2012 (23.08.2012) ENTIRE DOCUMENT	1-30

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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Date of the actual completion of the international search

09 MARCH 2020

Date of mailing of the international search report

08 APR 2020

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Facsimile No. 571-273-8300

Authorized officer

Lee Young

Telephone No. PCT Helpdesk: 571-272-4300