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Title: COMPOSITIONS AND METHODS FOR MODULATING UBAs

FIG. 2B

DKM 2-93 anti-tumorigenic effects in PaCa2 cells

control

DKM 2-93
(50 mg/kg)

Abstract: Disclosed herein, inter alia, are compositions and methods useful for inhibiting ubiquitin-like modifier activating enzyme 5.
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COMPOSITIONS AND METHODS FOR MODULATING UBA5

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/454,667, filed February 3, 2017, which is incorporated herein by reference in its 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 052103-502001WO Sequence Listing_ST25.txt, created February 1, 2018 97,319 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 number CA172667 awarded by The National Institutes of Health. The Government has certain rights in the invention.

BACKGROUND

[0004] In the United States, it is estimated that over 53,000 people will be diagnosed with pancreatic cancer and over 40,000 patients will die from pancreatic cancer with a dismal overall 5-year survival rate of 7.7%. Unfortunately, current treatment strategies are insufficient for current pancreatic cancer therapy and better strategies are needed to discover both novel anti-cancer agents and targets for combatting pancreatic cancer. However, a major bottleneck in this effort has been that many novel protein targets that control cancer considered difficult to target with small-molecules. Disclosed herein, inter alia, are solutions to these and other problems in the art.

BRIEF SUMMARY

[0005] Herein are provided, inter alia, compounds capable of modulating the level of activity of ubiquitin-like modifier activating enzyme 5 and methods of using the same.
In an aspect is provided a compound having the formula:

\[
(R^1)_z L^1 - L^2 - E
\]

(Ⅰ). \( R^1 \) is independently halogen, \(-C\text{X}^1_3, -C\text{H}X^1_2, -C\text{H}_2X^1, -OC\text{X}^1_3, \)
\(-O\text{CH}_2X^1, -O\text{CH}X^1, -CN, -SO\text{o}NR^1_{A, B}, -SO\text{v}iNR^1_{A, B}, -N\text{H} c (0) \text{NR}^1_{A, B}, -N (0)_{A, B}, -NR^1_{A, B}, -C (0)R^1_{A, B}, -C (0)\text{-OR}^1_{A, B}, -C (0)\text{NR}^1_{A, B}, -OR^1_{A, B}, -NR^1_{A}SO\text{2}^1_{A, B}, -NR^1_{A}C (0)R^1_{A, B}, -NR^1_{A}C (0)_{A, B}, -NR^1_{A}O R^1_{A, B}, -N3, \) substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, 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. \( L^1 \) and an adjacent \( R^1 \) substituent may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol \( z1 \) is an integer from 0 to 5. \( L^1 \) is a bond, \(-S (0)_{2, 3}, -NR^4_{A, B}, -O_-, -S_-, -C (0)\text{-OR}^4_{A, B}, -C (0)\text{-NR}^4_{A, B}, -NR^4_{A}C (0)_{A, B}, \) substituted or unsubstituted alkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. \( R^4 \) is hydrogen, \(-C\text{X}^4_{2, 3}, -CHX^4_{2, 3}, -CH\text{2X}^4_{2, 3}, -OC\text{X}^4_{2, 3}, -O\text{CHX}^4_{2, 3}, -CN, -C (0)\text{NR}^4_{A, B}, -C (0)\text{-OR}^4_{A, B}, -C (0)\text{NR}^4_{A}SO\text{2}_{A, B}, -OR^4_{A, B}, -NR^4_{A}C (0)_{A, B}, -NR^4_{A}O R^4_{A, B}, -N5, \) substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. \( L^2 \) is a bond, \(-S (0)_{2, 3}, -NR^5_{A, B}, -O_-, -S_-, -C (0)\text{-OR}^5_{A, B}, -C (0)\text{-NR}^5_{A, B}, -NR^5_{A}C (0)_{A, B}, -NH\text{C} (0)\text{NR}^5_{A, B}, -NH\text{C} (0)\text{-OR}^5_{A, B}, -NH\text{C} (0)\text{-OC} (0)_{A, B}, -CH\text{2NR}^5_{A, B}, \) substituted or unsubstituted alkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. \( R^5 \) is hydrogen, \(-C\text{X}^5_{3, 4}, -CH\text{X}^5_{2, 3}, -CH\text{2X}^5_{2, 3}, -OC\text{X}^5_{3, 4}, -O\text{CHX}^5_{2, 3}, -CN, -C (0)\text{R}^5_{A, B}, -C (0)\text{-OR}^5_{A, B}, -C (0)\text{NR}^5_{A}R^5_{B}, -OR^5_{A, B}, \) substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol \( E \) is an electrophilic moiety. Each \( R^1_{A, B} \),...
R$^{1B}$, R$^{1C}$, R$^{1D}$, R$^{4A}$, R$^{4B}$, R$^{5A}$, and R$^{5B}$ is independently hydrogen, -CX$_3$, -CN, -COOH, -CONH$_2$, -CH$_X$$_2$, -CH$_2$X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R$^{1A}$ and R$^{1B}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R$^{4A}$ and R$^{4B}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R$^{5A}$ and R$^{5B}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. The symbols are each X, X$^1$, X$^4$, and X$^5$ is independently -F, -Cl, -Br, or -I. The symbols n, n$^4$, and n$^5$ are independently an integer from 0 to 4. The symbols m, m$^4$, m$^5$, v, v$^4$, and v$^5$ are independently an integer from 1 to 2.

[0007] In an aspect is provided a pharmaceutical composition including a Ubiquitin-like modifier activating enzyme 5 inhibitor and a pharmaceutically acceptable excipient.

[0008] In an aspect is provided a pharmaceutical composition including a compound described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0009] In an aspect is provided a method of treating cancer, the method including administering to a subject in need thereof an effective amount of a Ubiquitin-like modifier activating enzyme 5 inhibitor.

[0010] In an aspect is provided a method of treating cancer including administering to a subject in need thereof an effective amount of a compound described herein.

[0011] In an aspect is provided a method of treating a disease associated with ubiquitin-like modifier activating enzyme 5 activity including administering to a subject in need thereof an effective amount of a Ubiquitin-like modifier activating enzyme 5 inhibitor.

[0012] In an aspect is provided a method of inhibiting ubiquitin-like modifier activating enzyme 5 activity including contacting the ubiquitin-like modifier activating enzyme 5 with a Ubiquitin-like modifier activating enzyme 5 inhibitor.
In an aspect is provided a method of inhibiting ubiquitin-like modifier activating enzyme 5 activity including contacting the Ubiquitin-like modifier activating enzyme 5 with a compound described herein.

In an aspect is provided a ubiquitin-like modifier activating enzyme 5 protein covalently bonded to a Ubiquitin-like modifier activating enzyme 5 inhibitor through the reacted residue of an electrophilic moiety.

In an aspect is provided a ubiquitin-like modifier activating enzyme 5 protein covalently bonded to a compound described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A-1D. Coupling Reactive Fragment Screening with isoTOP-ABPP to Identify Covalent Ligands, Targets, and Druggable Hotspots for Pancreatic Cancer (FIG. 1A), by coupling screening of cysteine-reactive fragment libraries with chemoproteomics. Shown schematically in FIGS. 1A-1D is isoTOP-ABPP for target identification of lead cysteine-reactive fragments that impair triple-negative breast cancer cell viability. A library of cysteine-reactive fragments was screened in pancreatic cancer cells to identify leads that impair pancreatic cancer pathogenicity and used isoTOP-ABPP platforms to identify the targets and site of labeling of these leads (FIG. 1B). The compounds tested, from left to right in FIG. 1B, are DKM 2-72, TRH 1-23, DKM 2-67, DKM 3-30, DKM 2-79, DKM 3-22, DKM 2-85, TRH 1-17, DKM 2-90, DKM 2-94, DKM 2-71, DKM 2-76, DKM 3-8, TRH, 1-65, DKM 2-52, DKM 3-29, DKM 2-19, DKM 3-10, DKM 2-101, DKM 2-93, DKM 2-80, DKM 2-95, DKM 2-40, DKM 2-91, TRH 1-55, TRH 1-12, DKM 2-83, DKM 2-107, DKM 2-114, DKM 2-59, DKM 3-5, DKM 2-84, TRH 1-56, DKM 2-86, DKM 3-13, DKM 3-43, DKM 3-16, TRH 1-32, DKM 2-95, TRH 1-54, DKM 2-113, DKM 3-41, DKM 2-87, DKM 3-7, DKM 3-12, DKM 3-42, DKM 2-47, DKM 3-31, DKM 3-32, TRH 1-115, DKM 3-4, DKM 2-97, DKM 2-11, DKM 2-108, TRH 1-13, DKM 2-106, TRH 1-19, DKM 2-106, TRH 1-19, DKM 2-50, DKM 3-3, DKM 2-60, DKM 2-110, DKM 2-103, DKM 2-102, DKM 2-43, DKM 2-67, DKM 2-37, DKM 2-32, DKM 2-33, DKM 3-15, DKM 2-117, TRH 1-20, DKM 2-120, DKM 3-11, DKM 2-42, DKM 2-48, DKM 2-16, DKM 3-9, DKM 2-31, DKM 2-100, DKM 2-34, DKM 3-36, DKM 2-109, DKM 2-49, DKM 2-58, and DKM 2-39 respectively. A library of cysteine-reactive acrylamides and chloroacetamides were screened in PaCa2 pancreatic cancer cells (50 μM) to identify any compounds that impaired PaCa2 48 h serum-free cell survival. Cell survival was assessed using Hoescht staining, (FIG. 1C). The

respective. A library of cysteine-reactive acrylamides and chloroacetamides were screened in PaCa2 pancreatic cancer cells (50 μM) to identify any compounds that impaired PaCa2 48 h serum-free cell survival. Cell survival was assessed using Hoescht staining, (FIG. 1C). The
compounds tested, from left to right in FIG. 1C are TRH 1-12, DKM 2-76, DKM 2-101, DKM 2-72, DKM 3-30, DKM 2-40, DKM 2-71, DKM 2-85, TRH 1-65, DKM 2-91, DKM 2-94, DKM 2-52, DKM 2-98, TRH 1-56, DKM 2-79, TRH 1-23, DKM 3-10, DKM 2-90, DKM 2-119, TRH 1-17, DKM 3-7, DKM 3-22, DKM 2-80, DKM 2-107, DKM 2-93, DKM 2-83, and DKM 2-67. Leads from this screen were counterscreened in HPDE cells to identify agents that did not significantly impair serum-free cell survival in these cells. (FIG. 1D) Shown are lead molecules that impaired PaCa2 cell survival, but showed the least degree of viability impairments in HPDE cells. Data in (FIGS. 1B, 1C) are presented as mean ± sem, n=3/group. Raw data for screen can be found in Table 1.

[0017] FIGS. 2A-2F. DKM 2-93 Targets the Catalytic Cysteine of UBA5, (FIG. 2A). Dose-response of DKM 2-93 in PaCa2 and Panel pancreatic cancer cells in a 48 h serum-free survival assay, (FIG. 2B). PaCa2 tumor xenograft growth in immune-deficient SCID mice. Mice were subcutaneously injected with PaCa2 cells to initiate the tumor xenograft study and treatments of mice were initiated with vehicle or DKM 2-93 (50 mg/kg ip, once per day) three days after injection of cancer cells (FIG. 2C). IsoTOP-ABPP analysis of DKM 2-93 in PaCa2 cells. PaCa2 proteomes were pre-treated with DMSO or DKM 2-93 (50 µM) prior to labeling proteomes with IAyne and appending a biotin-azide handle bearing a TEV protease recognition site and an isotopically light (for DMSO-treated) and heavy (for DKM 2-93-treated) tag. DMSO and DKM 2-93-treated proteomes were then mixed in a 1:1 ratio and subsequently avidin-enriched, tryptically digested, and then probe-modified tryptic peptides were released by TEV protease and analyzed using quantitative proteomic approaches. Peptide ratios shown are average ratios for those probe-modified peptides that were identified in at least 2 out of 3 biological replicates. A light to heavy ratio of 1 indicates that the probe-labeled cysteine-bearing peptide was not bound by DKM 2-93, whereas a ratio >3 indicates bound sites, (FIG. 2D). Gel-based ABPP validation of UBA5 as a target of DKM 2-93. DMSO or DKM 2-93 was preincubated with pure human UBA5 (30 min) prior to labeling with IAyne (10 µM, 30 min), followed by rhodamine-azide conjugation by CuAAC, SDS/PAGE, and readout of gel fluorescence. Shown is a representative gel from n=3. (FIG. 2E) UBA5 activity assay. UBA5 was pre-incubated with DMSO or DKM 2-93, then UFM1 and ATP were added to initiate the reaction. DTT is used as a negative control to release the UBA5-UFM1 thioester linkage. Shown is a representative gel from n=3. (FIG. 2F) IsoTOP-ABPP analysis of cysteine-reactivity in pooled primary human pancreatic ductal adenocarcinoma tumors. Ten primary human pancreatic tumor lysates were pooled together.
and labeled with 100 or 10 µM of IAyne followed by subsequent isoTOP-ABPP analysis. Shown are ratios of heavy (100 µM) to light (10 µM) peptides. Data in (Figures 2A, 2B) are presented as mean ± sem, n=5-8/group. Significance is expressed as *p<0.05 compared to vehicle-treated or siControl or shControl cells. Raw data for (FIGS. 2C, 2F) can be found in Table 2.

[0018] FIGS. 3A-3C. UBA5 Knockdown Impairs Pancreatic Cancer Pathogenicity. (FIG. 3A) UBA5 expression in PaCa2 cells. UBA5 was transiently knocked down with siRNA and stably knocked down with shRNA and expression was determined by qPCR. (FIG. 3B) Serum-free cell survival (48 h) from transient siRNA or stable shRNA knockdown of UBA5 in PaCa2 cells. (FIG. 3C) Tumor xenograft growth of shControl and shUBA5 PaCa2 cells in immune-deficient SCID mice. Data are presented as mean ± sem, n=3-6/group. Significance is expressed as *p<0.05 compared to sicontrol or shControl cells.

[0019] FIG. 4. Body weight of mice after tumor xenograft study. PaCa2 tumor xenograft growth in immune-deficient SCID mice. Mice were subcutaneously injected with PaCa2 cells to initiate the tumor xenograft study and treatments of mice were initiated with vehicle or DKM 2-93 (50 mg/kg ip, once per day) three days after injection of cancer cells. Body weight was measured at the end of the tumor xenograft study. Data are represented as mean ± sem, n=8 mice/group.

[0020] FIG. 5. DKM 2-93 selectively alkylates C250 on protein UBA5. C250 is the active site catalytic cysteine of UBA5, and projects outward toward into a small hole formed by the junctions of Ufml with UBA5. Surrounding C250 are amino acids Asn-210, Glu-209, Leu-254, Ser-253, and Ala-251. DKM 2-93 may be participating in hydrogen bonding with the protein backbone or these amino acids. Along with hydrogen bonding, these amino acids may impart steric limits which DKM 2-93 is able to overcome, thus providing specificity of this compound. We hypothesize that by binding to C250, DKM 2-93 blocks the active site cysteine thus preventing thioester bond formation between C250 on UBA5 and the adenylated C-terminal glycine of UFM1.

DETAILED DESCRIPTION
1. Definitions

[0021] 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.

[0022] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., -CH2O- is equivalent to -OCH2-.  

[0023] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals. The alkyl may include a designated number of carbons (e.g., C1-C10 means one to ten carbons). Alkyl is an unacyclic chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers.

An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). 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.

[0024] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -CH2CH2CH2CH2-. Typically, an alkyl (or alkyne) 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 alkyne" is a shorter chain alkyl or alkyne group, generally having eight or fewer carbon atoms. The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.
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, or S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., O, N, P, S, B, As, or Si) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -CH₂−CH₂−0−CH₃, -CH₂−CH₂−NH−CH₃, -CH₂−CH₂−N(CH₃)₂−CH₃, -CH₂−S−CH₂−CH₃, -CH₂−CH₂−S(0)−CH₃, -CH₂−CH₂−S(0)₂−CH₃, -CH=CH−0−CH₃, -Si(CH₃)₃, -CH₂−CH=N−OCH₃, -CH=CH−N(CH₃)−CH₃, -0−CH₃, -0−CH₂−CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂−NH−OCH₃ and -CH₂−0−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 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).

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, -CH₂−CH₂−S−CH₂−CH₂− and -CH₂−S−CH₂−CH₂−NH−CH₂−. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkylenoxy, alkylenediyoxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(0)−₂R'− represents both -C(0)−₂R'− and -R'−C(0)−₂-. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(0)−R', -C(0)−NR', -N−R'−, -OR, -SR, and/or -SO₂−R. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.
[0027] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0028] 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(\(\text{Cl}_{1-4}\))alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0029] The term "acyl" means, unless otherwise stated, -\(\text{C}(\text{O})\)R where \(\text{R}\) 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.

[0030] 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, benzoazoxyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, 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-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

[0031] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocyclic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a
heterocyclic ring and wherein each ring may be a different ring. When referring to a
spirocyclic ring system, substituted spirocyclic rings means that at least one ring is
substituted and each substituent may optionally be different.

[0032] The symbol “\( \sim \)" denotes the point of attachment of a chemical moiety to the
remainder of a molecule or chemical formula.

[0033] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon
atom.

[0034] The term "alkylarylene" as an arylene moiety covalently bonded to an alkylene
moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group
has the formula:

\[
\begin{align*}
\text{[6]_4} & \quad \text{[6]_4} \\
\text{[2]_4} & \quad \text{[2]_4}
\end{align*}
\]

or

[0035] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the
alkylene moiety or the arylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, -N\(_3\),
-CF\(_3\), -CCl\(_3\), -CBr\(_3\), -Cl\(_3\), -CN, -CHO, -OH, -NH\(_2\), -COOH, -CONH\(_2\), -N0\(_2\), -SH, -SO\(_2\)CH\(_3\),
-SO\(_3\)H, -OSO\(_2\)H, -S0\(_2\)NH\(_2\), -ONH\(_2\), -NH\(_2\)(C\(_0\))NH\(_2\), substituted or
unsubstituted C\(_1\)-C\(_5\) alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In
embodiments, the alkylarylene is unsubstituted.

[0036] 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.

[0037] 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', =0, =NR', =N-OR', =NR'R'', =SR, -halogen, -
SiRR'R'', -OC(0)R, -C(0)R, -C(0)\(_2\)R', -CONR'R'', -OC(0)NR'R'', -NR'C(0)R, -NR-
C(0)NR'R'', -NR'C(0)\(_2\)R', -NR-C(NR'R'R')=NR''', -NR-C(NR'R'R')=NR''', -S(0)R, -
S(0)\(_2\)R', -S(0)\(_2\)NR'R'', -NRSO\(_2\)R', -NRSO\(_2\)R', -ONR'R'', -NR'C(0)NR''R''', -CN, -
NO\(_2\), -NRSO\(_2\)R'', -NR(0)R'', -NR(0)-OR'', -NROR'', in a number ranging from zero to
(2m'+l), 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 heteroaryll, substituted or unsubstituted 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(0)CH₃, -C(0)CF₃, -C(0)CH₂OCH₃, and the like).

Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR, -NR'R", -SR, -halogen, -SiR'R", -OC(0)R, -C(0)R, -Cₐ₀₂R, -CONR'R", -OC(0)NR'R", -NR'C(0)R, -NR'C(0)NR"R", -NR'C(0)₂R, -NR-C(NR'R"R")=NR""", -NR-C(NR'R")=NR"", -S(0)R, -S(0)₂R, -S(0)₂NR'R", -NRSO₂R, -NRNR"R", -ONR'R", -NR'C(0)NR"NR"R"", -CN, -N0₂, -R, -N₃, -CH(Ph)₂, fluoro(Ci-₄)alkoxy, and fluoro(Ci-₄)alkyl, -NR'SO₂R", -NR'C(0)R", -NR'C(0)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R, R", R", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryll. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R, R", R", and R"" groups when more than one of these groups is present.

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

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.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(0)-(CRR')₉⁻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-(CH₂)₉⁻B⁻, wherein A and B are
independently -CRR', -0-, -NR-, -S-, -S(0) -, -S(0) 2 -, -S(0) 2 ' -, 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 -0-, -NR', -S-, -S(0)+, -S(0) 2 , or -S(0) 2 '. 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 aryloxo, and substituted or unsubstituted heteroaryl.

[0042] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0043] A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo,
halogen, -CCl 3, -CBr 3, -CF 3, -Cl 3, CN, -OH, -NH 2, -COOH, -CONH 2, -N 0 2, -SH, -S0 3H, -S 0 4H, -S0 2NH 2, -NH 2 NH 2, -ONH 2, -NH C(O)NH 2 NH 2, -NH C(O)NH 2, -NH HSO 2 H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCb, -OCF, -OCBr, -OCl, -OCHCl 2, -OCHBr 2, -OC H 1, -OCHF 2, unsubstituted alkyl (e.g., Cl-C 8 alkyl, Cl-C 6 alkyl, or Cl-C 4 alkyl),
unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C 3-C 8 cycloalkyl, C 3-C 6 cycloalkyl, or C 5-C 6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C 6-C 10 aryl, C 10 aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and
(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(i) oxo,
halogen, -CCl 3, -CBr 3, -CF 3, -Cl 3, CN, -OH, -NH 2, -COOH, -CONH 2, -N 0 2, -SH, -S0 3H, -S 0 4H, -S0 2NH 2, -NH 2 NH 2, -ONH 2, -NH C(O)NH 2 NH 2, -NH C(O)NH 2, -NH HSO 2 H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCb, -OCF, -OCBr, -OCl, -OCHCl 2, -OCHBr 2, -OC
H12, -OCHF2, unsubstituted alkyl (e.g., Ci-C8 alkyl, Ci-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-Cio 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, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, -CCl3, -CBr3, -CF3, -Cl3-CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -S03H, -SOH, -SO2NH2, -NH2OH, -NH2OH, -CHBr2, -OCH2, -OCHF2, unsubstituted alkyl (e.g., Ci-C8 alkyl, Ci-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-Cio 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, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -CCl3, -CBr3, -CF3, -Cl3-CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -S03H, -SOH, -SO2NH2, -NH2OH, -NH2OH, -OCB, -OCF3, -OCBr3, -OCI3, -OCHCl2, -OCHBr2, -OCH2, -OCHF2, unsubstituted alkyl (e.g., Ci-C8 alkyl, Ci-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-Cio 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).
A "size-limited substituent" or "size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C1-C20 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C3-C8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C6-C10 aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

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-Cs 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 C6-C10 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.

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 hetroarylene 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 the groups are substituted with at least one lower substituent group.

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 C_6-C_10 aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_20 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_10 arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0048] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_5 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_10 aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_10 arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0049] 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.

[0050] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one size-limited substituent group, wherein if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group is different.

[0051] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one lower substituent group, wherein if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group is different.

[0052] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted moiety is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group is different.
[0053] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0054] 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.

[0055] 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.

[0056] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0057] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0058] 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 $^{13}\text{C}$- or $^{14}\text{C}$-enriched carbon are within the scope of this invention.
[0059] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I), or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0060] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0061] "Analog," or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0062] The terms "a" or "an," as used 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.

[0063] 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 $R^{1,1}$, $R^{1,2}$, $R^{1,3}$, $R^{1,4}$, etc., wherein each of $R^{1,1}$, $R^{1,2}$, $R^{1,3}$, $R^{1,4}$, etc. is defined within the scope of the definition of $R^{1,1}$ and optionally differently.

[0064] A "covalent cysteine modifier moiety" as used herein refers to a substituent that is capable of reacting with the sulphydryl functional group of a cysteine amino acid (e.g.
cysteine corresponding to C250 of the human ubiquitin-like modifier activating enzyme 5 of SEQ ID NO:337) to form a covalent bond. Thus, the covalent cysteine modifier moiety is typically electrophilic.

[0065] Description of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0066] The term "pharmacologically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmacologically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmacologically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrigenesulfuric, 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 invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0067] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention 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.

[0068] 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.

[0069] In addition to salt forms, the present invention 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 invention. Prodrugs of the compounds described herein may be converted in vivo after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0070] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.
"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 pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

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.

A "Ubiquitin-like modifier activating enzyme 5 protein inhibitor" and "UBA5 inhibitor" is a substance (e.g., oligonucleotide, protein, composition, or compound) that negatively affects (e.g. decreases) the activity or function of ubiquitin-like modifier activating enzyme 5 relative to the activity or function of ubiquitin-like modifier activating enzyme 5 in the absence of the inhibitor (e.g., wherein the UBA5 inhibitor binds ubiquitin-like modifier activating enzyme 5). A "ubiquitin-like modifier activating enzyme 5 inhibitor compound" or "UBA5 inhibitor compound" refers to a compound (e.g. a compound described herein, including embodiments) that reduces the activity of ubiquitin-like modifier activating enzyme 5 when compared to a control (e.g., the absence of the compound or a compound with known inactivity).

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally 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 polymer.

[0075] 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.

[0076] An amino acid residue in a protein "corresponds" to a given residue when it occupies the same essential structural and/or spatial position within the protein as the given residue in a reference sequence. For example, a selected residue in a selected protein corresponds to Cys250 when the selected residue occupies the same essential structural and/or spatial position as Cys250 in SEQ ID NO:337. In some embodiments, where a selected protein is aligned for maximum homology with the ubiquitin-like modifier activating enzyme 5 protein, the position in the aligned selected protein aligning with Cys250 is said to correspond to Cys250. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, e.g., where the three dimensional structure of the selected protein is aligned for maximum correspondence with the human reticulon 4 protein (reference sequence) and the overall structures compared. In this case, the amino acid that occupies the same essential structural position as Cys250 in the structural model relative to the reference sequence is said to correspond to the Cys250 residue.

[0077] "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 that can be produced in the reaction mixture.
The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway.

As defined herein, the term "activation", "activate", "activating", "activator" and the like in reference to a protein-inhibitor interaction means positively affecting (e.g. increasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the activator. In embodiments activation means positively affecting (e.g. increasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the activator. The terms may reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

As defined herein, the term "inhibition", "inhibitor", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

The terms "ubiquitin-like modifier activating enzyme 5" and "UBA5" and "UBE1DC1" refer to a protein (including homologs, isoforms, and functional fragments thereof) with ubiquitin-like modifier activating enzyme 5 activity. The term includes any recombinant or naturally-occurring form of ubiquitin-like modifier activating enzyme 5 or variants thereof that maintain ubiquitin-like modifier activating enzyme 5 activity (e.g. within
at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype ubiquitin-like modifier activating enzyme 5). In embodiments, the ubiquitin-like modifier activating enzyme 5 protein encoded by the UBA5 gene has the amino acid sequence set forth in or corresponding to Entrez 79876, UniProt Q9GZZ9, UniProt E7EQ61, UniProt E7EWE1, or RefSeq (protein) NP_079094. In embodiments, the ubiquitin-like modifier activating enzyme 5 gene has the nucleic acid sequence set forth in RefSeq (mRNA) NM_024818. In embodiments, the amino acid sequence or nucleic acid sequence is the sequence known at the time of filing of the present application. In embodiments, the sequence corresponds to NP_079094.1. In embodiments, the sequence corresponds to NM_024818.4. In embodiments, the ubiquitin-like modifier activating enzyme 5 is a human ubiquitin-like modifier activating enzyme 5, such as a human cancer causing ubiquitin-like modifier activating enzyme 5. In embodiments, UBA5 has the following sequence:

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MAESVERLQVRQELARELAQERSLQVRPSGDGGGGRVRIEKMSSEWDNSFYSRLMALK
RGMIVSYEKIRFTAVAIYVGGYGVSTAEMLRCQGKLLFDYDKVELAMNRLFFQP
HQAQLSVKGAAEHTLRNINPDVLFEVHNYNITTVENFQHFDRISSNGGLEEGKPDVLVLS
CVDNEARMELQOTWMEGVSNAVSGHIQLIIPGESACFACAPWLAAIND
EKLKREGVCAASLPDAMGWALVQNYLKLNNFTGFVSFLGYNAMQDFPFTMSKPN
POCDDRNCRRKQMEYKKVAAILPKQEVIQEEEIIHEDNEWGIELVSEVSEEELKNFSGP
VPDLPITGTAVYTPKQEDSVTELTVEDGSESLEDLMKMN
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[0082] The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (e.g., ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, etc.).

[0083] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a cancer. In some further instances, "cancer" refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin's lymphomas (e.g., Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (including AML, ALL, and CML), or multiple myeloma.
As used herein, the term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. 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 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.

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 leukocyticemiac 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

[0086] As used herein, the term "lymphoma" refers to a group of cancers affecting hematopoietic and lymphoid tissues. It begins in lymphocytes, the blood cells that are found primarily in lymph nodes, spleen, thymus, and bone marrow. Two main types of lymphoma are non-Hodgkin lymphoma and Hodgkin's disease. Hodgkin's disease represents approximately 15% of all diagnosed lymphomas. This is a cancer associated with Reed-Sternberg malignant B lymphocytes. Non-Hodgkin's lymphomas (NHL) can be classified based on the rate at which cancer grows and the type of cells involved. There are aggressive (high grade) and indolent (low grade) types of NHL. Based on the type of cells involved, there are B-cell and T-cell NHLs. Exemplary B-cell lymphomas that may be treated with a compound or method provided herein include, but are not limited to, small lymphocytic lymphoma, Mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma, extranodal (MALT) lymphoma, nodal (monocytoid B-cell) lymphoma, splenic lymphoma, diffuse large cell B-lymphoma, Burkitt's lymphoma, lymphoblastic lymphoma, immunoblastic large cell lymphoma, or precursor B-lymphoblastic lymphoma. Exemplary T-cell lymphomas that may be treated with a compound or method provided herein include, but are not limited to, cuneateous T-cell lymphoma, peripheral T-cell lymphoma, anaplastic large cell lymphoma, mycosis fungoides, and precursor T-lymphoblastic lymphoma.

[0087] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chioroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma
of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocyte sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[0088] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

[0089] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchoalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypemephroid 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, 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

[0090] The terms "treating", or "treatment" refers to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing. In embodiments, the treating or treatment is no prophylactic treatment.

[0091] "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.

[0092] A "effective amount" is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a
drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and Remington: *The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0093] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0094] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0095] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within
the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0096] 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) compatible with the preparation. Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. In embodiments, the administering does not include administration of any active agent other than the recited active agent.

[0097] "Co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds 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 transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0098] 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.

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

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 relative to the absence of the composition. In some embodiments, a ubiquitin-like modifier activating enzyme 5 associated disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with ubiquitin-like modifier activating enzyme 5 (e.g. cancer). A ubiquitin-like modifier activating enzyme 5 modulator is a compound that increases or decreases the activity or function or level of activity or level of function of ubiquitin-like modifier activating enzyme 5. In embodiments, the modulator is an inhibitor of UBA5. In embodiments, the modulator is an activator of UBA5.

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. In embodiments, modulating is activating. In embodiments, modulating is inhibiting.

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, a cancer associated with ubiquitin-like modifier activating enzyme 5 activity, ubiquitin-like modifier activating enzyme 5 associated cancer, ubiquitin-like modifier activating enzyme 5 associated disease) means that the disease (e.g. 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. For example, a cancer associated with ubiquitin-like modifier activating enzyme 5 activity or function may be a cancer that results (entirely or partially) from aberrant ubiquitin-like modifier activating enzyme 5 function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or a cancer wherein a particular symptom of the disease is caused (entirely or partially) by aberrant ubiquitin-like modifier activating enzyme 5 activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a cancer associated with ubiquitin-like modifier activating enzyme 5 activity or function or a ubiquitin-like modifier activating enzyme 5 associated cancer, may be treated with a ubiquitin-like modifier activating enzyme 5 modulator or ubiquitin-like modifier activating enzyme 5 inhibitor, in the instance where ubiquitin-like modifier activating enzyme 5 activity or function (e.g. signaling pathway activity) causes the cancer.

[0103] The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function 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.

[0104] The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propagated to other signaling pathway components. For example, binding of a ubiquitin-like modifier activating enzyme 5 protein with a compound as described herein may reduce the interactions between the ubiquitin-like modifier activating enzyme 5 protein and downstream effectors or signaling pathway components, resulting in changes in cell growth, proliferation, or survival.

[0105] The term "electrophilic chemical moiety" is used in accordance with its plain ordinary chemical meaning and refers to a chemical group (e.g., monovalent chemical group) that is electrophilic.
The term "nucleophilic chemical moiety" is used in accordance with its plain ordinary chemical meaning and refers to a chemical group (e.g., monovalent chemical group) that is nucleophilic.

"Nucleic acid" refers to nucleotides (e.g., deoxyribonucleotides or ribonucleotides) and polymers thereof in either single-, double- or multiple-stranded form, or complements thereof. The terms "polynucleotide," "oligonucleotide," "oligo" or the like refer, in the usual and customary sense, to a linear sequence of nucleotides. 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.

Nucleic acids, including e.g., nucleic acids with a phosphothioate backbone, can include one or more reactive moieties. As used herein, the term reactive moiety includes any group capable of reacting with another molecule, e.g., a nucleic acid or polypeptide through covalent, non-covalent or other interactions. By way of example, the nucleic acid can include an amino acid reactive moiety that reacts with an amino acid on a protein or polypeptide through a covalent, non-covalent or other interaction.

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, 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.

[0110] 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.

[0111] 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 N210, E209, L254, S253, and A251 of SEQ ID NO:337) 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 N210, E209, L254, S253, and A251 of SEQ ID NO:337). 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 N210, E209, L254, S253, and A251 of SEQ ID NO:337) 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 N210, E209, L254, S253, and A251 of SEQ ID NO:337) 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 N210, E209, L254, S253, and A251 of SEQ ID NO:337) in an organism. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid (e.g. a nucleic acid coding for a nucleic acid coding for one or more amino acids corresponding to N210, E209, L254, S253, and A251 of SEQ ID NO:337) 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.

[0046] 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 N210, E209, L254, S253, and A251 of SEQ ID NO:337) 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 N210, E209, L254, S253, and A251 of SEQ ID NO:337) 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.

[0092] 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 guanidine 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 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 sequences, wherein the sense sequence contains complementary nucleotides to the antisense sequence and thus forms the complement of the antisense sequence.

[0112] 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 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).

[0113] The term "antibody" refers to a polypeptide encoded by an immunoglobulin gene or functional fragments thereof that specifically binds and recognizes an antigen. The 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.

[0114] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "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," "VH," or "VH" refer to the
variable region of an immunoglobulin heavy chain, including an Fv, scFv, dsFv or Fab; while the terms "variable light chain," "VL" or "vL" refer to the variable region of an immunoglobulin light chain, including of an Fv, scFv, dsFv or Fab.

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.

"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.
[0117] 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.

[0118] 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 nucleophilic moiety).

[0119] "Anti-cancer agent" and "anticancer agent" are used in accordance with their plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEKI, MEK2, or MEKI and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD3 18088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide,
ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechloretamine, cyclophosphamide, chlorambucil, meiphalan), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin), triazenes (decarbazine), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), etc.), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, etc.).

Among the many classes of compounds, there are several that are particularly important in the treatment of cancer. Antitumor antibiotics such as doxorubicin, daunorubicin, and mitomycin C are effective against a variety of tumors, including those of the breast, lung, and gastrointestinal tract. Other important classes of compounds include the alkylating agents, which cause DNA damage by cross-linking DNA strands, and the antimetabolites, which interfere with the synthesis of nucleic acids.

Other important classes of compounds include the tyrosine kinase inhibitors, which target the signaling pathways that are activated in cancer cells, and the bisphosphonates, which are used to treat bone metastases. In addition, there are several classes of compounds that are currently under development, including the immune checkpoint inhibitors, which are designed to boost the patient’s immune system to fight cancer.
benzochlorins; benzoylstaurosponne; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropririmine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; clomiphene; clostrimazole; combretastatin A4; combretastatin analogue; conagenin; cromoguanil; cytarabine ocfosfate; cytolytic factor; cytostatin; daciliximab; decitabine; dehydrodidemnin B; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxfene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; florodaunorunicin hydrochloride; forfenimex; formestane; fostriezin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idofoxifene; idramantone; ilomofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; intereron agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4--; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetrone; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptomustine; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprolrelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamid 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; mafpin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; metioninase; 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+mycobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldimalinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; 06-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxanomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegasparagase; 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-acidone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin 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; rogetlimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; Stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide;
tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin;
thrombopoietin mimetic; thymalfasin; thrombopoietin 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; turosteride; tyrosine kinase inhibitors;
typhostins; UBC inhibitors; ubiquinone; urogenital sinus-derived growth inhibitory factor;
urokinase receptor antagonists; vaptrotide; variolin B; vector system, erythrocyte gene
therapy; velaresol; verapamil; vinceristine; vinorelbine; vinxaline; vitaxin; vorozole;
zanoterone; zanplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin,

Bleomycin, Vinblastine, Cisplatin, acivicin; acarbose; acodazole hydrochloride; acronine;
adozelesin; aldoseleukin; altretamine; amboxacin; ametantrone acetate; aminoglutethimide;
amscrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa;
azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide
dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropririmine; busulfan;
cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin
hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crinsatol
mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride;
decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin;
doxorubicin hydrochloride; droloxfene; droloxfene citrate; dromostanolone propionate;
duazomycin; edatrexate; efophosphamide; elsamitracin; enloplatin; enpromate;
epipropidine; epirubicin hydrochloride; erboluzole; esorubicin hydrochloride; estramustine;
estramustine phosphate sodium; etanidazole; etosiposide; etoposide phosphate; etoprine;
fadrozole hydrochloride; fazarabine; flavulin; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine
hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; immofosine; interleukin II
(including recombinant interleukin II, or rIL.sub.2), interferon alfa-2a; interferon alfa-2b;
interferon alfa-nl; interferon alfa-n3; interferon beta-la; interferon gamma-lb; iproplatin;
irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; l iarozole
hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprolol;
maytansine; mechlorethamine hydrochloride; megastrol acetate; melengestrol acetate;
melphalan; menogaril; mercaptopurine; methotrexate; metothrexate sodium; metoprine;
meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin;
mitosper; mitotane; toboxantrone hydrochloride; mycophenolic acid; nocodazoie;
nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiroptatin; spiroplatin; streptonigrin; streptozocin; sulofenur; talismycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiopeta; tiazofurin; tirapazamine; toremifene citrate; trestalone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; veprentofin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepine sulfate; vinglycinate 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), Altorhrytins (e.g. Altorhrytin A and Altorhrytin 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. desoxeypothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxeypothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-3 10705), 21-hydroxy epothilone D (i.e. Desoxeypothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Sobloidin (i.e. TZZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-1 12378 (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-22365 1), 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, Lauimalide, 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), Nascape, D-24851 (Asta Medica), A-105972 (Abbott), Hemisterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetone, T-138026 (Tularik), Monsatrol, Inanocrine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, i.e. T-900607), RPR-1 15781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonomide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Dizostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-4341 1 (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-25041 1 (Sanofi), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adenocorticosteroids (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-Guerin (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 111In, 90Y, or 131I, etc.), tiotropide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan,itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted
therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, peltinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0120] The term "ubiquitin-like modifier activating enzyme 5 protein (UBA5) activity" as used herein refers to the biological activity of the protein. Ubiquitin-like modifier activating enzyme 5 protein (UBA5) activity may be quantified by measuring the rate of cell division, cell survival, cell migration, liver toxicity, or cell death.

[0121] The term "ubiquitin-like modifier activating enzyme 5 protein-ubiquitin-like modifier activating enzyme 5 inhibitor complex" as used herein refers to a ubiquitin-like modifier activating enzyme 5 protein bonded (e.g., covalently bonded) to a Ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., a compound described herein).

II. Compounds

[0122] In an aspect is provided a compound having the formula: \((R^1)_{z1}\) (I). \(R^1\) is independently halogen, -CXS, -CHX^, -CH2X^, -OCX^, -OCH2X^, -OCHX^, -CN, -SONiR^, -SOviNR^1A^R^1B^, -NH[C(0)NR^1AR^1B^, -N(0)^j, -NR^1AR^1B^, -C(0)OR^1C^, -C(0)-OR^1C^, -C(0)NR^1AR^1B^, -OR^1D^, -NR^1ASO^2R^1D^, -NR^1AC(0)R^1C^, -NR^1A(C(0))^0R^1C^, -NR^1AOR^1C^, -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; \(L^1\) and an adjacent \(R^1\) substituent may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol \(z1\) is an integer from 0 to 5. \(L^1\) is a bond, -S(0) 2-, -NR^4-, -O-, -S-, -C(O)-, -C(0)NR^4-, -NR^4C(0)-,
-NR^4C(0)NH-, -NHC(0)NR^4-, -C(0)O-, -OC(O)-, -CH_2NR^4-, substituted or unsubstituted alkenylene, substituted or unsubstituted heteroalkenylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. R^4 is hydrogen, -CX_3^4, -CHX_4^4, -CH_2X_4^4, -OCH_2X_4^4, -OCH_2X_4^4, -CN, -C(0)R_4^4A, -C(0)-OR_4^4A, -C(0)NR_4^4AR^4B, -OR_4^4A, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. L^2 is a bond, -S(0)_2^4-, -NR^5-, -O-, -S-, -C(O)-,
-C(0)NR^5-, -NR^5C(0)NR^5-, -NHC(0)NR^5-, -C(0)O-, -OC(O)-, -CH_2NR^5-, substituted or unsubstituted alkenylene, substituted or unsubstituted heteroalkenylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. R^5 is hydrogen, -CX_5^5, -CHX_5^5, -CH_2X_5^5, -OCH_5^5, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol E is an electrophilic moiety. Each R^1A, R^1B, R^1C, R^1D, R^4A, R^4B, R^5A, and R^5B is independently hydrogen, -CX_3^5, -CN, -COOH, -CONH_2, -CHX_5^5, -CH_2X_5^5, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^1A and R^1B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroarylene; R^4A and R^4B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroarylene; R^5A and R^5B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroarylene. The symbols are each X, X_1, X_4, and X_5 is independently - F, -Cl, -Br, or -I. The symbols n_l, n_4, and n_5 are independently an integer from 0 to 4. The symbols m_l, m_4, m_5, v_l, v_4, and v_5 are independently an integer from 1 to 2.
In embodiments, the compound has the formula: \((\text{Ia})\),
wherein \(R\), \(z\), \(L_2\), and \(E\) are as described herein including embodiments.

In embodiments, the compound has the formula: \((\text{lb})\),
wherein \(R\), \(z\), \(L_2\), and \(E\) are as described herein including embodiments.

In embodiments, the compound has the formula: \((\Pi)\),
wherein \(R\), \(L\), \(L_2\), and \(E\) are as described herein including embodiments.

In embodiments, the compound has the formula: \((\text{Ila})\),
wherein \(R\), \(L_2\), and \(E\) are as described herein including embodiments.

In embodiments, the compound has the formula: \((\text{lib})\),
wherein \(R\), \(L_2\), and \(E\) are as described herein including embodiments.

In embodiments, the compound has the formula: \((\text{He})\),
wherein \(R\), \(L_2\), and \(E\) are as described herein including embodiments.

In embodiments, the compound has the formula: \((\text{III})\),
wherein \(L\), \(L_2\), and \(E\) are as described herein including embodiments. \(R^1\) and \(R^2\) are independently hydrogen, halogen, \(-\text{CX}^n\), \(-\text{CHX}^n\), \(-\text{CH}_2\text{X}^n\), \(-\text{OC}X^n\), \(-\text{OCH}_2\text{X}^n\), \(-\text{OCHX}^n\), \(-\text{CN}\), \(-\text{SNiR}_A\text{R}_B\), \(-\text{SOviNR}_A\text{R}_B\), \(-\text{NHC}(0)\text{NR}_A\text{R}_B\), \(-\text{N}(0)\text{NR}_A\text{R}_B\), \(-\text{NR}_A\text{R}_B\), \(-\text{C}(0)\text{R}^1\text{C}\), \(-\text{C}(0)\text{R}^1\text{C}\), \(-\text{C}(0)\text{R}^1\text{C}\), \(-\text{C}(0)\text{R}^1\text{C}\), \(-\text{R}^1\text{R}^2\text{R}^1\text{C}\), \(-\text{R}^1\text{R}^2\text{R}^1\text{C}\), \(-\text{R}^1\text{R}^2\text{R}^1\text{C}\), \(-\text{R}^1\text{R}^2\text{R}^1\text{C}\), \(-\text{R}^1\text{R}^2\text{R}^1\text{C}\), substituted 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 R\textsuperscript{1,1} and R\textsuperscript{1,2} may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0130] In embodiments, the compound has the formula: (IIIa), wherein R\textsuperscript{1,1}, R\textsuperscript{1,2}, L\textsuperscript{2}, and E are as described herein including embodiments.

[0131] In embodiments, the compound has the formula: (IIIb), wherein R\textsuperscript{1,1}, R\textsuperscript{1,2}, L\textsuperscript{2}, and E are as described herein including embodiments.

[0132] In embodiments, the compound has the formula:

\[
(C_1-C_4 \text{ alkyl}) - O - \begin{array}{c}  \text{N} \\ L^2 \end{array} - E
\]

(IIIb), wherein L\textsuperscript{2}, and E are as described herein including embodiments.

[0133] In embodiments, R\textsuperscript{1} is independently halogen, -CX\textsuperscript{A}, -CHX\textsuperscript{A}, -CH\textsuperscript{A}X\textsuperscript{1}, -OCS\textsuperscript{A}, -OCH\textsuperscript{A}X\textsuperscript{1}, -OCH\textsuperscript{A}X\textsuperscript{2}, -CN, -SR\textsuperscript{1D}, -NR\textsuperscript{1AR}\textsuperscript{1B}, -C(0)R\textsuperscript{1C}, -C(0)OR\textsuperscript{1C}, -C(0)NR\textsuperscript{1AR}\textsuperscript{1B}, -OR\textsuperscript{1D}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0134] In embodiments, the compound has the formula: (IV), wherein L\textsuperscript{1}, L\textsuperscript{2}, and E are as described herein including embodiments. R\textsuperscript{1,1}, R\textsuperscript{1,2}, R\textsuperscript{1,3} and R\textsuperscript{1,5}; and R\textsuperscript{1,6} are independently hydrogen, halogen, -CX\textsuperscript{A}, -CHX\textsuperscript{A}, -CH\textsuperscript{A}X, -OCS\textsuperscript{A}, -OCH\textsuperscript{A}X, -CN, -SR\textsuperscript{1D}, -SO\textsuperscript{iR}\textsuperscript{1AR}\textsuperscript{1B}, -NHC(0)NR\textsuperscript{1AR}\textsuperscript{1B}, -N(0)\textsuperscript{m}, -NR\textsuperscript{1AR}\textsuperscript{1B}, -C(0)R\textsuperscript{1C}, -C(0)OR\textsuperscript{1C}, -C(0)NR\textsuperscript{1AR}\textsuperscript{1B}.
R<sup>1B</sup>, -OR<sup>1D</sup>, -NR<sup>1A</sup>S<sub>2</sub>R<sup>1D</sup>, -NR<sup>1A</sup>C(0)R<sup>1C</sup>, -NR<sup>1A</sup>C(0)OR<sup>1C</sup>, substituted 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<sup>1</sup> and R<sup>1.2</sup> 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<sup>1.1</sup> and R<sup>1.6</sup> 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<sup>1.3</sup> and R<sup>1.2</sup> may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

In embodiments, the compound has the formula:  

![Formula (IVa)](image)

L<sup>1</sup>, L<sup>2</sup>, R<sup>1.5</sup>, and E are as described herein including embodiments.

In embodiments, the compound has the formula:  

![Formula (IVb)](image)

L<sup>1</sup>, L<sup>2</sup>, R<sup>1.3</sup>, and E are as described herein including embodiments.

In embodiments, R<sup>1</sup> is independently halogen, -CX<sup>1</sup>, -CHX<sup>1</sup>, -CH<sub>2</sub>X<sup>1</sup>, -OCS<sub>2</sub>, -OCH<sub>2</sub>X<sup>1</sup>, -OCHX<sup>1</sup>, -CN, -SH, -NH<sub>2</sub>, -C(0)OH, -C(0)NH<sub>2</sub>, -OH, -OCH<sub>3</sub>, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C3-C8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C<sub>6</sub>-Ci<sub>2</sub> aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

In embodiments, R<sup>1</sup> is independently halogen, -CX<sup>1</sup>, -CHX<sup>1</sup>, -CH<sub>2</sub>X<sup>1</sup>, -OCS<sub>2</sub>, -OCH<sub>2</sub>X<sup>1</sup>, -OCHX<sup>1</sup>, -CN, -SH, -NH<sub>2</sub>, -C(0)OH, -C(0)NH<sub>2</sub>, -OH, -OCH<sub>3</sub>, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 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.

[0139] In embodiments, two adjacent R^1 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 R^1 substituents are joined to form an unsubstituted cycloalkyl. In embodiments, two adjacent R^1 substituents are joined to form an unsubstituted C3-C6 cycloalkyl.

[0140] In embodiments, R^1 is independently -CX_{1-3}. In embodiments, R^1 is independently -CHX_{1-2}. In embodiments, R^1 is independently -OCS. In embodiments, R^1 is independently -OCHX_{1-2}. In embodiments, R^1 is independently -OCHX_{1-2}. In embodiments, R^1 is independently -CN. In embodiments, R^1 is independently -SO_nR^{1b}. In embodiments, R^1 is independently -SO_nNR^{1a}R^{1b}. In embodiments, R^1 is independently -NHC(0)NR^{1a}R^{1b}. In embodiments, R^1 is independently -N(0)_{m}R. In embodiments, R^1 is independently -NR^{1a}R^{1b}. In embodiments, R^1 is independently -C(0)OR^{1c}. In embodiments, R^1 is independently -C(0)NR^{1a}R^{1b}. In embodiments, R^1 is independently -OR^{1d}. In embodiments, R^1 is independently -NR^{1a}SO_{2}R^{1b}. In embodiments, R^1 is independently -NR^{1a}C(0)R^{1c}. In embodiments, R^1 is independently -NR^{1a}C(0)OR^{1c}. In embodiments, R^1 is independently -NH_{2}. In embodiments, R^1 is independently -COOH. In embodiments, R^1 is independently -CONH_{2}. In embodiments, R^1 is independently -NO_{2}. In embodiments, R^1 is independently -SH. In embodiments, R^1 is independently halogen. In embodiments, R^1 is independently -F. In embodiments, R^1 is independently -Cl. In embodiments, R^1 is independently -Br. In embodiments, R^1 is independently -I. In embodiments, R^1 is independently -CF_{3}. In embodiments, R^1 is independently -CHF_{2}. In embodiments, R^1 is independently -CH_{2}F. In embodiments, R^1 is independently -OCF_{3}. In embodiments, R^1 is independently -OCHF_{2}. In embodiments, R^1 is independently -OCHF_{2}. In embodiments, R^1 is independently -OCF_{3}. In embodiments, R^1 is independently -OCH_{2}CH_{3}. In embodiments, R^1 is independently -OCH(CH_{3})_{2}. In embodiments, R^1 is independently -OC(CH_{3})_{3}. In embodiments, R^1 is independently -SCH_{3}. In embodiments, R^1 is independently -SCH_{2}CH_{3}. In embodiments, R^1 is independently -SCH_{2}CH_{2}CH_{3}. In embodiments, R^1 is independently -SCH(3)_{2}. In embodiments, R^1 is independently -SCH(3)_{2}.
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 -OCH2CH3. In embodiments, R¹ is independently -OCH3.

In embodiments, R¹ is independently -N₃. In embodiments, R¹ is independently -C(0)CH₃. In embodiments, R¹ is independently -C(0)OCH₃. In embodiments, R¹ is independently -C(0)OCH₂CH₂CH₃. In embodiments, R¹ is independently -C(0)OCH(CH₃)₂. In embodiments, R¹ is independently -C(0)OC(CH₃)₃.

[0141] In embodiments, R¹ is independently hydrogen, halogen, -CX₁⁻³, -CHX₁⁻², -CH₂X¹, -OCX₁⁻³, -OCH₂X¹, -OCHX₃⁻⁵, -CN, -SO₃R, -SO₂NR₁⁻³, -HNHC(0)ₐNR₂⁻³, -N₁⁻⁰ₐR₂⁻³, -NH₁⁻₀R₂⁻³, -NR₁⁻⁰ₐR₂⁻³, -C(0)R₁⁻⁰ₐ, -C(0)OR₁⁻⁰ₐ, -C(0)NR₁⁻⁰ₐR₂⁻³, -NR₁⁻⁰ₐSO₂Rₐ, -NR₁⁻⁰ₐC(0)ₐR₁⁻⁰ₐ, -N₁⁻⁰ₐC(0)OR₁⁻⁰ₐ, -NR₁⁻⁰ₐOR₁⁻⁰ₐ, substituted or unsubstituted alkyl (e.g., C₁⁻₈, C₂⁻₆, C₁⁻₄, C₁⁻₂), 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., C₃⁻₅, C₄⁻₆, C₄⁻₇, or C₅⁻₈), 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., C₆⁻₁₂, C₁₀⁻₁₆, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 12, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0142] In embodiments, R¹ is independently substituted or unsubstituted alkyl (e.g., C₁⁻₈, C₁⁻₄, C₁⁻₂). In embodiments, R¹ is independently substituted alkyl (e.g., C₁⁻₈, C₁⁻₄, C₁⁻₂). In embodiments, R¹ is independently unsubstituted alkyl (e.g., C₁⁻₈, C₁⁻₄, C₁⁻₂). 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 tert-butyl. In embodiments, R¹ is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R¹ 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, R¹ 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, \( R^1 \) is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, \( R^1 \) is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, \( R^1 \) is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, \( R^1 \) 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, \( R^1 \) 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, \( R^1 \) 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, \( R^1 \) is independently substituted or unsubstituted aryl (e.g., \( C_6^-C_{12} \), \( C_6^-C_{10} \), or phenyl). In embodiments, \( R^1 \) is independently substituted aryl (e.g., \( C_6^-C_{12} \), \( C_6^-C_{10} \), or phenyl). In embodiments, \( R^1 \) is independently unsubstituted aryl (e.g., \( C_6^-C_{12} \), \( C_6^-C_{10} \), or phenyl). In embodiments, \( R^1 \) is independently 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, \( R^1 \) is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( R^1 \) is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0143] In embodiments, two adjacent \( R^1 \) substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent \( R^1 \) substituents may optionally be joined to form a substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent \( R^1 \) substituents may optionally be joined to form an unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent \( R^1 \) substituents may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent \( R^1 \) substituents may optionally 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, two adjacent \( R^1 \) substituents may optionally 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). In embodiments, two adjacent \( R^1 \) substituents may optionally be joined to form a substituted or unsubstituted aryl (e.g., \( C_6^-C_{12} \), \( C_6^-C_{10} \), or phenyl). In embodiments, two adjacent \( R^1 \) substituents may optionally be joined to form a
substituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, two adjacent R¹ substituents may optionally be joined to form an unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl). In embodiments, two adjacent R¹ substituents may optionally be joined to form a 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, two adjacent R¹ substituents may optionally be joined to form a substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R¹ substituents may optionally be joined to form an unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0144] In embodiments, R¹A is independently hydrogen. In embodiments, R¹A is independently -CX¹A₃. In embodiments, R¹A is independently -CHX¹A₂. In embodiments, R¹A is independently -CH₂X¹A. In embodiments, R¹A is independently -CN. In embodiments, R¹A is independently -COOH. In embodiments, R¹A is independently -CONH₂. In embodiments, X¹A is independently -F, -Cl, -Br, or -I.

[0145] In embodiments, R¹A is independently substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹A is independently substituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹A is independently unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂). In embodiments, R¹A is independently unsubstituted methyl. In embodiments, R¹A is independently unsubstituted propyl. In embodiments, R¹A is independently unsubstituted isopropyl. In embodiments, R¹A is independently unsubstituted tert-butyl. In embodiments, R¹A 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, R¹A 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, R¹A is independently substituted or unsubstituted cycloalkyl (e.g., C₅-C₈, C₅-C₆, C₄-G₅, or C₅-C₆). In embodiments, R¹A is independently substituted cycloalkyl (e.g., C₅-C₈, C₅-C₆, C₄-C₆, or C₅-C₆). In embodiments, R¹A is independently unsubstituted cycloalkyl (e.g., C₅-C₈, C₅-C₆, C₄-C₆, or C₅-C₆). In embodiments, R¹A 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, R¹A 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).
6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1A} 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\textsuperscript{1A} is independently substituted or unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{12}, C\textsubscript{6}-C\textsubscript{10}, or phenyl). In embodiments, R\textsuperscript{1A} is independently substituted aryl (e.g., C\textsubscript{6}-C\textsubscript{12}, C\textsubscript{6}-C\textsubscript{10}, or phenyl). In embodiments, R\textsuperscript{1A} is independently unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{12}, C\textsubscript{6}-C\textsubscript{10}, or phenyl). In embodiments, R\textsuperscript{1A} is independently 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\textsuperscript{1A} is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1A} is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0146] In embodiments, R\textsuperscript{1B} is independently hydrogen. In embodiments, R\textsuperscript{1B} is independently -CX\textsuperscript{1A}. In embodiments, R\textsuperscript{1B} is independently -CHX\textsuperscript{1B}. In embodiments, R\textsuperscript{1B} is independently -COOH. In embodiments, R\textsuperscript{1B} is independently -CONH\textsubscript{2}. In embodiments, X\textsuperscript{1B} is independently -F, -Cl, -Br, or -I.

[0147] In embodiments, R\textsuperscript{1B} is independently substituted or unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, Ci-C\textsubscript{4}, or Ci-C\textsubscript{2}). In embodiments, R\textsuperscript{1B} is independently substituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, Ci-C\textsubscript{4}, or Ci-C\textsubscript{2}). In embodiments, R\textsuperscript{1B} is independently unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, Ci-C\textsubscript{4}, or Ci-C\textsubscript{2}). In embodiments, R\textsuperscript{1B} is independently unsubstituted ethyl. In embodiments, R\textsuperscript{1B} is independently unsubstituted propyl. In embodiments, R\textsuperscript{1B} is independently unsubstituted isopropyl. In embodiments, R\textsuperscript{1B} is independently unsubstituted tert-butyl. In embodiments, R\textsuperscript{1B} is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R\textsuperscript{1B} is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R\textsuperscript{1B} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R\textsuperscript{1B} is independently substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{5}, or C\textsubscript{5}-C\textsubscript{6}). In embodiments, R\textsuperscript{1B} is independently substituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}). In embodiments, R\textsuperscript{1B} is independently unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}). In
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^{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^{1B} 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^{1A} is independently substituted or unsubstituted aryl (e.g., C_6-C_{12}, C_6-Cio, or phenyl). In embodiments, R^{1B} is independently substituted aryl (e.g., C_6-C_{12}, C_6-Cio, or phenyl). In embodiments, R^{1B} is independently unsubstituted aryl (e.g., C_6-C_{12}, C_6-Cio, or phenyl). In embodiments, R^{1B} is independently 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^{1A} is independently substituted heteroaryl (e.g., 5 to 12 membered, 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 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0148] In embodiments, R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). 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 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).

[0149] 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 12 membered, 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 12 membered, 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 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
In embodiments, R is independently hydrogen. In embodiments, R is independently -CX. In embodiments, R is independently -CHX. In embodiments, R is independently -CN. In embodiments, R is independently -COOH. In embodiments, R is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 9 membered, 6 to 10 membered, 6 to 8 membered). In embodiments, R is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 9 membered, 6 to 10 membered, 6 to 8 membered).

In embodiments, R is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R is independently unsubstituted methyl. In embodiments, R is independently unsubstituted ethyl. In embodiments, R is independently unsubstituted propyl. In embodiments, R is independently unsubstituted isopropyl. In embodiments, R is independently unsubstituted tert-butyl. In embodiments, R 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 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 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 is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-G5, or C5-G). In embodiments, R is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-G6, or C5-G). In embodiments, R is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-G6, or C5-G). In embodiments, R 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 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 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 is independently substituted or unsubstituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, R is independently substituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, R is independently 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 is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
membered, or 5 to 6 membered). In embodiments, \( R^{1c} \) is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0152] In embodiments, \( R^{1d} \) is independently hydrogen. In embodiments, \( R^{1d} \) is independently -CX\(^{1b} \)\(^3\). In embodiments, \( R^{1d} \) is independently -CHX\(^{1b} \)\(^2\). In embodiments, \( R^{1d} \) is independently -CH\(_2\)X\(^{1d}\). In embodiments, \( R^{1d} \) is independently -CN. In embodiments, \( R^{1d} \) is independently -COOH. In embodiments, \( R^{1d} \) is independently -CONH\(_2\). In embodiments, \( X^{1d} \) is independently -F, -Cl, -Br, or -I.

[0153] In embodiments, \( R^{1d} \) is independently substituted or unsubstituted alkyl (e.g., CI-C\(_8\), CI-C\(_6\), CI-C\(_4\), or CI-C\(_2\)). In embodiments, \( R^{1d} \) is independently substituted alkyl (e.g., CI-C\(_8\), CI-C\(_6\), CI-C\(_4\), CI-C\(_2\)). In embodiments, \( R^{1d} \) is independently unsubstituted alkyl (e.g., CI-C\(_8\), CI-C\(_6\), CI-C\(_4\), CI-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 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 unsubstituted heteroalkyl (e.g., CI-C\(_8\), CI-C\(_6\), CI-C\(_4\), or CI-C\(_2\)). In embodiments, \( R^{1d} \) is independently substituted or unsubstituted cycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_5\), 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 independently substituted or unsubstituted aryl (e.g., C\(_6\)-C\(_{12}\), C\(_6\)-C\(_{10}\), or phenyl). In embodiments, \( R^{1d} \) is independently substituted aryl (e.g., C\(_6\)-C\(_{12}\), C\(_6\)-C\(_{10}\), or phenyl). In embodiments, \( R^{1d} \) is independently unsubstituted aryl (e.g., C\(_6\)-C\(_{12}\), C\(_6\)-C\(_{10}\), or phenyl). In
embodiments, \( R^{10} \) is independently 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, \( R^{10} \)
is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). In embodiments, \( R^{10} \) is independently unsubstituted
heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6
membered).

[0154] In embodiments, \( R^1 \) is independently hydrogen,
halogen, -CX\(^{\alpha} \), -CHX\(^{\alpha} \), -CH2X\(^{\alpha} \), -OCX\(^{\alpha} \), -OCH2X\(^{\alpha} \), -OCHX\(^{\alpha} \), -CN, -OH, -NH\(_2\), -COOH, -
CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NH2NH2, -ONH2, -NHCl=(0)NHNH\(_2\),
-\( NH\(_2\)Cl=(0)NH\(_2\), -NHSO2H, -NHC=(0)H, -NHC=(0)OH, -NHOH, -OCH3, R\(^{20}\)-substituted or
unsubstituted alkyl (e.g., C\(_2\)-C\(_8\), C\(_6\)-C\(_6\), C\(_1\)-C\(_4\), or C\(_1\)-C\(_2\)), R\(^{20}\)-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\(^{20}\)-substituted or unsubstituted cycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-
C\(_8\)), R\(^{20}\)-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\(^{20}\)-substituted or
unsubstituted aryl (e.g., C\(_6\)-C\(_2\), C\(_6\)-C\(_6\), or phenyl), or R\(^{20}\)-substituted or unsubstituted
heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6
membered).

[0155] In embodiments, \( R^1 \) is independently hydrogen,
halogen, -CX\(^{\alpha} \), -CHX\(^{\alpha} \), -CH2X\(^\alpha \), -OCX\(^{\alpha} \), -OCH2X\(^{\alpha} \), -OCHX\(^{\alpha} \), -CN, -OH, -NH\(_2\), -COOH, -
CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NH2NH2, -ONH2, -NHCl=(0)NHNH\(_2\),
-\( NH\(_2\)Cl=(0)NH\(_2\), -NHSO2H, -NHC=(0)H, -NHC=(0)OH, -NHOH, unsubstituted alkyl (e.g.,
C\(_2\)-C\(_8\), C\(_6\)-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, 4 to 5 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\(_8\)), 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\(_2\), C\(_6\)-C\(_6\), or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12
membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). \( X^1 \) is independently
-F, -Cl, -Br, or -I. In embodiments, \( R^1 \) is independently hydrogen. In embodiments, \( R^1 \) is
independently unsubstituted methyl. In embodiments, \( R^1 \) is independently unsubstituted
ethyl. In embodiments, \( R^1 \) is independently -OCH3.
[0156] In embodiments, two adjacent R₁ substituents may optionally be joined to form a
substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In
embodiments, two adjacent R₁ substituents may optionally be joined to form a R²₀-substituted
cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, two adjacent R₁
substituents may optionally be joined to form an unsubstituted cycloalkyl (e.g., C3-C8, C3-C6,
C4-C6, or C5-C6). In embodiments, two adjacent R₁ substituents may optionally be joined to form
a R²₀-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, two
adjacent R₁ substituents may optionally be joined to form a R²₀-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 R₁ substituents may optionally 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). In embodiments, two adjacent R₁ substituents may
optionally be joined to form a R²₀-substituted or unsubstituted aryl (e.g., C₅-C₁₂, C₆-C₁₅, or
phenyl). In embodiments, two adjacent R₁ substituents may optionally be joined to form a
R²₀-substituted aryl (e.g., C₅-C₁₂, C₆-C₁₅, or phenyl). In embodiments, two adjacent R₁
substituents may optionally be joined to form an unsubstituted aryl (e.g., C₅-C₁₂, C₆-C₁₅, or
phenyl). In embodiments, two adjacent R₁ substituents may optionally be joined to form a
R²₀-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, two adjacent R₁ substituents may
optionally be joined to form a R²₀-substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R₁
substituents may optionally be joined to form an unsubstituted heteroaryl (e.g., 5 to 12
membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

25 [0157] R²₀ is independently oxo,
halogen, -CX₃, -CHX₂, -CH₂X, -OCX₂, -OCH₂X, -OCHX₃, -CN, -OH, -NH₂, -CO
OH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₂H₂, -NHₓHₓ, -ONH₂, -NHₓHₓ, -NHC=O (NHₓHₓ),
-NHₓ=O, -NHSO₂H, -NHC=O, -NHC=O-OH, -NH₂H₂, -R₂₁-substituted or
unsubstituted alkyl (e.g., C₁-C₆, C₁-C₈, C₁-C₄, or C₁-C₂), R₂₁-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), R₂₁-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-
C₆), R₂₁-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), R₂₁-substituted or
unsubstituted aryl (e.g., C₆₋₁₂, C₆₋₁₀, or phenyl), or R²₁-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, R²⁰ is independently oxo, halogen, -CX₂₃₋₁₂, -CHX₂₁₋₁₀, -CH₂X₂₀, -OCX₂₁₋₁₀, -OCH₂X₂₀, -OCHX₂₁₋₁₀, -CN, -OH, -NH₂, -COO H, -CONH₂, -N0₂, -SH, -S0₂H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NH, H, -NH=(O)NH, -NH=OHNH, unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, Ci-C₄, or Ci-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃₋₅, C₆₋₇, C₆₋₈, or C₅₋₆), 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., C₆₋₁₀, C₆₋₁₀-C₅, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²⁰ is independently -F, -Cl, -Br, or -I. In embodiments, R²⁰ is independently unsubstituted methyl. In embodiments, R²⁰ is independently unsubstituted ethyl. In embodiments, R²⁰ is independently substituted phenyl. In embodiments, R²⁰ is independently unsubstituted phenyl. In embodiments, R²⁰ is independently -CH₃. In embodiments, R²⁰ is independently -OCH₃. In embodiments, R²⁰ is independently -SCH₃. In embodiments, R²⁰ is independently -CN. In embodiments, R²⁰ is independently R²₁-substituted phenyl. In embodiments, R²⁰ is independently R²₁-substituted phenyl. In embodiments, R²⁰ is independently halogen. In embodiments, R²⁰ is independently -Cl. In embodiments, R²⁰ is independently -F.

[0158] R²¹ is independently oxo, halogen, -CX₂¹₋₁₁, -CHX₂¹₋₁₀, -CH₂X₂₀, -OCX₂₁₋₁₀, -OCH₂X₂₀, -OCHX₂₁₋₁₀, -CN, -OH, -NH₂, -COO H, -CONH₂, -N0₂, -SH, -S0₂H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NH, H, -NH=(O)NH, -NH=OHNH, unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, Ci-C₄, or Ci-C₂), R²²-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), R²²-substituted or unsubstituted cycloalkyl (e.g., C₃₋₅, C₆₋₇, C₆₋₈, or C₅₋₆), R²²-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), R²²-substituted or unsubstituted aryl (e.g., C₆₋₁₀, C₆₋₁₀-C₅, or phenyl), R²²-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, R²¹ is independently oxo, halogen, -CX₂¹₋₁₁, -CHX₂¹₋₁₀, -CH₂X₂₀, -OCX₂₁₋₁₀, -OCH₂X₂₀, -OCHX₂₁₋₁₀, -CN, -OH, -NH₂, -COO
H, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NHNH2, -ONH2, -NHC=(0)NHNH2, -NHC=(0)NH2, -NHSO2H, -NHC=(O)H, -NH(0)-OH, -NH2, unsubstituted alkyl (e.g., Ci-C8, Ci-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). X21 is independently -F, -Cl, -Br, or -I. In embodiments, R21 is independently unsubstituted methyl. In embodiments, R21 is independently unsubstituted ethyl. In embodiments, R21 is -CN.

[0159] R22 is independently oxo, halogen, -CX223, -CH2X22, -CH2X22, -OCX223, -OCH2X22, -OCHX22, -CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NHNH2, -ONH2, -NHC=(0)NHNH2, -NHC=(0)NH2, -NHSO2H, -NHC=(0)H, -NHC(0)-OH, -NH2, unsubstituted alkyl (e.g., Ci-C8, Ci-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). X22 is independently -F, -Cl, -Br, or -I. In embodiments, R22 is independently unsubstituted methyl. In embodiments, R22 is independently unsubstituted ethyl.

[0160] In embodiments, R1a is independently hydrogen, -CX1A3, -CHX1A2, -CH2X1A, -CN, -COOH, -CONH2, R20A-substituted or unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2). R20A-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). R20A-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6), R20A-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). R20A-substituted or unsubstituted aryl (e.g., C6-C12, C6-C10, or phenyl), or R20A-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, R1a is independently
hydrogen, -CX\textsuperscript{1A}, -CHX\textsuperscript{1A}, -\text{CH}_2\text{X}\textsuperscript{1A}, -CN, -COOH, -CONH\textsubscript{2}, unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, Ci-C\textsubscript{4}, or Ci-C\textsubscript{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\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{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\textsubscript{6}Ci-C\textsubscript{2}, C\textsubscript{6}Ci-C\textsubscript{6}, 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\textsuperscript{1A} is independently -F, -Cl, -Br, or -I. In embodiments, R\textsuperscript{1A} is independently hydrogen. In embodiments, R\textsuperscript{1A} is independently unsubstituted ethyl.

[0161] In embodiments, R\textsuperscript{1A} and R\textsuperscript{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{20A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or R\textsuperscript{20A}-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\textsuperscript{1A} and R\textsuperscript{1B} substituents bonded to the same nitrogen atom may optionally 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) 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\textsuperscript{1A} and R\textsuperscript{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{20A}-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\textsuperscript{1A} and R\textsuperscript{1B} substituents bonded to the same nitrogen atom may optionally 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).

[0162] R\textsuperscript{20A} is independently oxo, halogen, -CX\textsuperscript{20A}, -CHX\textsuperscript{20A}, -\text{CH}_2\text{X}\textsuperscript{20A}, -OCX\textsuperscript{20A}, -\text{OCH}_2\text{X}\textsuperscript{20A}, -OCHX\textsuperscript{20A}, -\text{CN}, -\text{OH}, -\text{NH}_2, -\text{COOH}, -\text{CONH}_2, -\text{NO}_2, -\text{SH}, -\text{SO}_2\text{H}, -\text{SO}_2\text{NH}_2, -\text{NHNH}_2, -\text{ONH}_2, -\text{NHC}=\text{(0)}\text{NHNH}_2, -\text{NHC}=\text{(0)}\text{NH}_2, -\text{NHSO}_2\text{H}, -\text{NHC}=\text{(O)}\text{H}, -\text{NHC}(\text{0})-\text{OH}, -\text{NHOH}, R\textsuperscript{21A}-substituted or unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, Ci-C\textsubscript{4}, or Ci-C\textsubscript{2}), R\textsuperscript{21A}-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\textsuperscript{21A}-substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}), R\textsuperscript{21A}-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), \( R^{21A} \)-substituted or unsubstituted aryl (e.g., \( C_6-C_{12} \), \( C_6-C_{10} \), or phenyl), or \( R^{21A} \)-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, \( R^{20A} \) is independently oxo,

halogen, \(-CX^{20A}_3\), \(-CHX^{20A}_2\), \(-CH_2X^{20A}\), \(-OCX^{20A}_3\), \(-OCH_2X^{21A}\), \(-OCHX^{21A}_2\), \(-CN\), \(-OH\), \(-NH_2\), \(-COOH\), \(-CONH_2\), \(-N_2\), \(-SH\), \(-SO_2\), \(-SO_2NH_2\), \(-NHHNH_2\), \(-ONH_2\), \(-NHC=(0)NH\), \(-NHC=NH\), \(-NHCO\), \(-NHCONH\), \(-NHC\(=\(O\)\)H), \(-NHС\(=\)\(O\)\)H), \(-NH=O\)H, \(-NH=O\)H, unsubstituted alkyl (e.g., \( Ci-C_8 \), \( Ci-C_6 \), \( Ci-C_4 \), or \( Ci-C_2 \)), 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., \( C_6-C_12 \), \( C_6-C_10 \), or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). \( X^{20A} \) is independently \(-F\), \(-Cl\), \(-Br\), or \(-I\). In embodiments, \( R^{20A} \) is independently unsubstituted methyl.

[0163] \( R^{21A} \) is independently oxo,

halogen, \(-CX^{21A}_3\), \(-CHX^{21A}_2\), \(-CH_2X^{21A}\), \(-OCX^{21A}_3\), \(-OCH_2X^{21A}\), \(-OCHX^{21A}_2\), \(-CN\), \(-OH\), \(-NH_2\), \(-COOH\), \(-CONH_2\), \(-N_2\), \(-SH\), \(-SO_2\), \(-SO_2NH_2\), \(-NHHNH_2\), \(-ONH_2\), \(-NHC=(0)NH\), \(-NHC=NH\), \(-NHCO\), \(-NHCONH\), \(-NHC\(=\)\(O\)\)H), \(-NHС\(=\)\(O\)\)H), \(-NH=O\)H, \(-NH=O\)H, \( R^{22A} \)-substituted or unsubstituted alkyl (e.g., \( Ci-C_8 \), \( Ci-C_6 \), \( Ci-C_4 \), or \( Ci-C_2 \)), \( R^{22A} \)-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), \( R^{22A} \)-substituted or unsubstituted cycloalkyl (e.g., \( C_3-C_8 \), \( C_3-C_6 \), \( C_4-C_6 \), or \( C_5-C_6 \)), \( R^{22A} \)-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), \( R^{22A} \)-substituted or unsubstituted aryl (e.g., \( C_6-C_12 \), \( C_5-C_10 \), or phenyl), or \( R^{22A} \)-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, \( R^{21A} \) is independently oxo,

halogen, \(-CX^{21A}_3\), \(-CHX^{21A}_2\), \(-CH_2X^{21A}\), \(-OCX^{21A}_3\), \(-OCH_2X^{21A}\), \(-OCHX^{21A}_2\), \(-CN\), \(-OH\), \(-NH_2\), \(-COOH\), \(-CONH_2\), \(-N_2\), \(-SH\), \(-SO_2\), \(-SO_2NH_2\), \(-NHHNH_2\), \(-ONH_2\), \(-NHC=(0)NH\), \(-NHC=NH\), \(-NHCO\), \(-NHCONH\), \(-NHC\(=\)\(O\)\)H), \(-NHС\(=\)\(O\)\)H), \(-NH=O\)H, \(-NH=O\)H, unsubstituted alkyl (e.g., \( Ci-C_8 \), \( Ci-C_6 \), \( Ci-C_4 \), or \( Ci-C_2 \)), 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., C₆-H₉, 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). X²¹α is independently -F, -Cl, -Br, or -I. In embodiments, R²¹α is independently unsubstituted methyl. In embodiments, R²¹α is independently unsubstituted ethyl.

[0064] R²²α is independently oxo, halogen, -C₆H₅, -CHX²²α, -CH₂X²²α, -OCX²²α, -OCH₂X²²α, -OCHX²²α, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₂H₂, -NH₂H₂, -ON₂H₂, -NHCOH, unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, Ci-C₄, or Ci-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, C₅-C₆, C₆-C₈, 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). X²²α is independently -F, -Cl, -Br, or -I. In embodiments, R²²α is independently unsubstituted methyl. In embodiments, R²²α is independently unsubstituted ethyl.

[0065] In embodiments, R¹b is independently hydrogen, -C₆H₅, -CHX¹b, -CH₂X¹b, -CN, -COOH, -CONH₂, R²⁰b-substituted or unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, Ci-C₄, or Ci-C₂), R²⁰b-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), R²⁰b-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₅-C₆, C₆-C₈, or C₅-C₆), R²⁰b-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), R²⁰b-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R²⁰b-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, R¹b is independently hydrogen, -C₆H₅, -CHX¹b, -CH₂X¹b, -CN, -COOH, -CONH₂, unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, Ci-C₄, or Ci-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, C₅-C₆, C₆-C₈, 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., to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X is independently -F, -Cl, -Br, or -I. In embodiments, R is independently hydrogen. In embodiments, R is independently unsubstituted methyl. In embodiments, R is independently unsubstituted ethyl.

[0166] In embodiments, R and R substituents bonded to the same nitrogen atom may optionally be joined to form a -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or R-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 and R substituents bonded to the same nitrogen atom may optionally 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) 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 and R substituents bonded to the same nitrogen atom may optionally be joined to form a -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R and R substituents bonded to the same nitrogen atom may optionally 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).

[0167] R is independently oxo, halogen, -CX, -CHX, -CH₂X, -OCX, -OCH₂X, -OCHX, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂H, -SO₂NH₂, -NH₂, -O,NH₂, R-substituted or unsubstituted alkyl (e.g., C₇, C₆-C₄, C₁-C₄, or C₁-C₂), R-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-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₅-C₆, C₆-C₄, or C₅-C₆), R-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-substituted or unsubstituted aryl (e.g., C₆-C₁₂, G-C₁₀, or phenyl), or R-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 is independently oxo, halogen, -CX, -CHX, -CH₂X, -OCX, -OCH₂X, -OCHX, -CN, -OH, -NH₂,
-COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NH₂, -OH₂, -HC=\(0\)NH₂, -HC=\(0\)H₂, ... embodiments, R₂₁B is independently unsubstituted methyl. In embodiments, R²₀B is independently unsubstituted ethyl.

[0168] R²¹B is independently oxo, halogen, -CXL₂₁B₃, -CHXL₂₁B₂, -CH₂X₂₁B₁, -OCH₂X₂₁B₁, -OCHX₂₁B₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SₐH₃, -SO₄H, -SO₂NH₂, -NH₂, -OH₂, -NHC\(=\)(0)NH₂, -NHC\(=\)(0)H₂, -NHC\(=\)(0)OH, -NHOH, unsubstituted alkyl (e.g., Ci-C₈, Ci-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, C₅-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). In embodiments, R²¹B is independently oxo, halogen, -CXL₂₁B₃, -CHXL₂₁B₂, -CH₂X₂₁B₁, -OCH₂X₂₁B₁, -OCHX₂₁B₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SₐH₃, -SO₄H, -SO₂NH₂, -NH₂, -OH₂, -NHC\(=\)(0)NH₂, -NHC\(=\)(0)H₂, -NHC\(=\)(0)OH, -NHOH, unsubstituted alkyl (e.g., Ci-C₈, Ci-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., C₅-C₈, C₅-C₆, C₄-C₅, 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). X²¹B is independently -F, -Cl, -Br, or -I. In embodiments, R²¹B is independently unsubstituted methyl. In embodiments, R²¹B is independently unsubstituted ethyl.
[0169] R^{22B} is independently oxo, halogen, -CX^{22B}, -CHX^{22B}, -CH_2X^{22B}, -OCX^{22B}, -OCH_2X^{22B}, -OCHX^{22B}, -CN, -OH, -NH_2, -COOH, -CONH_2, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, -NH_2H_2 - ONH_2, -NH=C(=0)NHNH_2, - NH=C(=0)NH_2, -NHSO_2H, -NHC(=0)H, -NH(0)-OH, -NHOH, unsubstituted alkyl (e.g., C_5-C_8, C_5-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_5-C_8, C_5-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_1, C_6-Cio, 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^{22B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{22B} is independently unsubstituted methyl. In embodiments, R^{22B} is independently unsubstituted ethyl.

[0170] In embodiments, R^1C is independently hydrogen, -CX^1C, -CHX^1C, -CH_2X^1C, -CN, -COOH, -CONH_2, R^{20C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{20C}-substituted or unsubstituted cycloalkyl (e.g., C_5-C_8, C_5-C_6, C_4-C_6, or C_5-C_6), R^{20C}-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^{20C}-substituted or unsubstituted aryl (e.g., C_6-Ci, C_6-Cio, or phenyl), or R^{20C}-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^1C is independently hydrogen, -CX^1C, -CHX^1C, -CH_2X^1C, -CN, -COOH, -CONH_2, unsubstituted alkyl (e.g., C_5-C_8, C_5-C_6, C_1-C_4, or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_5-C_8, C_5-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-Ci, C_6-Cio, 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^1C is independently -F, -Cl, -Br, or -I. In embodiments, R^1C is independently hydrogen. In embodiments, R^1C is independently unsubstituted methyl. In embodiments, R^1C is independently unsubstituted ethyl.
R independent oxo, halogen, -CX\textsuperscript{20C}, -CHX\textsuperscript{20C}, -CH\textsubscript{2}X\textsuperscript{20C}, -OCX\textsuperscript{20C}, -OCH\textsubscript{2}X\textsuperscript{20C}, -OCHX\textsuperscript{20C}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NH\textsubscript{2}, -NHC\textsubscript{=}H\textsubscript{NHNH}, -NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NH\textsubscript{2}, -NHC\textsubscript{=}H\textsubscript{OH}, -NH\textsubscript{OH},

R\textsuperscript{21C}-substituted or unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, C1-C4, or C1-C2), R\textsuperscript{21C}-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\textsuperscript{21C}-substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C4-C6, or C5-C\textsubscript{6}), R\textsuperscript{21C}-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\textsuperscript{21C}-substituted or unsubstituted aryl (e.g., C\textsubscript{6}-Cl\textsubscript{2}, C\textsubscript{6}-Ci\textsubscript{2}, or phenyl), or R\textsuperscript{21C}-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\textsuperscript{30C} is independently oxo, halogen, -CX\textsuperscript{20C}, -CHX\textsuperscript{20C}, -CH\textsubscript{2}X\textsuperscript{20C}, -OCX\textsuperscript{20C}, -OCH\textsubscript{2}X\textsuperscript{20C}, -OCHX\textsuperscript{20C}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NH\textsubscript{2}, -NHC\textsubscript{=}H\textsubscript{NHNH}, -NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NH\textsubscript{2}, -NHC\textsubscript{=}H\textsubscript{OH}, -NH\textsubscript{OH}, unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, 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., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C4-G5, or C5-C\textsubscript{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\textsubscript{6}-Cl\textsubscript{2}, C\textsubscript{6}-Ci\textsubscript{2}, 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\textsuperscript{20C} is independently -F, -Cl, -Br, or -I. In embodiments, R\textsuperscript{20C} is independently unsubstituted methyl. In embodiments, R\textsuperscript{20C} is independently unsubstituted ethyl.

R\textsuperscript{21C} is independently oxo, halogen, -CX\textsuperscript{21C}, -CHX\textsuperscript{21C}, -CH\textsubscript{2}X\textsuperscript{21C}, -OCX\textsuperscript{21C}, -OCH\textsubscript{2}X\textsuperscript{21C}, -OCHX\textsuperscript{21C}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NH\textsubscript{2}, -NHC\textsubscript{=}H\textsubscript{NHNH}, -NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NH\textsubscript{2}, -NHC\textsubscript{=}H\textsubscript{OH}, -NH\textsubscript{OH}, R\textsuperscript{22C}-substituted or unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, C1-C4, or C1-C2), R\textsuperscript{22C}-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\textsuperscript{22C}-substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C4-C6, or C5-C\textsubscript{6}), R\textsuperscript{22C}-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\textsuperscript{22C}-substituted or unsubstituted aryl (e.g., C\textsubscript{6}-Cl\textsubscript{2}, C\textsubscript{8}-C10, or phenyl), or R\textsuperscript{22C}-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, R⁷¹ is independently oxo,
halogen, -CX₂⁻¹⁻¹(3), -CHX⁻¹⁻¹(1), -CH₂X⁻¹⁻¹(1), -OCX⁻¹⁻¹(2), -OCH₂X⁻¹⁻¹(2), -OCHX⁻¹⁻¹(2), -CN, -OH, -NH₂,
-COOH, -CONH₂, -N0 2, -SH, -S0 3 H, -S0 4 H, -S0 2 NH₂, -NH₂ NH₂, - ONH₂,
- NHC=(O)NH₂, - NH₂ (O)NH₂, -NH S0 2 H, -NH C= (O)H, -NH C(0)-OH, -NH OH,
unsubstituted alkyl (e.g., C$i$-C₆, C$i$-C₅, C$i$-C₄, or C$i$-C₃), 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). X²⁻¹ is independently -F, -Cl, -Br, or -I. In embodiments, R⁷¹ is independently unsubstituted methyl. In embodiments, R²—he is independently unsubstituted ethyl.

R²—he is independently oxo,
halogen, -CX₂⁻¹⁻¹(2), -CHX⁻¹⁻¹(2), -CH₂X⁻¹⁻¹(2), -OCX⁻¹⁻¹(3), -OCH₂X⁻¹⁻¹(3), -OCHX⁻¹⁻¹(3), -CN, -OH, -NH₂,
-COOH, -CONH₂, -N0 2, -SH, -S0 3 H, -S0 4 H, -S0 2 NH₂, -NH₂ NH₂, - ONH₂,
- NHC=(O)NH₂, - NH₂ (O)NH₂, -NH S0 2 H, -NH C= (O)H, -NH C(0)-OH, -NH OH,
unsubstituted alkyl (e.g., C$i$-C₈, C$i$-C₆, C$i$-C₄, or C$i$-C₃), 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). X²—he is independently -F, -Cl, -Br, or -I. In embodiments, R²—he is independently unsubstituted methyl. In embodiments, R²—he is independently unsubstituted ethyl.

R²—he is independently hydrogen, -CX⁻¹⁻¹(3), -CHX⁻¹⁻¹(2), -CH₂X⁻¹⁻¹(2), -CN, -COOH, -CONH₂, R⁻¹-D-substituted or unsubstituted alkyl (e.g., C$i$-C₈, C$i$-C₆, C$i$-C₄, or C$i$-C₃), R⁻¹-D-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⁻¹-D-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R⁻¹-D-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R⁻¹-D-substituted or
unsubstituted aryl (e.g., C$_6$-C$_{12}$, C$_6$-C$_{10}$, or phenyl), or R$^{20D}$-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$^{1D}$ is independently hydrogen, -CX$^{1D}$, -CHX$^{1D}$, -CH$_2$X$^{1D}$, -CN, -COOH, -CONH$_2$, unsubstituted alkyl (e.g., C$_8$-C$_{10}$, C$_1$-C$_4$, or C$1$-C$2$), unsubstituted heteroaryl (e.g., 5 to 6 membered), unsubstituted aryl (e.g., C$_6$-C$_{10}$, C$_6$-C$_{10}$, or phenyl), or unsubstituted heteroaryl (e.g., C$_8$-C$_{10}$, C$_1$-C$_4$, or C$1$-C$2$), unsubstituted heteroaryl (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$_{10}$, C$_6$-C$_{10}$, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X$^{1D}$ is independently -F, -Cl, -Br, or -I. In embodiments, R$^{1D}$ is independently unsubstituted methyl. In embodiments, R$^{1D}$ is independently unsubstituted ethyl.

[0175] R$^{20D}$ is independently oxo,

halogen, -CX$^{20D}$, -CHX$^{20D}$, -CH$_2$X$^{20D}$, -OCX$^{20D}$, -OCH$_2$X$^{20D}$, -OCHX$^{20D}$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -NO$_2$, -SH, -SO$_2$H, -SO$_2$NH$_2$, -ONH$_2$, -NHC=(0)NH$_2$ -NHC=(0)NH$_2$, -NHSO$_2$H, -NHC=O, -NHC(0)-OH, -NHOH, R$^{21D}$-substituted or unsubstituted alkyl (e.g., C$_1$-C$_8$, C$_1$-C$_4$, or C$1$-C$2$), R$^{21D}$-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$^{21D}$-substituted or unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_3$-C$_6$, C$_4$-C$_6$, or C$5$-C$6$), R$^{21D}$-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$^{21D}$-substituted or unsubstituted aryl (e.g., C$_6$-C$_{10}$, C$_6$-C$_{10}$, or phenyl), or R$^{21D}$-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$^{20D}$ is independently oxo,

halogen, -CX$^{20D}$, -CHX$^{20D}$, -CH$_2$X$^{20D}$, -OCX$^{20D}$, -OCH$_2$X$^{20D}$, -OCHX$^{20D}$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -NO$_2$, -SH, -SO$_2$H, -SO$_2$NH$_2$, -ONH$_2$, -NHC=(0)NH$_2$ -NHC=(0)NH$_2$, -NHSO$_2$H, -NHC=O, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g., C$_1$-C$_8$, 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$_{10}$, C$_6$-C$_{10}$, or phenyl), or unsubstituted heteroaryl
(e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). \(X^{20D}\) is independently -F, -Cl, -Br, or -I. In embodiments, \(R^{20D}\) is independently unsubstituted methyl. In embodiments, \(R^{20D}\) is independently unsubstituted ethyl.

[0176] \(R^{21D}\) is independently oxo,

5 halogen, \(-CX^{21D}\), \(-CHX^{21D}\), \(-CH\_2\_X^{21D}\), \(-OCX^{21D}\), \(-OCH\_2\_X^{21D}\), \(-OCHX^{21D}\), \(-CN\), \(-OH\), \(-NH\_2\), \(-COOH\), \(-CONH\_2\), \(-NO\_2\), \(-SH\), \(-SO\_3\_H\), \(-SO\_4\_H\), \(-SO\_2\_NH\_2\), \(-NH\_2\), \(-NHC=(O)\_NH\_2\), \(-NHC=(0)\_NH\_2\), \(-NHSO\_2\_H\), \(-NHC=(O)\_H\), \(-NHC(0)-OH\), \(-NH\_OH\), \(R^{22D}\)-substituted or unsubstituted alkyl (e.g., \(C\_5-C\_8\), \(C\_3-C\_6\), or \(C\_5-C\_6\)), \(R^{22D}\)-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), \(R^{22D}\)-substituted or unsubstituted aryl (e.g., \(C\_6-C\_12\), \(C\_6-Cio\), or phenyl), or \(R^{22D}\)-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, \(R^{21D}\) is independently oxo,

10 halogen, \(-CX^{21D}\), \(-CHX^{21D}\), \(-CH\_2\_X^{21D}\), \(-OCX^{21D}\), \(-OCH\_2\_X^{21D}\), \(-OCHX^{21D}\), \(-CN\), \(-OH\), \(-NH\_2\), \(-COOH\), \(-CONH\_2\), \(-NO\_2\), \(-SH\), \(-SO\_3\_H\), \(-SO\_4\_H\), \(-SO\_2\_NH\_2\), \(-NH\_2\), \(-NHC=(0)\_NH\_2\), \(-NHC=(0)\_NH\_2\), \(-NHSO\_2\_H\), \(-NHC=(O)\_H\), \(-NHC(0)-OH\), \(-NH\_OH\), unsubstituted alkyl (e.g., \(C\_5-C\_8\), \(C\_3-C\_6\), \(C\_5-C\_6\), \(C\_1-C\_4\), 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., \(C\_5-C\_8\), \(C\_3-C\_6\), or \(C\_5-C\_6\)), unsubstituted heterocycloalkyl (e.g., \(C\_3-C\_8\), \(C\_5-C\_6\), \(C\_4-C\_5\), or \(C\_5-C\_6\)), unsubstituted heteroaryl (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., \(C\_6-C\_12\), \(C\_6-Cio\), or phenyl), or unsubstituted heteroaryl (e.g., \(5\) to \(12\) membered, \(5\) to \(10\) membered, \(5\) to \(9\) membered, or \(5\) to \(6\) membered). \(X^{21D}\) is independently oxo, -F, -Cl, -Br, or -I. In embodiments, \(R^{21D}\) is independently unsubstituted methyl. In embodiments, \(R^{21D}\) is independently unsubstituted ethyl.

[0177] \(R^{22D}\) is independently oxo,

25 halogen, \(-CX^{22D}\), \(-CHX^{22D}\), \(-CH\_2\_X^{22D}\), \(-OCX^{22D}\), \(-OCH\_2\_X^{22D}\), \(-OCHX^{22D}\), \(-CN\), \(-OH\), \(-NH\_2\), \(-COOH\), \(-CONH\_2\), \(-NO\_2\), \(-SH\), \(-SO\_3\_H\), \(-SO\_4\_H\), \(-SO\_2\_NH\_2\), \(-NH\_2\), \(-NHC=(0)\_NH\_2\), \(-NHC=(0)\_NH\_2\), \(-NHSO\_2\_H\), \(-NHC=(O)\_H\), \(-NHC(0)-OH\), \(-NH\_OH\), unsubstituted alkyl (e.g., \(C\_5-C\_8\), \(C\_3-C\_6\), \(C\_5-C\_6\), \(C\_1-C\_4\), or \(C\_1-C\_2\)), unsubstituted heteroalkyl (e.g., \(2\) to \(8\) membered, \(2\) to \(6\) membered, \(4\) to \(6\) membered, \(2\) to \(3\) membered, or \(4\) to \(5\) membered),
unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵²D is independently -F, -Cl, -Br, or -I. In embodiments, R⁵²D is independently unsubstituted methyl. In embodiments, R⁵²D is independently unsubstituted ethyl.

[0178] 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. In embodiments, z₁ is 0, 1, or 2.

[0179] In embodiments, L₁ is a bond, substituted or unsubstituted C₁-C₈ alkylene, substituted or unsubstituted 2 to 8 membered heteroalkylene, substituted or unsubstituted C₃-C₈ cycloalkylene, substituted or unsubstituted 3 to 8 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene. In embodiments, L₁ is a bond.

[0180] In embodiments, L₁ is a bond. In embodiments, L₁ is -S(0)₂⁻. In embodiments, L₁ is -NR₄⁻. In embodiments, L₁ is -O⁻. In embodiments, L₁ is -S⁻. In embodiments, L₁ is -C(O)⁻. In embodiments, L₁ is -C(0)NR₄⁻. In embodiments, L₁ is -NR₄C(0)⁻. In embodiments, L₁ is -NR₄C(0)NH⁻. In embodiments, L₁ is -NH₄C(0)NR₄⁻. In embodiments, L₁ is -NH₄C(0)NH⁻. In embodiments, L₁ is -OC(O)⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻. In embodiments, L₁ is -CH₂⁻.
or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0182] In embodiments, \( L^1 \) is independently substituted or unsubstituted alkyylene (e.g., \( \text{C}_1-\text{C}_8 \), \( \text{C}_1-\text{C}_9 \), \( \text{C}_1-\text{C}_4 \), or \( \text{C}_1-\text{C}_2 \)). In embodiments, \( L^1 \) is independently substituted alkyylene (e.g., \( \text{C}_1-\text{C}_8 \), \( \text{C}_1-\text{C}_9 \), \( \text{C}_1-\text{C}_4 \), or \( \text{C}_1-\text{C}_2 \)). In embodiments, \( L^1 \) is independently unsubstituted alkyylene (e.g., \( \text{C}_1-\text{C}_8 \), \( \text{C}_1-\text{C}_9 \), \( \text{C}_1-\text{C}_4 \), or \( \text{C}_1-\text{C}_2 \)). In embodiments, \( L^1 \) is independently unsubstituted methylene. In embodiments, \( L^1 \) is independently unsubstituted ethylene. In embodiments, \( L^1 \) is independently unsubstituted propylene. In embodiments, \( L^1 \) is independently unsubstituted isopropylene. In embodiments, \( L^1 \) is independently unsubstituted tert-butylene. In embodiments, \( L^1 \) is independently 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). In embodiments, \( L^1 \) is independently substituted heteroalkylene (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, \( L^1 \) is independently 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). In embodiments, \( L^1 \) is independently substituted or unsubstituted cycloalkylene (e.g., \( \text{C}_3-\text{C}_8 \), \( \text{C}_3-\text{C}_9 \), \( \text{C}_4-\text{C}_6 \), or \( \text{C}_5-\text{C}_6 \)). In embodiments, \( L^1 \) is independently substituted cycloalkylene (e.g., \( \text{C}_3-\text{C}_8 \), \( \text{C}_3-\text{C}_9 \), \( \text{C}_4-\text{C}_6 \), or \( \text{C}_5-\text{C}_6 \)). In embodiments, \( L^1 \) is independently unsubstituted cycloalkylene (e.g., \( \text{C}_3-\text{C}_8 \), \( \text{C}_3-\text{C}_9 \), \( \text{C}_4-\text{C}_6 \), or \( \text{C}_5-\text{C}_6 \)). In embodiments, \( L^1 \) is independently 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). In embodiments, \( L^1 \) is independently substituted heterocycloalkylene (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, \( L^1 \) is independently 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). In embodiments, \( L^1 \) is independently substituted or unsubstituted arylene (e.g., \( \text{C}_6-\text{C}_{10} \) or phenylene). In embodiments, \( L^1 \) is independently substituted arylene (e.g., \( \text{C}_6-\text{C}_{10} \) or phenylene). In embodiments, \( L^1 \) is independently unsubstituted arylene (e.g., \( \text{C}_6-\text{C}_{10} \) or phenylene). In embodiments, \( L^1 \) is independently substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( L^1 \) is independently substituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( L^1 \) is independently unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
In embodiments, $L^1$ is independently bond, $-\text{S}(0)_2^-$, $-\text{N}(R^3)^-$, $-\text{O}_-$, $-\text{C}(O)_-$, $-\text{C}(O)\text{N}(R^4)^{-}$, $-\text{N}(R^4)^{-}\text{C}(O)^{-}$, $-\text{N}(R^4)^{-}\text{C}(O)\text{NH}_-$, $-\text{NHC}(O)\text{N}(R^4)^{-}$, $-\text{C}(O)^{\text{-OC}(O)^{-}}$, $R^{35}$-substituted or unsubstituted alkylene (e.g., $\text{C}_8^\text{-C}_8$, $\text{C}_6^\text{-C}_6$, $\text{C}_1^\text{-C}_4$, or $\text{C}_1^\text{-C}_2$), $R^{35}$-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, or 4 to 5 membered), $R^{35}$-substituted or unsubstituted cycloalkylene (e.g., $\text{C}_3^\text{-C}_8$, $\text{C}_3^\text{-C}_6$, $\text{C}_4^\text{-C}_6$, or $\text{C}_5^\text{-C}_6$), $R^{35}$-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), $R^{35}$-substituted or unsubstituted areylene (e.g., $\text{C}_6^\text{-C}_1$ or phenylene), or $R^{35}$-substituted or unsubstituted heteroareylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $L^1$ is independently bond, $-\text{S}(0)_2^-$, $-\text{N}(R^3)^-$, $-\text{O}_-$, $-\text{C}(O)_-$, $-\text{C}(O)\text{N}(R^4)^{-}$, $-\text{N}(R^4)^{-}\text{C}(O)^{-}$, $-\text{N}(R^4)^{-}\text{C}(O)\text{NH}_-$, $-\text{NHC}(O)\text{N}(R^4)^{-}$, $-\text{C}(O)^{\text{-OC}(O)^{-}}$, $R^{35}$-substituted or unsubstituted alkylene (e.g., $\text{C}_8^\text{-C}_8$, $\text{C}_6^\text{-C}_6$, $\text{C}_1^\text{-C}_4$, or $\text{C}_1^\text{-C}_2$), 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), unsubstituted cycloalkylene (e.g., $\text{C}_3^\text{-C}_8$, $\text{C}_3^\text{-C}_6$, $\text{C}_4^\text{-C}_6$, or $\text{C}_5^\text{-C}_6$), 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), unsubstituted areylene (e.g., $\text{C}_6^\text{-C}_1$ or phenylene), or unsubstituted heteroareylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $L^1$ is independently unsubstituted methylene. In embodiments, $L^1$ is independently unsubstituted ethylene. In embodiments, $L^1$ is independently methyl-substituted methylene.

In embodiments, $L^1$ is independently $-\text{NH}_-$, In embodiments, $L^1$ is independently $-\text{CH}_2\text{-NH}_-$, In embodiments, $L^1$ is independently $-\text{OCH}_2\text{CH}_2\text{NH}_-$, In embodiments, $L^1$ is independently $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_-$, In embodiments, $L^1$ is independently $-\text{NHC}(O)\text{N}(R^4)^{-}$, $-\text{C}(O)^{\text{-OC}(O)^{-}}$, $R^{35}$-substituted or unsubstituted methylene. In embodiments, $L^1$ is independently $-\text{NH}_-$, In embodiments, $L^1$ is independently $-\text{CH}_2\text{-NH}_-$, In embodiments, $L^1$ is independently $-\text{OCH}_2\text{CH}_2\text{NH}_-$, In embodiments, $L^1$ is independently $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_-$.
[0185] R\textsuperscript{35} is independently oxo,
halogen, -\textit{CX}\textsubscript{3}\textsuperscript{5}, -\textit{CHX}\textsubscript{3}\textsuperscript{5}, -\textit{CH}_{2}\textsubscript{X}\textsuperscript{35}, -\textit{OCX}\textsubscript{3}\textsuperscript{5}, -\textit{OCH}_{2}\textsubscript{X}\textsuperscript{35}, -\textit{OCHX}\textsubscript{3}\textsuperscript{5}, -\textit{CN}, -\textit{OH}, -\textit{NH}_{2}, -\textit{COOH}, -\textit{CONH}\textsubscript{2}, -\textit{N}=\textit{O}, -\textit{SH}, -\textit{S=O}, -\textit{NH}_{2}, -\textit{SO}_{4}, -\textit{ONH}_{2}, -\textit{NHC}=(\textit{O}), -\textit{NHOH}, \textit{R}\textsuperscript{36}-substituted or unsubstituted alkyl (e.g., \textit{Ci}-\textit{C}_{8}, \textit{Ci}-\textit{C}_{6}, \textit{Ci}-\textit{C}_{4}, or \textit{Ci}-\textit{C}_{3}), R\textsuperscript{36}-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\textsuperscript{36}-substituted or unsubstituted cycloalkyl (e.g., \textit{C}_{3}-\textit{C}_{8}, \textit{C}_{3}-\textit{C}_{6}, \textit{C}_{4}-\textit{C}_{6}, or \textit{C}_{5}-\textit{C}_{6}), R\textsuperscript{36}-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\textsuperscript{36}-substituted or unsubstituted aryl (e.g., \textit{C}_{6}-\textit{C}_{10} or \textit{phenyl}), or R\textsuperscript{36}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{35} is independently oxo,
halogen, -\textit{CX}\textsubscript{3}\textsuperscript{5}, -\textit{CHX}\textsubscript{3}\textsuperscript{5}, -\textit{CH}_{2}\textsubscript{X}\textsuperscript{35}, -\textit{OCX}\textsubscript{3}\textsuperscript{5}, -\textit{OCH}_{2}\textsubscript{X}\textsuperscript{35}, -\textit{OCHX}\textsubscript{3}\textsuperscript{5}, -\textit{CN}, -\textit{OH}, -\textit{NH}_{2}, -\textit{COOH}, -\textit{CONH}\textsubscript{2}, -\textit{N}=\textit{O}, -\textit{SH}, -\textit{S=O}, -\textit{NH}_{2}, -\textit{SO}_{4}, -\textit{ONH}_{2}, -\textit{NHC}=(\textit{O}), -\textit{NHOH}, unsubstituted alkyl (e.g., \textit{Ci}-\textit{C}_{8}, \textit{Ci}-\textit{C}_{6}, \textit{Ci}-\textit{C}_{4}, or \textit{Ci}-\textit{C}_{3}), 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., \textit{C}_{3}-\textit{C}_{8}, \textit{C}_{3}-\textit{C}_{6}, \textit{C}_{4}-\textit{C}_{6}, or \textit{C}_{5}-\textit{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., \textit{C}_{6}-\textit{C}_{10} or \textit{phenyl}), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X\textsuperscript{35} is independently -\textit{F}, -\textit{Cl}, -\textit{Br}, or -\textit{I}.

In embodiments, R\textsuperscript{35} is independently unsubstituted methyl. In embodiments, R\textsuperscript{35} is independently unsubstituted ethyl. In embodiments, R\textsuperscript{35} is independently unsubstituted phenyl.

[0186] R\textsuperscript{36} is independently oxo,
halogen, -\textit{CX}\textsubscript{3}\textsuperscript{6}, -\textit{CHX}\textsubscript{3}\textsuperscript{6}, -\textit{CH}_{2}\textsubscript{X}\textsuperscript{36}, -\textit{OCX}\textsubscript{3}\textsuperscript{6}, -\textit{OCH}_{2}\textsubscript{X}\textsuperscript{36}, -\textit{OCHX}\textsubscript{3}\textsuperscript{6}, -\textit{CN}, -\textit{OH}, -\textit{NH}_{2}, -\textit{COOH}, -\textit{CONH}\textsubscript{2}, -\textit{N}=\textit{O}, -\textit{SH}, -\textit{S=O}, -\textit{NH}_{2}, -\textit{SO}_{4}, -\textit{ONH}_{2}, -\textit{NHC}=(\textit{O}), -\textit{NHOH}, R\textsuperscript{37}-substituted or unsubstituted alkyl (e.g., \textit{Ci}-\textit{C}_{8}, \textit{Ci}-\textit{C}_{6}, \textit{Ci}-\textit{C}_{4}, or \textit{Ci}-\textit{C}_{3}), R\textsuperscript{37}-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\textsuperscript{37}-substituted or unsubstituted cycloalkyl (e.g., \textit{C}_{3}-\textit{C}_{8}, \textit{C}_{3}-\textit{C}_{6}, \textit{C}_{4}-\textit{C}_{6}, or \textit{C}_{5}-\textit{C}_{6}), R\textsuperscript{37}-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\textsuperscript{37}-substituted or
unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or R³⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R³⁶ is independently oxo,
halogen, -CX³⁶₋₃, -CHX³⁶₋₂, -CH₂X³⁶, -OCX³⁶₋₃, -OCH₂X³⁶, -OCHX³⁶₋₂, -CN, -OH, -NH₂, -COO
H, -CONH₂, -N₃, -SH, -S₀₋₃H, -SO₂₋₄H₂, -NHNH₂₋₁, -ONH₂₋₁, -NH₂=)(O)NHNH₂₋₁,
-NHC=)(0)NHNH₂₋₁, -NHSO₂₋₄H₂, -NHC=)(0)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g.,
C₆-C₈, C₅-C₆, C₄-C₄, or C₅-C₆), 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, C₅-C₆, C₆-C₇, 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). X³⁶ is independently -F, -Cl, -Br, or -I.
In embodiments, R³⁶ is independently unsubstituted methyl. In embodiments, R³⁶ is independently unsubstituted ethyl.

[0187] R³⁷ is independently oxo,
halogen, -CX³⁷₋₃, -CHX³⁷₋₂, -CH₂X³⁷, -OCX³⁷₋₃, -OCH₂X³⁷, -OCHX³⁷₋₂, -CN, -OH, -NH₂, -COO
H, -CONH₂, -N₃, -SH, -S₀₋₃H, -SO₂₋₄H₂, -NHNH₂₋₁, -ONH₂₋₁, -NH₂=)(O)NHNH₂₋₁,
-NHC=)(0)NHNH₂₋₁, -NHSO₂₋₄H₂, -NHC=)(0)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g.,
C₆-C₈, C₅-C₆, C₄-C₄, or C₅-C₆), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₅-C₆, C₆-C₇, 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). X³⁷ is independently -F, -Cl, -Br, or -I.
In embodiments, R³⁷ is independently unsubstituted methyl. In embodiments, R³⁷ is independently unsubstituted ethyl.

[0188] In embodiments, R⁴ is independently hydrogen, -CX⁴₋₃, -CHX⁴₋₂, -CH₂X⁴, -OCX⁴₋₃, -OCH₂X⁴, -OCHX⁴₋₂, -CN, -C(0)R⁴₈, -C(0)OR⁴₈, -C(0)NR⁴₉₋₄₈, -OR⁴₉₋₄₈, substituted or unsubstituted alkyl (e.g., C₆-C₈, C₅-C₆, C₄-C₄, or C₅-C₆), 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., C₅-C₈, C₅-C₆, C₆-C₇, 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., 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).

[0189] In embodiments, R^4 is independently hydrogen. In embodiments, R^4 is
independently -CX_4, in embryos R^4 is independently -CHX_2. In embodiments, R^4 is
independently -CH_2X. In embodiments, R^4 is independently -CN. In embodiments, R^4 is
independently -C(O)R^4. In embodiments, R^4 is independently -C(O)OR^4. In embryos, R^4 is
independently -COOH. In embodiments, R^4 is independently -CONH_2. In embodiments, R^4
is independently -CF_3. In embryos, R^4 is independently -CHF. In embryos, R^4 is
independently -CH_2F. In embryos, R^4 is independently -CH_3. In embryos, R^4 is
independently -CH_2CH_3. In embryos, R^4 is independently -CH_2CH_2CH_3. In
embodies, R^4 is independently -CH(CH_3)_2. In embryos, R^4 is independently -
C(CH_3)_3.

[0190] In embryos, R^4 is independently substituted or unsubstituted alkyl (e.g., Ci-C_8,
Ci-C_6, C_1-C_4, or Ci-C_2). In embryos, R^4 is independently substituted alkyl (e.g., Ci-C_8,
Ci-C_6, C_1-C_4, or Ci-C_2). In embryos, R^4 is independently unsubstituted alkyl (e.g., Ci-
C_8, Ci-C_6, C_1-C_4, or Ci-C_2). In embryos, R^4 is independently unsubstituted methyl. In
embodies, R^4 is independently unsubstituted ethyl. In embryos, R^4 is independently
unsubstituted propyl. In embryos, R^4 is independently unsubstituted isopropyl. In
embodies, R^4 is independently unsubstituted tert-butyl. In embryos, R^4 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 embryos, R^4 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 embryos, R^4 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 embryos, R^4 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 embryos, R^4 is
independently substituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6). In embryos,
R^4 is independently unsubstituted cycloalkyl (e.g., C_3-C_8, C_3-C_6, C_4-C_6, or C_5-C_6). In
embodies, R^4 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
embodies, R^4 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, R4 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, R4 is independently substituted or unsubstituted aryl (e.g., C6H1 or phenyl). In embodiments, R4 is independently substituted aryl (e.g., C6H1 or phenyl). In embodiments, R4 is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R4 is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R4 is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0191] In embodiments, R4A is independently hydrogen. In embodiments, R4A is independently -CX4A3. In embodiments, R4A is independently -CHX4A2. In embodiments, R4A is independently -CH2X4A. In embodiments, R4A is independently -CN. In embodiments, R4A is independently -COOH. In embodiments, R4A is independently -CONH2. In embodiments, X4A is independently -F, -Cl, -Br, or -I.

[0192] In embodiments, R4A is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R4A is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R4A is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R4A is independently unsubstituted methyl. In embodiments, R4A is independently unsubstituted ethyl. In embodiments, R4A is independently unsubstituted propyl. In embodiments, R4A is independently unsubstituted isopropyl. In embodiments, R4A is independently unsubstituted tert-butyl. In embodiments, R4A 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, R4A 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, R4A is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-G5, or C5-G0). In embodiments, R4A is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R4A is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R4A 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

80
In embodiments, R\textsuperscript{4A} 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\textsuperscript{4A} 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\textsuperscript{4A} is independently substituted or unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{io} or phenyl). In embodiments, R\textsuperscript{4A} is independently substituted aryl (e.g., C\textsubscript{6}-C\textsubscript{io} or phenyl). In embodiments, R\textsuperscript{4A} is independently unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{io} or phenyl). In embodiments, R\textsuperscript{4A} is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{4A} is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0193] In embodiments, R\textsuperscript{4B} is independently hydrogen. In embodiments, R\textsuperscript{4B} is independently -CX\textsuperscript{4B}\textsubscript{3}. In embodiments, R\textsuperscript{4B} is independently -CHX\textsuperscript{4B}\textsubscript{2}. In embodiments, R\textsuperscript{4B} is independently -CF\textsubscript{4}X\textsuperscript{4B}. In embodiments, R\textsuperscript{4B} is independently -CN. In embodiments, R\textsuperscript{4B} is independently -COOH. In embodiments, R\textsuperscript{4B} is independently -CONH\textsubscript{2}. In embodiments, X\textsuperscript{4B} is independently -F, -Cl, -Br, or -I.

[0194] In embodiments, R\textsuperscript{4B} is independently substituted or unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, C1-C4, or C1-C2). In embodiments, R\textsuperscript{4B} is independently substituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, C1-C4, or C1-C2). In embodiments, R\textsuperscript{4B} is independently unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, C1-C4, or C1-C2). In embodiments, R\textsuperscript{4B} is independently unsubstituted methyl. In embodiments, R\textsuperscript{4B} is independently unsubstituted ethyl. In embodiments, R\textsuperscript{4B} is independently unsubstituted propyl. In embodiments, R\textsuperscript{4B} is independently unsubstituted isopropyl. In embodiments, R\textsuperscript{4B} is independently unsubstituted tert-butyl. In embodiments, R\textsuperscript{4B} 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\textsuperscript{4B} 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\textsuperscript{4B} 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\textsuperscript{4B} is independently substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C4-G5, or C5-C\textsubscript{6}). In embodiments, R\textsuperscript{4B} is independently substituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C4-C6, or C5-C\textsubscript{6}). In embodiments, R\textsuperscript{4B} is independently unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C4-C6, or C5-G5).
embodyments, \( R^{4B} \) 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, \( R^{4B} \) 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, \( R^{4B} \) 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, \( R^{4B} \) is independently unsubstituted aryl (e.g., \( C_6 \)-Cio or phenyl). In embodiments, \( R^{4B} \) is independently substituted aryl (e.g., \( C_6 \)-Cio or phenyl). In embodiments, \( R^{4B} \) is independently unsubstituted aryl (e.g., \( C_6 \)-Cio or phenyl). In embodiments, \( R^{4B} \) is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( R^{4B} \) is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0195] In embodiments, \( R^{4A} \) and \( R^{4B} \) substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, \( R^{4A} \) and \( R^{4B} \) 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, \( R^{4A} \) and \( R^{4B} \) 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).

[0196] In embodiments, \( R^{4A} \) and \( R^{4B} \) 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, \( R^{4A} \) and \( R^{4B} \) 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, \( R^{4A} \) and \( R^{4B} \) 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).

[0197] In embodiments, \( R^4 \) is independently hydrogen, \(-\text{CX}^4_3\), \(-\text{CHX}^4_2\), \(-\text{CH}_2\text{X}^4\), \(-\text{CN}\), \(-\text{COOH}\), \(-\text{CO}_2\text{NH}_2\), \(R^{29}\)-substituted or unsubstituted alkyl (e.g., \(\text{Ci-C}_8\), \(\text{Ci-C}_6\), \(\text{Cl-C}_4\), or \(\text{Ci-C}_2\)), \(R^{29}\)-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), R⁴ substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R⁴ 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), R⁴ substituted or unsubstituted aryl (e.g., C₆-C₉ or phenyl), or R⁴ substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R⁴ is independently hydrogen, -CX³, -CHX², -CH₂X, -OCX², -OCH₂X, -OCHX², -CN, -OH, -NH₂, -COOH, -CONH₂, -N₂, -SH, -S⁻H, -SO₄H, -S⁻NH₂, -N₂H₂, -ONH₂, -NHC=(0)NH, -NHC=(0)NHNH₂, -NHC=(0)NH, -NHSO₂H, -NHC= (0)H, -NHC(0)-OH, -NHOH, R³⁰-substituted or unsubstituted alkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R³⁰-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), R³⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R³⁰-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), R³⁰-substituted or unsubstituted aryl (e.g., C₆-C₉ or phenyl), or R³⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁴ is independently -F, -Cl, -Br, or -I. In embodiments, R⁴ is independently hydrogen. In embodiments, R⁴ is independently unsubstituted methyl. In embodiments, R⁴ is independently unsubstituted ethyl.

[0198] R⁹ is independently oxo, halogen, -CX³, -CHX², -CH₂X, -OCX², -OCH₂X, -OCHX², -CN, -OH, -NH₂, -COOH, -CONH₂, -N₂, -SH, -S⁻H, -SO₄H, -S⁻NH₂, -N₂H₂, -ONH₂, -NHC=(0)NH, -NHC=(0)NHNH₂, -NHC=(0)NH, -NHSO₂H, -NHC= (0)H, -NHC(0)-OH, -NHOH, R³⁰-substituted or unsubstituted alkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R³⁰-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), R³⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R³⁰-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), R³⁰-substituted or unsubstituted aryl (e.g., C₆-C₉ or phenyl), or R³⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R⁹ is independently oxo, halogen, -CX³, -CHX², -CH₂X, -OCX², -OCH₂X, -OCHX², -CN, -OH, -NH₂, -COOH, -CONH₂, -N₂, -SH, -S⁻H, -SO₄H, -S⁻NH₂, -N₂H₂, -ONH₂, -NHC=(0)NH, -NHC=(0)NHNH₂, -NHC=(0)NH, -NHSO₂H, -NHC= (0)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆H₅ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X₉ is independently -F, -CI, -Br, or -I. In embodiments, R₂₉ is independently unsubstituted methyl. In embodiments, R₂₉ is independently unsubstituted ethyl.

[0199] R₃₀ is independently oxo, halogen, -CX₃₋₄, -CHX₃₋₂, -CH₂X₋₂, -OCX₃₋₄, -OCH₂X₋₂, -OCHX₃₋₂, -CN, -OH, -NH₂, -COO H, -CONH₂, -NO₂, -SH, -S𝑂₂H, -S𝑂₃H, -NH₂, -NHSO₂H, -ONH₂, -NHC=(O)NH₂, -NHC=NH₂, -NHSO₂H, -ONH₂, -NHC=(0)NHNH₂, -NHC=(0)NHSO₂H, -NHC=(0)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(0)-OH, -NHOH, R₃₁-substituted or unsubstituted alkyl (e.g., C₆H₅, C₆H₄, C₆H₃, or C₆H₂), R₃₁-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), R₃₁-substituted or unsubstituted cycloalkyl (e.g., C₅H₅, C₅H₄, C₄H₄, or C₃H₃), R₃₁-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), R₃₁-substituted or unsubstituted aryl (e.g., C₆H₅ or phenyl), or R₃₁-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R₃₀ is independently oxo, halogen, -CX₃₋₄, -CHX₃₋₂, -CH₂X₋₂, -OCX₃₋₄, -OCH₂X₋₂, -OCHX₃₋₂, -CN, -OH, -NH₂, -COO H, -CONH₂, -NO₂, -SH, -S𝑂₂H, -S𝑂₃H, -NH₂, -NHSO₂H, -ONH₂, -NHC=(O)NH₂, -NHC=NH₂, -NHSO₂H, -ONH₂, -NHC=(0)NHNH₂, -NHC=(0)NHSO₂H, -NHC=(0)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g., C₆H₅, C₆H₄, C₆H₃, or C₆H₂), 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., C₅H₅, C₅H₄, C₄H₄, or C₃H₃), 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., C₆H₅ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X₉ is independently -F, -CI, -Br, or -I. In embodiments, R₃₀ is independently unsubstituted methyl. In embodiments, R₃₀ is independently unsubstituted ethyl.

[0200] R₃₁ is independently oxo, halogen, -CX₃₋₄, -CHX₃₋₂, -CH₂X₋₂, -OCX₃₋₄, -OCH₂X₋₂, -OCHX₃₋₂, -CN, -OH, -NH₂, -COO H, -CONH₂, -NO₂, -SH, -S𝑂₂H, -S𝑂₃H, -NH₂, -NHSO₂H, -ONH₂, -NHC=(0)NHNH₂, -NHC=(0)NHSO₂H, -NHC=(0)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g.,
Ci-C₈, Ci-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., C₅-C₈, C₅-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). X₁ is independently -F, -Cl, -Br, or -I.

In embodiments, R¹ is independently unsubstituted methyl. In embodiments, R¹ is independently unsubstituted ethyl.

[0201] In embodiments, R⁴A is independently hydrogen, -CX⁴A₁, -CHX⁴A₁, -CH₂X⁴A₁, -CN, -COOH, -CONH₂, R²⁹A-substituted or unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, C₁-C₄, or C₁-C₂), R²⁹A-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), R²⁹A-substituted or unsubstituted cycloalkyl (e.g., C₅-C₈, C₅-C₆, C₄-C₆, or C₅-C₆). R²⁹A-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), 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). In embodiments, R⁴A is independently hydrogen, -CX⁴A₁, -CHX⁴A₁, -CH₂X⁴A₁, -CN, -COOH, -CONH₂, unsubstituted alkyl (e.g., Ci-C₈, Ci-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., C₅-C₈, C₅-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). X is independently -F, -Cl, -Br, or -I.

In embodiments, R⁴A is independently unsubstituted methyl. In embodiments, R⁴A is independently unsubstituted ethyl.

[0202] In embodiments, R⁴A and R⁴B substituents bonded to the same nitrogen atom may optionally be joined to form a R²⁹A-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or R²⁹A-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R⁴A and R⁴B substituents bonded to the same nitrogen atom may optionally 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) or unsubstituted
heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, 
R\textsuperscript{4A} and R\textsuperscript{4B} substituents bonded to the same nitrogen atom may optionally be joined to form 
a R\textsuperscript{29A}-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\textsuperscript{4A} and R\textsuperscript{4B} 
substituents bonded to the same nitrogen atom may optionally 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).

\[0203\] R\textsuperscript{29A} is independently oxo,

halogen, -CX\textsuperscript{29A}\textsubscript{3}, -CHX\textsuperscript{29A}\textsubscript{2}, -CH\textsubscript{2}X\textsuperscript{29A}, -OCX\textsuperscript{29A}\textsubscript{3}, -OCH\textsubscript{2}X\textsuperscript{29A}, -OCHX\textsuperscript{29A}\textsubscript{2}, -CN, -OH, -NH\textsubscript{2}, 
-COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{2}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, - ON\textsubscript{2}H, 
-NHC=(0)NHNNH\textsubscript{2}, - NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC= (0)H, -NHC(0)-OH, -NH\textsubscript{2}OH, 
R\textsuperscript{30A}-substituted or unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-Ce, C1-C4, or C1-C2), R\textsuperscript{30A}-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\textsuperscript{30A}-substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}C\textsubscript{6}, 
C\textsubscript{3}C\textsubscript{6}, C4-C6, or C5-C6), R\textsuperscript{30A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 
membered, 3 to 6 membered, 4 to 6 membered, or 5 to 6 membered), R\textsuperscript{30A}-substituted or unsubstituted aryl (e.g., C\textsubscript{6}C\textsubscript{6} or phenyl), or R\textsuperscript{30A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, 
R\textsuperscript{29A} is independently oxo,

halogen, -CX\textsuperscript{29A}\textsubscript{3}, -CHX\textsuperscript{29A}\textsubscript{2}, -CH\textsubscript{2}X\textsuperscript{29A}, -OCX\textsuperscript{29A}\textsubscript{3}, -OCH\textsubscript{2}X\textsuperscript{29A}, -OCHX\textsuperscript{29A}\textsubscript{2}, -CN, -OH, -NH\textsubscript{2}, 
-COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{2}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, - ON\textsubscript{2}H, 
-NHC=(0)NHNNH\textsubscript{2}, - NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC= (0)H, -NHC(0)-OH, -NH\textsubscript{2}OH, 
unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, 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., C\textsubscript{3}C\textsubscript{6}, C\textsubscript{3}C\textsubscript{6}, C4-G5, or C5-C\textsubscript{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\textsubscript{6}C\textsubscript{6} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 
10 membered, 5 to 9 membered, or 5 to 6 membered). X\textsuperscript{29A} is independently -F, -Cl, -Br, or 
-I. In embodiments, R\textsuperscript{29A} is independently unsubstituted methyl. In embodiments, R\textsuperscript{29A} is 
independently unsubstituted ethyl.

\[0204\] R\textsuperscript{30A} is independently oxo,

halogen, -CX\textsuperscript{30A}\textsubscript{3}, -CHX\textsuperscript{30A}\textsubscript{2}, -CH\textsubscript{2}X\textsuperscript{30A}, -OCX\textsuperscript{30A}\textsubscript{3}, -OCH\textsubscript{2}X\textsuperscript{30A}, -OCHX\textsuperscript{30A}\textsubscript{2}, -CN, -OH, -NH\textsubscript{2}
5, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NH2NH2, -ONH2, -NHC(=O)NH2, -NHC(=O)NH2, -NHSO2H, -NHC(=O)H, -NHC(=O)-OH, -NH2OH, R

31A-substituted or unsubstituted alkyl (e.g., C1-C8, C1-C4, or C1-C2), R

31A-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

31A-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6), R

31A-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

31A-substituted or unsubstituted aryl (e.g., C6-C10 or phenyl), or R

31A-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R

30A is independently unsubstituted methyl. In embodiments, R

30A is independently unsubstituted ethyl.

[0205] R

31A is independently oxo, halogen, -CX

30A, -CHX

30A, -CH2X

30A, -OCX

30A, -OCH2X

30A, -OCHX

30A, -CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NH2NH2, -ONH2, -NHC(=O)NH2, -NHC(=O)NH2, -NHSO2H, -NHC(=O)H, -NHC(=O)-OH, -NH2OH, unsubstituted alkyl (e.g., C1-C8, 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-C5, 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). X

30A is independently -F, -Cl, -Br, or -I. In embodiments, R

30A is independently unsubstituted methyl. In embodiments, R

30A is independently unsubstituted ethyl.
In embodiments, R is independently hydrogen, -CX\textsubscript{4B}, -CHX\textsubscript{4B}, -CH\textsubscript{2}X\textsubscript{4B}, -CN, -COOH, -CONH\textsubscript{2}, R\textsuperscript{29B}-substituted or unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, C1-C4, or Ci-C\textsubscript{2}), R\textsuperscript{29B}-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\textsuperscript{29B}-substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{7}-C\textsubscript{9}), R\textsuperscript{29B}-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\textsuperscript{29B}-substituted or unsubstituted aryl (e.g., C\textsubscript{6}-Ci or phenyl), or R\textsuperscript{29B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{4B} is independently hydrogen, -CX\textsubscript{4B}, -CHX\textsubscript{4B}, -CH\textsubscript{2}X\textsubscript{4B}, -CN, -COOH, -CONH\textsubscript{2}, unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, C1-C4, or Ci-C\textsubscript{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\textsubscript{3}-C\textsubscript{8}, C\textsubscript{4}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{9}), 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\textsubscript{6}-Ci or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X\textsuperscript{4B} is independently -F, -Cl, -Br, or -I.

In embodiments, R\textsuperscript{4B} is independently hydrogen. In embodiments, R\textsuperscript{4B} is independently unsubstituted methyl. In embodiments, R\textsuperscript{4B} is independently unsubstituted ethyl.

In embodiments, R\textsuperscript{4A} and R\textsuperscript{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{29B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or R\textsuperscript{29B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{4A} and R\textsuperscript{4B} substituents bonded to the same nitrogen atom may optionally be joined to form an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, or 5 to 6 membered) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{4A} and R\textsuperscript{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a R\textsuperscript{29B}-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\textsuperscript{4A} and R\textsuperscript{4B} substituents bonded to the same nitrogen atom may optionally 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).
[0208] R^{29B} is independently oxo, halogen, -CX^{29B}, -CHX^{29B}, -CH_{2}X^{29B}, -OCX^{29B}, -OCH_{2}X^{29B}, -OCHX^{29B}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -NO_{2}, -SH, -SO_{3}H, -SO_{4}H, -SO_{2}NH_{2}, -NH_{2}, -NHC=(O)NH_{2}, -NH_{2}, -NHC=(O)H, -NHC(OH), -NH_{2},

5 R^{30B}-substituted or unsubstituted alkyl (e.g., Ci-C_{8}, Ci-Ce, C1-C4, or C1-C2), R^{30B}-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^{30B}-substituted or unsubstituted cycloalkyl (e.g., C_{3}-C_{8}, C_{3}-C_{6}, C4-C6, or C5-C6), R^{30B}-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^{30B}-substituted or unsubstituted aryl (e.g., C_{6}-Cio or phenyl), or R^{30B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{29B} is independently oxo, halogen, -CX^{29B}, -CHX^{29B}, -CH_{2}X^{29B}, -OCX^{29B}, -OCH_{2}X^{29B}, -OCHX^{29B}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -NO_{2}, -SH, -SO_{3}H, -SO_{4}H, -SO_{2}NH_{2}, -NH_{2},

15 -NHC=(O)NH_{2}, -NHC=(O)NH_{2}, -NHC=(O)H, -NHC(OH), -NH_{2}, unsubstituted alkyl (e.g., Ci-C_{8}, Ci-C_{6}, 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., C_{3}-C_{8}, C_{3}-C_{6}, C4-G5, or C5-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}-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). \( X^{29B} \) is independently \( -F, -Cl, -Br, \) or \( -I. \) In embodiments, R^{29B} is independently unsubstituted methyl. In embodiments, R^{29B} is independently unsubstituted ethyl.

[0209] R^{30B} is independently oxo, halogen, -CX^{30B}, -CHX^{30B}, -CH_{2}X^{30B}, -OCX^{30B}, -OCH_{2}X^{30B}, -OCHX^{30B}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -NO_{2}, -SH, -SO_{3}H, -SO_{4}H, -SO_{2}NH_{2}, -NH_{2}, -NHC=(O)NH_{2}, -NHC=(O)NH_{2}, -NHC=(O)H, -NHC(OH), -NH_{2},

25 R^{31B}-substituted or unsubstituted alkyl (e.g., Ci-C_{8}, Ci-Ce, C1-C4, or C1-C2), R^{31B}-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^{31B}-substituted or unsubstituted cycloalkyl (e.g., C_{3}-C_{8}, C_{3}-C_{6}, C4-C6, or C5-C_{6}), R^{31B}-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^{31B}-substituted or unsubstituted aryl (e.g., C_{6}-Cio or phenyl), or R^{31B}-substituted or unsubstituted
heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{30B}$ is independently oxo,
halogen, -$\text{CX}^{30B}_3$, -$\text{CHX}^{30B}_2$, -$\text{CH}_2\text{X}^{30B}$, -$\text{OCX}^{30B}_3$, -$\text{OCH}_2\text{X}^{30B}$, -$\text{OCHX}^{30B}_2$, -CN, -OH, -$\text{NH}_2$, -COOH, -CONH$_2$, -N0$_2$, -SH, -S0$_3$H, -S0$_4$H, -S0$_2$NH$_2$, -NHNH$_2$, -ONH$_2$,
- $\text{NHC}=(0)\text{NHNH}_2$, - $\text{NHC}=(0)\text{NH}_2$, - $\text{NHSO}_2$H, - $\text{NHC}=\text{(O)H}$, - $\text{NHC}(0)-\text{OH}$, - $\text{NHOH}$,
unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or Ci-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-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^{30B}$ is independently -F, -Cl, -Br, or -I. In embodiments, $R^{30B}$ is independently unsubstituted methyl. In embodiments, $R^{30B}$ is independently unsubstituted ethyl.

$[0210]$ $R^{31B}$ is independently oxo,
halogen, -$\text{CX}^{31B}_3$, -$\text{CHX}^{31B}_2$, -$\text{CH}_2\text{X}^{31B}$, -$\text{OCX}^{31B}_3$, -$\text{OCH}_2\text{X}^{31B}$, -$\text{OCHX}^{31B}_2$, -CN, -OH, -$\text{NH}_2$, -COOH, -CONH$_2$, -N0$_2$, -SH, -S0$_3$H, -S0$_4$H, -S0$_2$NH$_2$, -NHNH$_2$, -ONH$_2$,
- $\text{NHC}=(0)\text{NHNH}_2$, - $\text{NHC}=(0)\text{NH}_2$, - $\text{NHSO}_2$H, - $\text{NHC}=\text{(O)H}$, - $\text{NHC}(0)-\text{OH}$, - $\text{NHOH}$,
unsubstituted alkyl (e.g., Ci-C8, Ci-C6, Ci-C4, or Ci-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, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C6-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^{31B}$ is independently -F, -Cl, -Br, or -I. In embodiments, $R^{31B}$ is independently unsubstituted methyl. In embodiments, $R^{31B}$ is independently unsubstituted ethyl.

$[0211]$ In embodiments, $L^2$ is -$\text{NR}^{5}$- or substituted or unsubstituted heterocycloalkyl e-ne including a ring nitrogen bonded directly to E. In embodiments, $L^2$ is -$\text{NR}^{5}$-.

$[0212]$ In embodiments, $L^2$ is a bond. In embodiments, $L^2$ is -$\text{S}(0)_{2}$-. In embodiments, $L^2$ is -$\text{NR}^{5}$-. In embodiments, $L^2$ is -$\text{O}$-. In embodiments, $L^2$ is -$\text{S}$-. In embodiments, $L^2$ is -$\text{C}(0)$-.. In embodiments, $L^2$ is -$\text{C}(0)\text{NR}^{5}$-. In embodiments, $L^2$ is -$\text{NR}^{5}\text{C}(0)$-. In embodiments, $L^2$ is -$\text{C}(0)\text{NH}$-. In embodiments, $L^2$ is -$\text{NHC}(0)\text{NR}^{5}$-. In embodiments, $L^2$ is -$\text{C}(0)\text{O}$-. In embodiments, $L^2$ is -$\text{OC}(0)$-. In embodiments, $L^2$ is -$\text{NH}$-.
embodiments, \( L^2 \) is -C(0)NH-. In embodiments, \( L^2 \) is -NHC(O)-. In embodiments, \( L^2 \) is -NHC(O)NH-. In embodiments, \( L^2 \) is -CH₂-. In embodiments, \( L^2 \) is -OCH₂-. In embodiments, \( L^2 \) is -CH₂O-. In embodiments, \( L^2 \) is -NHCH₂-. In embodiments, \( L^2 \) is -CH₂NH-.

[0213] In embodiments, \( L^2 \) is a bond, -S(0)₂-, -NR⁵-, -0-, -S-, -C(O)-, -C(0)NR⁵-, -NR⁵C(O)NH-, -NHC(O)NR⁵-, -C(0)0-, -OC(O)-, substituted or unsubstituted alkyne (e.g., C₈-C₈, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyne (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C₆-C₈ or phenyl), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0214] In embodiments, \( L^2 \) is independently substituted or unsubstituted alkyne (e.g., C₈-C₈, C₆-C₆, C₄-C₄, or C₂-C₂). In embodiments, \( L^2 \) is independently substituted alkyne (e.g., C₈-C₈, C₆-C₆, C₄-C₄, or C₂-C₂). In embodiments, \( L^2 \) is independently unsubstituted alkyne (e.g., C₈-C₈, C₆-C₆, C₄-C₄, or C₂-C₂). In embodiments, \( L^2 \) is independently unsubstituted methylene. In embodiments, \( L^2 \) is independently unsubstituted ethylene. In embodiments, \( L^2 \) is independently unsubstituted propylene. In embodiments, \( L^2 \) is independently unsubstituted isopropylene. In embodiments, \( L^2 \) is independently unsubstituted tert-butylene. In embodiments, \( L^2 \) is independently 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). In embodiments, \( L^2 \) is independently substituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 4 to 5 membered). In embodiments, \( L^2 \) is independently 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). In embodiments, \( L^2 \) is independently substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, \( L^2 \) is independently substituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, \( L^2 \) is independently unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆). In embodiments, \( L^2 \) is independently 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). In embodiments, \( L^2 \) is independently substituted
heterocycloalkylene (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, \( L^2 \) is independently 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). In embodiments, \( L^2 \) is independently substituted or unsubstituted arylene (e.g., \( C_6 \)-Cio or phenylene). In embodiments, \( L^2 \) is independently substituted arylene (e.g., \( C_6 \)-Cio or phenylene). In embodiments, \( L^2 \) is independently unsubstituted arylene (e.g., \( C_6 \)-Cio or phenylene). In embodiments, \( L^2 \) is independently substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( L^2 \) is independently substituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( L^2 \) is independently unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0215] In embodiments, \( L^2 \) is independently

bond, \(-S(0)\) \(_2\), \(-N(R^5)\), \(-O-\), \(-S-\), \(-C(O)-\), \(-C(0)N(R^5)\), \(-N(R^5)C(0)NH-\), \(-NH\) \(_2\), \(-NC(0)N(R^5)\) \(_2\), \(-C(0)O-\), \(-OC(0)-\), \( R^{38} \)-substituted or unsubstituted alkylene (e.g., \( C_8 \), \( C_6 \)), \( C_4 \)-Cio, or \( C_5 \)-Cio), \( R^{38} \)-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), \( R^{38} \)-substituted or unsubstituted cycloalkylene (e.g., \( C_3 \)-Cio, \( C_4 \)-Cio, \( C_4 \)-Cio, or \( C_5 \)-Cio), \( R^{38} \)-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), \( R^{38} \)-substituted or unsubstituted arylene (e.g., \( C_6 \)-Cio or phenylene), or \( R^{38} \)-substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( L^2 \) is independently

bond, \(-S(0)\) \(_2\), \(-N(R^5)\), \(-O-\), \(-S-\), \(-C(O)-\), \(-C(0)N(R^5)\), \(-N(R^5)C(0)NH-\), \(-NH\) \(_2\), \(-NC(0)N(R^5)\) \(_2\), \(-C(0)O-\), \(-OC(0)-\), unsubstituted alkylene (e.g., \( C_8 \), \( C_6 \)), \( C_4 \)-Cio, or \( C_5 \)-Cio), 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), unsubstituted cycloalkylene (e.g., \( C_3 \)-Cio, \( C_4 \)-Cio, \( C_4 \)-Cio, or \( C_5 \)-Cio), 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), unsubstituted arylene (e.g., \( C_6 \)-Cio or phenylene), or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( L^2 \) is independently unsubstituted methylene. In embodiments, \( L^2 \) is independently unsubstituted ethylene. In embodiments, \( L^2 \) is independently methyl-substituted methylene.

[0216] \( R^{38} \) is independently oxo,

halogen, \(-CX^{38} \), \(-CHX^{38} \), \(-CH_xX^{38} \), \(-OCX^{38} \), \(-OCH_xX^{38} \), \(-OCHX^{38} \), \(-CN \), \(-OH \), \(-NH^{2} \), \(-CO \)
OH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -ONH2, -NHC=O), NHNH2, -NHC=(O)NH2, -NHSO2H, -NHC=(O)H, -NHC(OH), -NHOH, R39-substituted or unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2), R39-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), R39-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C9), R39-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), R39-substituted or unsubstituted aryl (e.g., C6-Cio or phenyl), or R39-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R38 is independently oxo, halogen, -CH3, -CH2X38, -CHX38, -OCX38, -OCH2X38, -OCHX38, -CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -ONH2, -NHC=(O)NH2, -NHSO2H, -NHC=(O)H, -NHC(OH), -NHOH, unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2), unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C9), 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-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X38 is independently -F, -Cl, -Br, or -I. In embodiments, R38 is independently unsubstituted methyl. In embodiments, R38 is independently unsubstituted ethyl.

[0217] R39 is independently oxo, halogen, -CH3, -CH2X38, -CHX38, -OCX38, -OCH2X38, -OCHX38, -CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -ONH2, -NHC=(O)NH2, -NHSO2H, -NHC=(O)H, -NHC(OH), -NHOH, R40-substituted or unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2), R40-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), R40-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C9), R40-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), R40-substituted or unsubstituted aryl (e.g., C6-Cio or phenyl), or R40-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R39 is independently oxo,
halogen, -CX\textsuperscript{39}, -CHX\textsuperscript{39}, -CH\textsubscript{2}X\textsuperscript{39}, -OCX\textsuperscript{39}, -OCH\textsubscript{2}X\textsuperscript{39}, -OCHX\textsuperscript{39}, -CN, -OH, -NH\textsubscript{2}, -COO
H, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHNH\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NH\textsubscript{2},
-NHC=(0)NHS0\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g.,
Ci-C\textsubscript{8}, Ci-C\textsubscript{6}-Cl-C\textsubscript{4} or Ci-C\textsubscript{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\textsubscript{3}-C\textsubscript{8}, C\textsubscript{5}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{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\textsubscript{6}C\textsubscript{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X\textsuperscript{39} is independently -F, -Cl, -Br, or -I.

In embodiments, R\textsuperscript{39} is independently unsubstituted methyl. In embodiments, R\textsuperscript{39} is
independently unsubstituted ethyl.

[0218] R\textsuperscript{40} is independently oxo,
halogen, -CX\textsuperscript{40}, -CHX\textsuperscript{40}, -CH\textsubscript{2}X\textsuperscript{40}, -OCX\textsuperscript{40}, -OCH\textsubscript{2}X\textsuperscript{40}, -OCHX\textsuperscript{40}, -CN, -OH, -NH\textsubscript{2}, -COO
H, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHNH\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NH\textsubscript{2},
-NHC=(0)NHS0\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g.,
Ci-C\textsubscript{8}, Ci-C\textsubscript{6}-Cl-C\textsubscript{4} or Ci-C\textsubscript{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\textsubscript{3}-C\textsubscript{8}, C\textsubscript{5}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{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\textsubscript{6}C\textsubscript{10} or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X\textsuperscript{40} is independently -F, -Cl, -Br, or -I.
In embodiments, R\textsuperscript{40} is independently unsubstituted methyl. In embodiments, R\textsuperscript{40} is
independently unsubstituted ethyl.

[0219] In embodiments, R\textsuperscript{5} is hydrogen, substituted or unsubstituted Ci-C\textsubscript{6} alkyl, or
substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R\textsuperscript{5} is hydrogen or
unsubstituted Ci-C\textsubscript{3} alkyl. In embodiments, R\textsuperscript{5} is hydrogen, unsubstituted methyl,
unsubstituted ethyl, unsubstituted hexyl, or unsubstituted benzyl. In embodiments, R\textsuperscript{5} is
hydrogen.

[0220] In embodiments, R\textsuperscript{5} is independently hydrogen, -CX\textsuperscript{5}, -CHX\textsuperscript{5}, -CH\textsubscript{2}X\textsuperscript{5}, -OCX\textsuperscript{5},
-OCH\textsubscript{2}X\textsuperscript{5}, -OCHX\textsuperscript{5}, -CN, -C(0)R\textsuperscript{5A}, -C(0)OR\textsuperscript{5A}, -C(0)NR\textsuperscript{5A}R\textsuperscript{5B}, -OR\textsuperscript{5A}, substituted or
unsubstituted alkyl (e.g., Ci-C\textsubscript{8}, Ci-C\textsubscript{6}, Ci-C\textsubscript{4}, or Ci-C\textsubscript{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., 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 -CX5. In embodiments, R5 is independently -CHX5. In embodiments, R5 is independently -CH2X5. In embodiments, R5 is independently -CN. In embodiments, R5 is independently -C(0)R5A. In embodiments, R5 is independently -C(0)-OR5A. In embodiments, R5 is independently -COOH. In embodiments, R5 is independently -CONH2. In embodiments, R5 is independently -CF3. In embodiments, R5 is independently -CHF2. In embodiments, R5 is independently -CH2F. In embodiments, R5 is independently -CH3. In embodiments, R5 is independently -CH2CH3. In embodiments, R5 is independently -CH2CH2CH3. In embodiments, R5 is independently -C(CH3)2. In embodiments, R5 is independently -C(CH3)3. In embodiments, R5 is hydrogen, substituted or unsubstituted Ci-C6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R5 is hydroxyl or unsubstituted Ci-C6 alkyl. In embodiments, R5 is hydrogen, unsubstituted methyl, unsubstituted ethyl, unsubstituted hexyl, or unsubstituted benzyl.

In embodiments, R5 is independently substituted or unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2). In embodiments, R5 is independently substituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2). In embodiments, R5 is independently unsubstituted alkyl (e.g., Ci-C8, Ci-C6, C1-C4, or C1-C2). 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 isopropyl. In embodiments, R5 is independently unsubstituted tert-butyl. In embodiments, R5 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, R5 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, R5 is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R5 is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R5 is independently substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered).
independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R5 is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R5 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, R5 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, R5 is independently substituted or unsubstituted aryl (e.g., C6-C1o or phenyl). In embodiments, R5 is independently substituted aryl (e.g., C6-C1o or phenyl). In embodiments, R5 is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R5 is independently substituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R5 is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0223] In embodiments, R5A is independently hydrogen. In embodiments, R5A is independently C-X5A3. In embodiments, R5A is independently C-HX5A2. In embodiments, R5A is independently C-F4XY5A. In embodiments, R5A is independently C-CN. In embodiments, R5A is independently C-COOH. In embodiments, R5A is independently C-CONH2. In embodiments, X5A is independently F, Cl, Br, or I.

[0224] In embodiments, R5A is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R5A is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R5A is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R5A is independently unsubstituted methyl. In embodiments, R5A is independently unsubstituted ethyl. In embodiments, R5A is independently unsubstituted propyl. In embodiments, R5A is independently unsubstituted isopropyl. In embodiments, R5A is independently unsubstituted tert-butyl. In embodiments, R5A 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, R5A 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, R5A is independently unsubstituted or
unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R5A is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R5A is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R5A 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, R5A 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, R5A 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, R5A is independently substituted or unsubstituted aryl (e.g., C6-C10 or phenyl). In embodiments, R5A is independently substituted aryl (e.g., C6-C10 or phenyl). In embodiments, R5A is independently unsubstituted aryl (e.g., C6-C10 or phenyl). In embodiments, R5A is independently substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R5A is independently unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0225] In embodiments, R5B is independently hydrogen. In embodiments, R5B is independently -CX 5n 3. In embodiments, R5B is independently -CHX 5n 2. In embodiments, R5B is independently -CH2X 5n. In embodiments, R5B is independently -CN. In embodiments, R5B is independently -COOH. In embodiments, R5B is independently -CONH2. In embodiments, X 5n is independently -F, -Cl, -Br, or -I.

[0226] In embodiments, R5B is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R5B is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R5B is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R5B is independently unsubstituted methyl. In embodiments, R5B is independently unsubstituted ethyl. In embodiments, R5B is independently unsubstituted propyl. In embodiments, R5B is independently unsubstituted isopropyl. In embodiments, R5B is independently unsubstituted tert-butyl. In embodiments, R5B 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, R5B 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, R5B 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, R5B 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, R5B 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, R5B 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).
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, $R^5$ is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, $R^5$ is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, $R^6$ is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, $R^6$ is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6).

In embodiments, $R^5$ and $R^6$ substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, $R^5$ and $R^6$ 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, $R^5$ and $R^6$ 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).

In embodiments, $R^5$ and $R^6$ substituents bonded to the same nitrogen atom may be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^5$ and $R^6$ substituents bonded to the same nitrogen atom may be joined to form a substituted heterocycloalkyl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^5$ and $R^6$ 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, $R^5$ and $R^6$ 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, $R^5$ and $R^6$ 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).
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).

[0229] In embodiments, $R^5$ is independently hydrogen, -CX$_{3}^{3}$, -CHX$_{3}^{3}$, -CH$_{2}$X$_{3}$, -CN, -COOH, -CONH$_2$, R$_{32}$-substituted or unsubstituted alkyl (e.g., Ci-C$_8$, Ci-C$_6$, C1-C4, or Ci-C$_2$), R$_{32}$-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$_{32}$-substituted or unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_3$-C$_6$, C4-C6, or C5-C$_6$), R$_{32}$-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$_{32}$-substituted or unsubstituted aryl (e.g., C$_6$-Cio or phenyl), or R$_{32}$-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^5$ is independently hydrogen, -CX$_{3}^{3}$, -CHX$_{3}^{3}$, -CH$_{2}$X$_{3}$, -CN, -COOH, -CONH$_2$, unsubstituted alkyl (e.g., Ci-C$_8$, Ci-C$_6$, C1-C4, or Ci-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$_6$, C4-C6, or C5-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$_6$-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^5$ is independently -F, -Cl, -Br, or -I. In embodiments, $R^5$ is independently hydrogen. In embodiments, $R^5$ is independently unsubstituted methyl. In embodiments, $R^5$ is independently unsubstituted ethyl.

[0230] $R^3$ is independently oxo, halogen, -CX$_{3}^{32}$, -CHX$_{3}^{32}$, -CH$_{2}$X$_{3}^{32}$, -OCX$_{3}^{32}$, -OCH$_{2}$X$_{3}^{32}$, -OCHX$_{3}^{32}$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -NO$_2$, -SH, -S0$_2$H, -SO$_2$NH$_2$, -NHNH$_2$, -ONH$_2$, -NHC=(0)NHNH$_{2}$, -NHC=(0)NH$_2$, -NHSO$_2$H, -NHC=(0)H, -NHC(0)-OH, -NHOH, R$_{33}$-substituted or unsubstituted alkyl (e.g., Ci-C$_8$, Ci-C$_6$, C1-C4, or Ci-C$_2$), R$_{33}$-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$_{33}$-substituted or unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_3$-C$_6$, C4-C6, or C5-C$_6$), R$_{33}$-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$_{33}$-substituted or unsubstituted aryl (e.g., C$_6$-Cio or phenyl), or R$_{33}$-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^3$ is independently oxo,
halogen, -CX$_{2}$, -CH$_{2}$X$_{2}$, -OCX$_{2}$, -OCH$_{2}$X$_{2}$, -CN, -OH, -NH$_{2}$, -COOH, -CONH$_2$, -NO$_2$, -SH, -SO$_2$H, -SO$_2$NH$_2$, -NHNH$_2$, -ON$_2$H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g., C$_i$-C$_8$, C$_i$-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$_5$-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$_i$ or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X$_{32}$ is independently -F, -Cl, -Br, or -I.

In embodiments, R$_{32}$ is independently unsubstituted methyl. In embodiments, R$_{32}$ is independently unsubstituted ethyl.

[0231] R$_{33}$ is independently oxo,

halogen, -CX$_{3}$, -CH$_X$$_{3}$, -CH$_2$X$_{3}$, -OCX$_{3}$, -OCH$_{2}$X$_{3}$, -CN, -OH, -NH$_{2}$, -COOH, -CONH$_2$, -NO$_2$, -SH, -SO$_2$H, -SO$_2$NH$_2$, -NHNH$_2$, -ON$_2$H, -NHC(0)-OH, -NHOH, R$_{34}$-substituted or unsubstituted alkyl (e.g., C$_i$-C$_8$, C$_i$-C$_{6}$, C$_1$-C$_4$, or C$_1$-C$_2$), R$_{34}$-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R$_{34}$-substituted or unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_5$-C$_6$, C$_4$-C$_6$, or C$_5$-C$_6$), R$_{34}$-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R$_{34}$-substituted or unsubstituted aryl (e.g., C$_6$-C$_i$ or phenyl), or R$_{34}$-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R$_{33}$ is independently oxo,
In embodiments, $R^{33}$ is independently unsubstituted methyl. In embodiments, $R^{33}$ is independently unsubstituted ethyl.

[0232] $R^{34}$ is independently oxo, halogen, -CX$_3^{34}$, -CHX$_2^{34}$, -CH$_2$X$_3^{34}$, -OCH$_2$X$_3^{34}$, -OCHX$_3^{34}$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -N0$_2$, -SH, -SO$_2$H, -SO$_3$H, -R$_2$NH, -R$_2$N=I, -NH=I, -N=I, -NHC=(0)H, -NHC(0)-OH, -NH-0H, unsubstituted alkyl (e.g., Ci-C$_8$, Ci-C$_6$, Ci-C$_4$, or Ci-C$_2$), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_5$-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$_6$-Ci or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^{34}$ is independently -F, -Cl, -Br, or -I.

In embodiments, $R^{34}$ is independently unsubstituted methyl. In embodiments, $R^{34}$ is independently unsubstituted ethyl.

[0233] In embodiments, $R^{5A}$ is independently hydrogen, -CX$_3^{5A}$, -CHX$_2^{5A}$, -CH$_2$X$_3^{5A}$, -CN, -COOH, -CONH$_2$, R$_{32A}$-substituted or unsubstituted alkyl (e.g., Ci-C$_8$, Ci-C$_6$, Ci-C$_4$, or Ci-C$_2$), R$_{32A}$-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$_{32A}$-substituted or unsubstituted cycloalkyl (e.g., C$_3$-C$_8$, C$_5$-C$_6$, C$_4$-C$_6$, or C$_5$-C$_6$), R$_{32A}$-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$_{32A}$-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{5A}$ is independently hydrogen, -CX$_3^{5A}$, -CHX$_2^{5A}$, -CH$_2$X$_3^{5A}$, -CN, -COOH, -CONH$_2$, unsubstituted alkyl (e.g., Ci-C$_8$, Ci-C$_6$, Ci-C$_4$, or Ci-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$_5$-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$_6$-Ci or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). $X^{5A}$ is independently -F, -Cl, -Br, or -I.

In embodiments, $R^{5A}$ is independently hydrogen. In embodiments, $R^{5A}$ is independently unsubstituted methyl. In embodiments, $R^{5A}$ is independently unsubstituted ethyl.
In embodiments, \( R^A \) and \( R^B \) substituents bonded to the same nitrogen atom may optionally be joined to form a \( R^{32A} \)-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or \( R^{32A} \)-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( R^A \) and \( R^B \) substituents bonded to the same nitrogen atom may optionally 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) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( R^A \) and \( R^B \) substituents bonded to the same nitrogen atom may optionally 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). In embodiments, \( R^A \) and \( R^B \) substituents bonded to the same nitrogen atom may optionally 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). In embodiments, \( R^A \) and \( R^B \) substituents bonded to the same nitrogen atom may optionally 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). In embodiments, \( R^A \) and \( R^B \) substituents bonded to the same nitrogen atom may optionally 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). In embodiments, \( R^A \) and \( R^B \) substituents bonded to the same nitrogen atom may optionally 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).

\( R^{32A} \) is independently oxo,
halogen, -\( \text{CX}^{32A}_3 \), -\( \text{CHX}^{32A}_2 \), -\( \text{CH}_2\text{X}^{32A} \), -\( \text{OCX}^{32A}_3 \), -\( \text{OCH}_2\text{X}^{32A} \), -\( \text{OCHX}^{32A}_2 \), -CN, -OH, -NH_2, -COOH, -CONH_2, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, -NHNH_2, -ONH_2, -NHC=(0)NH_2, -NHC=(0)NH, -NHOH, -NHC=\( \text{(0)} \)NHNH_2, -NHSO_2H, -NHC=\( \text{(0)} \)OH, -NHC=\( \text{(0)} \)-OH, -NH, R^{33A}-substituted or unsubstituted alkyl (e.g., \( \text{C}_1\text{-C}_8 \), \( \text{C}_1\text{-C}_4 \), or \( \text{C}_1\text{-C}_2 \)), R^{33A}-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^{33A}-substituted or unsubstituted cycloalkyl (e.g., \( \text{C}_3\text{-C}_6 \), \( \text{C}_4\text{-C}_6 \), or \( \text{C}_5\text{-C}_6 \)), R^{33A}-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^{33A}-substituted or unsubstituted aryl (e.g., \( \text{C}_6\text{-Cio} \) or phenyl), or R^{33A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{32A} is independently oxo,
halogen, -\( \text{CX}^{32A}_3 \), -\( \text{CHX}^{32A}_2 \), -\( \text{CH}_2\text{X}^{32A} \), -\( \text{OCX}^{32A}_3 \), -\( \text{OCH}_2\text{X}^{32A} \), -\( \text{OCHX}^{32A}_2 \), -CN, -OH, -NH_2, -COOH, -CONH_2, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, -NHNH_2, -ONH_2, -NHC=(0)NHN_2, -NHC=(0)NH, -NHOH, -NHC=\( \text{(0)} \)NHNH_2, -NHSO_2H, -NHC=\( \text{(0)} \)OH, -NHC=\( \text{(0)} \)-OH, -NH, unsubstituted alkyl (e.g., \( \text{C}_1\text{-C}_8 \), \( \text{C}_1\text{-C}_6 \), \( \text{C}_1\text{-C}_4 \), or \( \text{C}_1\text{-C}_2 \)), 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., \( \text{C}_3\text{-C}_8 \), \( \text{C}_3\text{-C}_6 \), \( \text{C}_4\text{-G5} \), or \( \text{C}_5\text{-C}_6 \)), 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).
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). X³²A is independently -F, -Cl, -Br, or -I. In embodiments, R³²A is independently unsubstituted methyl. In embodiments, R³²A is independently unsubstituted ethyl.

5 [0236] R³³A is independently oxo,
halogen, -CX³³A₃, -CHX³³A₂, -CH₂X³³A, -OCX³³A₃, -OCH₂X³³A, -OCHX³³A₂, -CN, -OH, -NH₂,
-COOH, -CONH₂, -N0₂, -SH, -S0₃H, -S0₂NH₂, -NHNH₂, -O NH₂,
-NHC=(0)NHNH₂, -NHC=(0)NH₂, -NHS0₂H₂, -NHC= (O)H, -NHC(0)-OH, -NHOH,
R³⁴A-substituted or unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, Ci-C₄, or Ci-C₂), R³⁴A-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), R³⁴A-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R³⁴A-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), R³⁴A-substituted or unsubstituted aryl (e.g., C₆-Cio or phenyl), or R³⁴A-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R³³A is independently oxo,
halogen, -CX³³A₃, -CHX³³A₂, -CH₂X³³A, -OCX³³A₃, -OCH₂X³³A, -OCHX³³A₂, -CN, -OH, -NH₂,
-COOH, -CONH₂, -N0₂, -SH, -S0₃H, -S0₂NH₂, -NHNH₂, -O NH₂,
-NHC=(0)NHNH₂, -NHC=(0)NH₂, -NHS0₂H₂, -NHC= (O)H, -NHC(0)-OH, -NHOH,
unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, Ci-C₄, or Ci-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-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³³A is independently -F, -Cl, -Br, or -I. In embodiments, R³³A is independently unsubstituted methyl. In embodiments, R³³A is independently unsubstituted ethyl.

[0237] R³⁴A is independently oxo,
halogen, -CX³⁴A₃, -CHX³⁴A₂, -CH₂X³⁴A, -OCX³⁴A₃, -OCH₂X³⁴A, -OCHX³⁴A₂, -CN, -OH, -NH₂,
-COOH, -CONH₂, -N0₂, -SH, -S0₃H, -S0₂NH₂, -NHNH₂, -O NH₂,
-NHC=(0)NHNH₂, -NHC=(0)NH₂, -NHS0₂H₂, -NHC= (O)H, -NHC(0)-OH, -NHOH,
unsubstituted alkyl (e.g., Ci-C₈, Ci-C₆, Ci-C₄, or Ci-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-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R34A is independently -F, -Cl, -Br, or -I. In embodiments, R34A is independently unsubstituted methyl. In embodiments, R34A is independently unsubstituted ethyl.

[0238] In embodiments, R5B is independently hydrogen, -CX3B, -CHX3B, -CH2X3B, -CN, -COOH, -CONH2, R32B-substituted or unsubstituted alkyl (e.g., Ci-C8, Ci-C6, Ci-C4, or Ci-C2), R32B-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), R32B-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6), R32B-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), R32B-substituted or unsubstituted aryl (e.g., C6-Cio or phenyl), or R32B-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R5B is independently hydrogen, -CX3B, -CHX3B, -CH2X3B, -CN, -COOH, -CONH2, unsubstituted alkyl (e.g., Ci-C8, Ci-C6, Ci-C4, or Ci-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-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X5B is independently -F, -Cl, -Br, or -I. In embodiments, R5B is independently hydrogen. In embodiments, R5B is independently unsubstituted methyl. In embodiments, R5B is independently unsubstituted ethyl.

[0239] In embodiments, R5A and R5B substituents bonded to the same nitrogen atom may optionally be joined to form a R32B-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or R32B-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R5A and R5B substituents bonded to the same nitrogen atom may optionally 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) or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments,
R^5B and R^3B substituents bonded to the same nitrogen atom may optionally be joined to form a R^{3B}-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^{5A} and R^{3B} substituents bonded to the same nitrogen atom may optionally 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).

[0240] R^{3B} is independently oxo,
halogen, -CX^3B_3, -CHX^3B_2, -CH_2X^3B, -OCX^3B_3, -OCH_2X^3B, -OCHX^3B_2, -CN, -OH, -NH_2, -COOH, -CONH_2, -N0_2, -SH, -SO_3H, -S0_2H, -S0_2NH_2, -NHNH_2, -ONH_2.

- NHC=(O)NHNH_2, - NH=C(0)NH_2, - NH=SO_2H, - NH=SO_2NH_2, -NHC=(O)H, -NHC(0)-OH, -NHOH, R^{3B}-substituted or unsubstituted alkyl (e.g., C_8-C_8, C_7-C_7, C_6-C_6, C_5-C_5), R^{3B}-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^{3B}-substituted or unsubstituted cycloalkyl (e.g., C_3-C_8, C_4-C_4, C_5-C_5), R^{3B}-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^{3B}-substituted or unsubstituted aryl (e.g., C_6-Cio or phenyl), or R^{3B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{3B} is independently oxo,
halogen, -CX^3B_3, -CHX^3B_2, -CH_2X^3B, -OCX^3B_3, -OCH_2X^3B, -OCHX^3B_2, -CN, -OH, -NH_2, -COOH, -CONH_2, -N0_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, -NHNH_2, -ONH_2.

- NHC=(O)NHNH_2, - NH=C(0)NH_2, - NH=SO_2H, - NH=SO_2NH_2, -NHC=(O)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g., C_8-C_8, C_7-C_7, C_6-C_6, C_5-C_5), 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_4-C_4, C_5-C_5), 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-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{3B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{3B} is independently unsubstituted methyl. In embodiments, R^{3B} is independently unsubstituted ethyl.

[0241] R^{3B} is independently oxo,
halogen, -CX^{3B}_3, -CHX^{3B}_2, -CH_2X^{3B}, -OCX^{3B}_3, -OCH_2X^{3B}, -OCHX^{3B}_2, -CN, -OH, -NH_2, -COOH, -CONH_2, -N0_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, -NHNH_2, -ONH_2.
- NHC=(0)NHNH₂, - NH₂ - NH₂, - HSO₂H, - NHC= (O)H, - NHC(0)-OH, - NHOH,
R₃⁴B-substituted or unsubstituted alkyl (e.g., C₃-C₈, C₇-Ce, C₁-C₄, or C₁-C₂), R₃⁴B-substituted or unsubstituted heteroalkyl (e.g., 2 to 8membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R₃⁴B-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R₃⁴B-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), R₃⁴B-substituted or unsubstituted aryl (e.g., C₆-Cio or phenyl), or R₃⁴B-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R₃³B is independently unsubstituted alkyl.

halogen, -CX₃₃B, -CHX₃₄B, -CH₂X₃₄B, -OCX₃₃B, -OCH₂X₃₄B, -OCHX₃₄B, -CN, -OH, -NH₂,
-COOH, -CONH₂, -NO₂, -SH, -SΟ₂H, -SO₂H₂, - NH₂H₂, - OΝH₂,
-NHC=(0)NHNH₂, - NH₂ = (0)NH₂, -NSΟ₂H, - NH₂C= (0)H, - NH₃(0)-OH, - NHOH,
unsubstituted alkyl (e.g., C₃-C₈, C₇-Ce, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8membered, 2 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₇-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-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X₃⁴B is independently -F, -Cl, -Br, or -I.

In embodiments, R₃³B is independently unsubstituted methyl. In embodiments, R₃³B is independently unsubstituted ethyl.

[R0242] R₃⁴B is independently oxo,

halogen, -CX₃₃B, -CHX₃₄B, -CH₂X₃₄B, -OCX₃₃B, -OCH₂X₃₄B, -OCHX₃₄B, -CN, -OH, -NH₂,
-COOH, -CONH₂, -NO₂, -SH, -SΟ₂H, -SO₂H₂, - NH₂H₂, - OΝH₂,
-NHC=(0)NHNH₂, - NH₂ = (0)NH₂, -NSΟ₂H, - NH₂C= (0)H, - NH₃(0)-OH, - NHOH,
unsubstituted alkyl (e.g., C₃-C₈, C₇-Ce, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8membered, 2 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₇-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-Cio or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X₃⁴B is independently -F, -Cl, -Br, or -I.

In embodiments, R₃⁴B is independently unsubstituted methyl. In embodiments, R₃⁴B is independently unsubstituted ethyl.

106
In embodiments, X is -F. In embodiments, X is -Cl. In embodiments, X is -Br. In embodiments, X is -I. In embodiments, \( X^1 \) is -F. In embodiments, \( X^1 \) is -Cl. In embodiments, \( X^1 \) is -Br. In embodiments, \( X^1 \) is -I. In embodiments, \( X^4 \) is -F. In embodiments, \( X^4 \) is -Cl. In embodiments, \( X^4 \) is -Br. In embodiments, \( X^4 \) is -I. In embodiments, \( X^5 \) is -F. In embodiments, \( X^5 \) is -Cl. In embodiments, \( X^5 \) is -Br. In embodiments, \( X^5 \) is -I.

In embodiments, \( n_1 \) is 0. In embodiments, \( n_1 \) is 1. In embodiments, \( n_1 \) is 2. In embodiments, \( n_1 \) is 3. In embodiments, \( n_1 \) is 4. In embodiments, \( n_4 \) is 0. In embodiments, \( n_4 \) is 1. In embodiments, \( n_4 \) is 2. In embodiments, \( n_4 \) is 3. In embodiments, \( n_4 \) is 4. In embodiments, \( n_5 \) is 0. In embodiments, \( n_5 \) is 1. In embodiments, \( n_5 \) is 2. In embodiments, \( n_5 \) is 3. In embodiments, \( n_5 \) is 4.

In embodiments, \( m_1 \) is 1. In embodiments, \( m_1 \) is 2. In embodiments, \( m_4 \) is 1. In embodiments, \( m_4 \) is 2. In embodiments, \( m_5 \) is 1. In embodiments, \( m_5 \) is 2.

In embodiments, \( v_1 \) is 1. In embodiments, \( v_1 \) is 2. In embodiments, \( v_4 \) is 1. In embodiments, \( v_4 \) is 2. In embodiments, \( v_5 \) is 1. In embodiments, \( v_5 \) is 2.

In embodiments, \( R^{1,1} \) is independently halogen, -CX\(^\wedge\), -CHX\(^\wedge\), -CH2X \(^1\), -OCS, -OCH2X \(^1\), -OCHX\(^1\)_2, -CN, -SH, -NH\(_2\), -C(0)OH, -C(0)NH\(_2\), -OH, -OCH3, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C3-C8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C\(_6\)-Ci\(_2\) aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

In embodiments, \( R^{1,1} \) is independently halogen, -CX\(^\wedge\), -CHX\(^\wedge\), -CH2X \(^1\), -OCS, -OCH2X \(^1\), -OCHX\(^1\)_2, -CN, -SH, -NH\(_2\), -C(0)OH, -C(0)NH\(_2\), -OH, -OCH3, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 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, \( R^{1,1} \) is independently -CXV. In embodiments, \( R^{1,1} \) is independently -CHX\(^\wedge\). In embodiments, \( R^{1,1} \) is independently -CH2X \(^1\). In embodiments, \( R^{1,1} \) is independently -OCS. In embodiments, \( R^{1,1} \) is independently -OCH2X \(^1\). In embodiments, \( R^{1,1} \) is independently -OCHX\(^1\)_2. In embodiments, \( R^{1,1} \) is independently -CN.
In embodiments, R is independently -SO₂NR. In embodiments, R is independently -SO₂NR₂. In embodiments, R is independently -NH(C(0))NR. In embodiments, R is independently -N(0)₂. In embodiments, R is independently -NR₁A. In embodiments, R is independently -C(0)R. In embodiments, R is independently -C(0)-OR. In embodiments, R is independently -C(0)NR. In embodiments, R is independently -OR. In embodiments, R is independently -OH. In embodiments, R is independently -CH₃. In embodiments, R is independently -C(OH)CH₃. In embodiments, R is independently -OCH₂CH₂CH₃. In embodiments, R is independently -OCH₂CH₂CH₃. In embodiments, R is independently -OCH₂. In embodiments, R is independently -OCH₃. In embodiments, R is independently -OCH₂CH₂. In embodiments, R is independently -OCH₂CH₂. In embodiments, R is independently -OCH₂. In embodiments, R is independently -OCH₂CH₂. In embodiments, R is independently -OCH₂CH₂. In embodiments, R is independently -OCH₂CH₂. In embodiments, R is independently -CH₂. In embodiments, R is independently -CH₂. In embodiments, R is independently -C(CH₃)₂.

[0250] In embodiments, R is independently hydrogen, halogen, -CX₃, -CHX₃, -CH₂X₃, -OCHX₃, -CN, -SO₂R, -SO₂NR₁A, -NH(C(0))NR₁A, -N(0)₂, -NR₁A, -C(0)R, -C(0)-OR, -C(0)NR, -OR, -NR₁A, -SO₂R, -NR₁A, -C(0)R, -NR₁A, -OCH₂CH₂CH₃, substituted or unsubstituted alkyl (e.g., C₁-C₆, C₂-C₄, or C₂-C₆), 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-C12, C6-C10, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0251] In embodiments, R11 is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R11 is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R11 is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R11 is independently unsubstituted methyl. In embodiments, R11 is independently unsubstituted ethyl. In embodiments, R11 is independently unsubstituted propyl. In embodiments, R11 is independently unsubstituted isopropyl. In embodiments, R11 is independently unsubstituted tert-butyl. In embodiments, R11 is independently substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R11 is independently substituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R11 is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 2 to 3 membered, or 4 to 5 membered). In embodiments, R11 is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R11 is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R11 is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R11 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, R11 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, R11 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, R11 is independently substituted or unsubstituted aryl (e.g., C6-Ci2, C6-Cio, or phenyl). In embodiments, R11 is independently substituted aryl (e.g., C6-Ci2, C6-Cio, or phenyl). In embodiments, R11 is independently unsubstituted aryl (e.g., C6-Ci2, C6-Cio, or phenyl). In embodiments, R11 is independently 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, R11 is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, \( R^{1,1} \) is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0252] In embodiments, \( R^{1,1} \) is independently hydrogen, halogen, -CX\(^ \text{\textsuperscript{1}} \), -CHX\(^ \text{\textsuperscript{1}} \), -CH2X\(^ \text{\textsuperscript{1}} \), -OCX\(^ \text{\textsuperscript{1}} \), -OCH2X\(^ \text{\textsuperscript{1}} \), -OCHX\(^ \text{\textsuperscript{1}} \), -CN, -OH, -NH\(_2\), -COOH, -CONH\(_2\), -NO\(_2\), -SH, -SO\(_3\)H, -SO\(_4\)H, -SO\(_2\)NH\(_2\), -OH, -NH\(_2\), -NHC(\(0\))\(\text{\textsuperscript{0}}\)NH\(_2\), -NHC(\(0\))H, -NHC(\(0\))O-H, -NHOH, -OCH\(_3\), R\(_{20}\)-substituted or unsubstituted heteroalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_5\), C\(_4\)-C\(_5\), or C\(_5\)-C\(_6\)), R\(_{20}\)-substituted or unsubstituted heterocycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-C\(_6\)), R\(_{20}\)-substituted or unsubstituted heterocycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-C\(_6\)), R\(_{20}\)-substituted or unsubstituted heterocycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-C\(_6\)), R\(_{20}\)-substituted or unsubstituted heteroaryl (e.g., C\(_6\)-C\(_2\), C\(_6\)-C\(_6\), or phenyl), or R\(_{20}\)-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0253] In embodiments, \( R^{1,1} \) is independently hydrogen, halogen, -CX\(^ \text{\textsuperscript{1}} \), -CHX\(^ \text{\textsuperscript{1}} \), -CH2X\(^ \text{\textsuperscript{1}} \), -OCX\(^ \text{\textsuperscript{1}} \), -OCH2X\(^ \text{\textsuperscript{1}} \), -OCHX\(^ \text{\textsuperscript{1}} \), -CN, -OH, -NH\(_2\), -COOH, -CONH\(_2\), -NO\(_2\), -SH, -SO\(_3\)H, -SO\(_4\)H, -SO\(_2\)NH\(_2\), -OH, -NH\(_2\), -NHC(\(0\))\(\text{\textsuperscript{0}}\)NH\(_2\), -NHC(\(0\))H, -NHC(\(0\))O-H, -NHOH, -OCH\(_3\), unsubstituted alkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-C\(_6\)), 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\(_2\), C\(_6\)-C\(_6\), or phenyl), or unsubstituted aryl (e.g., C\(_6\)-C\(_2\), C\(_6\)-C\(_6\), 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\(^ \text{\textsuperscript{1}} \) is independently -F, -Cl, -Br, or -I. In embodiments, \( R^{1,1} \) is independently hydrogen. In embodiments, \( R^{1,1} \) is independently unsubstituted methyl. In embodiments, \( R^{1,1} \) is independently unsubstituted ethyl. In embodiments, \( R^{1,1} \) is independently -OCH\(_3\). In embodiments, \( R^{1,1} \) is independently -OCH\(_2\)CH\(_3\).

[0254] \( R^{1,1} \) and \( R^{1,2} \) may optionally be joined to form a substituted or unsubstituted cycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_5\), C\(_4\)-C\(_5\), or C\(_5\)-C\(_5\)). In embodiments, \( R^{1,1} \) and \( R^{1,2} \) are joined to
form a substituted or unsubstituted cyclobutyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to
form a substituted or unsubstituted cyclopentyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to
form a substituted or unsubstituted cyclohexyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to
form a substituted cyclobutyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form a substituted
cyclopentyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form a substituted cyclohexyl. In
embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form an unsubstituted cyclobutyl. In embodiments,
$R^{1,1}$ and $R^{1,2}$ are joined to form an unsubstituted cyclopentyl. In embodiments, $R^{1,1}$ and $R^{1,2}$
are joined to form an unsubstituted cyclohexyl. $R^{1,1}$ and $R^{1,2}$ may optionally be joined to
form a substituted or unsubstituted cycloalkenyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In
embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted cyclobutenyl. In
embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted cyclopentenyl. In
embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted cyclohexenyl. In
embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form an unsubstituted cyclobutyl. In embodiments,
$R^{1,1}$ and $R^{1,2}$ are joined to form an unsubstituted cyclopentyl. In embodiments, $R^{1,1}$ and $R^{1,2}$
are joined to form an unsubstituted cyclohexyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form
an unsubstituted cyclobutyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form an
unsubstituted cyclopentenyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form an
unsubstituted cyclohexenyl.

[0255] $R^{1,1}$ and $R^{1,2}$ may optionally be joined to form a substituted or unsubstituted 3 to 8
membered heterocycloalkyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form a substituted or
unsubstituted 4 membered heterocycloalkyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form
a substituted or unsubstituted 5 membered heterocycloalkyl. In embodiments, $R^{1,1}$ and $R^{1,2}$
are joined to form a substituted or unsubstituted 6 membered heterocycloalkyl. In
embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form a substituted 4 membered heterocycloalkyl. In
embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form a substituted 5 membered heterocycloalkyl. In
embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form a substituted 6 membered heterocycloalkyl. In
embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form an unsubstituted 4 membered heterocycloalkyl.
In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form an unsubstituted 5 membered
heterocycloalkyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined to form an unsubstituted 6
membered heterocycloalkyl. $R^{1,1}$ and $R^{1,2}$ may optionally be joined to form a substituted or
unsubstituted 3 to 8 membered heterocycloalkenyl. In embodiments, $R^{1,1}$ and $R^{1,2}$ are joined
to form a substituted or unsubstituted 4 membered heterocycloalkenyl. In embodiments, $R^{1,1}$
and $R^{1,2}$ are joined to form a substituted or unsubstituted 5 membered heterocycloalkenyl. In
embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted or unsubstituted 6 membered heterocycloalkenyl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted 4 membered heterocycloalkenyl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted 5 membered heterocycloalkenyl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted 6 membered heterocycloalkenyl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted 4 membered heterocycloalkenyl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted 5 membered heterocycloalkenyl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted 6 membered heterocycloalkenyl.

[0256] R\textsuperscript{11} and R\textsuperscript{12} may optionally be joined to form a substituted or unsubstituted C\textsubscript{6}-Ci2 aryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted or unsubstituted C\textsubscript{6} aryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted or unsubstituted Co aryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted C\textsubscript{6} aryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted C\textsubscript{12} aryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted C\textsubscript{6} aryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted C\textsubscript{12} aryl.

[0257] R\textsuperscript{11} and R\textsuperscript{12} may optionally be joined to form a substituted or unsubstituted 5 to 12 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted or unsubstituted 5 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted or unsubstituted 6 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted or unsubstituted 7 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted or unsubstituted 8 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted 5 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted 6 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted 7 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form a substituted 8 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted 5 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted 6 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted 7 membered heteroaryl. In embodiments, R\textsuperscript{11} and R\textsuperscript{12} are joined to form an unsubstituted 8 membered heteroaryl.

[0258] R\textsuperscript{11} and R\textsuperscript{16} may optionally be joined to form a substituted or unsubstituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-G\textsubscript{5}, C\textsubscript{4}-G\textsubscript{5}, or C\textsubscript{5}-G\textsubscript{5}). In embodiments, R\textsuperscript{11} and R\textsuperscript{16} are joined to form a substituted or unsubstituted cyclobutyl. In embodiments, R\textsuperscript{11} and R\textsuperscript{16} are joined to
form a substituted or unsubstituted cyclopentyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted cyclohexyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted cyclobutyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted cyclopentyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted cyclohexyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form an unsubstituted cyclobutyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form an unsubstituted cyclopentyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form an unsubstituted cyclohexyl. \( R^{1.1} \) and \( R^{1.6} \) may optionally be joined to form a substituted or unsubstituted cycloalkenyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted cyclobutenyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted cyclopropenyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted cyclohexenyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form an unsubstituted cyclohexenyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form an unsubstituted cyclopropenyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form an unsubstituted cyclohexenyl.

[0259] \( R^{1.1} \) and \( R^{1.6} \) may optionally be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 4 membered heterocycloalkyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 5 membered heterocycloalkyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 6 membered heterocycloalkyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 4 membered heterocycloalkyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 5 membered heterocycloalkyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 6 membered heterocycloalkyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 4 membered heterocycloalkyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 5 membered heterocycloalkyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form an unsubstituted 3 to 8 membered heterocycloalkenyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 4 membered heterocycloalkenyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 5 membered heterocycloalkenyl. In embodiments, \( R^{1.1} \) and \( R^{1.6} \) are joined to form a substituted or unsubstituted 6 membered heterocycloalkenyl.
heterocycloalkenyl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form a substituted 4
membered heterocycloalkenyl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form a substituted
5 membered heterocycloalkenyl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form a
substituted 6 membered heterocycloalkenyl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form an
unsubstituted 4 membered heterocycloalkenyl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form an
unsubstituted 5 membered heterocycloalkenyl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are
joined to form an unsubstituted 6 membered heterocycloalkenyl.

[0260] $R^{1,1}$ and $R^{1,6}$ may optionally be joined to form a substituted or unsubstituted $C_6$-$C_{12}$
aryl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form a substituted or unsubstituted $C_6$ aryl.

In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form a substituted or unsubstituted $C_6$ aryl. In
embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form a substituted $C_6$ aryl. In embodiments, $R^{1,1}$ and
$R^{1,6}$ are joined to form a substituted $C_{12}$ aryl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form an
unsubstituted $C_6$ aryl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form an unsubstituted
$C_{12}$ aryl.

[0261] $R^{1,1}$ and $R^{1,6}$ may optionally be joined to form a substituted or unsubstituted 5 to 12
membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form a substituted or
unsubstituted 5 membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form a
substituted or unsubstituted 6 membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to form a
substituted or unsubstituted 7 membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$
are joined to form a substituted or unsubstituted 8 membered heteroaryl. In embodiments, $R^{1,1}$
and $R^{1,6}$ are joined to form a substituted 5 membered heteroaryl. In embodiments, $R^{1,1}$ and
$R^{1,6}$ are joined to form a substituted 6 membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$
are joined to form a substituted 7 membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$
are joined to form a substituted 8 membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$
are joined to form an unsubstituted 5 membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$
are joined to form an unsubstituted 6 membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to
form an unsubstituted 7 membered heteroaryl. In embodiments, $R^{1,1}$ and $R^{1,6}$ are joined to
form an unsubstituted 8 membered heteroaryl.

[0262] In embodiments, $R^{1,2}$ is independently halogen, -CX, -CHX, -CH2X, -OCSX, -
OCH2X, -OCHX, -CN, -SH, -NH2, -C(0)OH, -C(0)NH2, -OH, -OCH3, substituted or
unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl;
substituted or unsubstituted C3-C8 cycloalkyl, substituted or unsubstituted 3 to 8 membered
heterocycloalkyl, substituted or unsubstituted C₆-C₁₂ aryl, or substituted or unsubstituted 5 to
12 membered heteroaryl.

[0263] In embodiments, R¹₂ is independently halogen, -CXⁿ, -CHXⁿ, -CH₂X, -OCXS, -OCH₂X, -CN, -SH, -(C(0)OH), -C(0)NH₂, -OH, -OCH₃, substituted or unsubstituted Cl-C₈ alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0264] In embodiments, R¹₂ is independently -CXⁿ. In embodiments, R¹₂ is independently -CH₂X. In embodiments, R¹₂ is independently -OCXS. In embodiments, R¹₂ is independently -OCH₂X. In embodiments, R¹₂ is independently -CN. In embodiments, R¹₂ is independently -SO₃Rⁿ. In embodiments, R¹₂ is independently -N(0)me. In embodiments, R¹₂ is independently -NRⁿ. In embodiments, R¹₂ is independently -C(0)R. In embodiments, R¹₂ is independently -C(0)OR. In embodiments, R¹₂ is independently -OH. In embodiments, R¹₂ is independently -OCH₃. In embodiments, R¹₂ is independently -NH₂. In embodiments, R¹₂ is independently -COOH. In embodiments, R¹₂ is independently -CONH₂. In embodiments, R¹₂ is independently -NO₂. In embodiments, R¹₂ is independently -SH. In embodiments, R¹₂ is independently halogen. In embodiments, R¹₂ is independently -F. In embodiments, R¹₂ is independently -Cl. In embodiments, R¹₂ is independently -Br. In embodiments, R¹₂ is independently -I. In embodiments, R¹₂ is independently -CF₃. In embodiments, R¹₂ is independently -CHF₂. In embodiments, R¹₂ is independently -CH₂F. In embodiments, R¹₂ is independently -OCF₃. In embodiments, R¹₂ is independently -OCH₂F. In embodiments, R¹₂ is independently -OCH₂CH₂F. In embodiments, R¹₂ is independently -OCH₂CH₂CH₃. In embodiments, R¹₂ is independently -OCH( CH₃)₂. In embodiments, R¹₂ is independently -OCH(C( CH₃)₃).
SCH3. In embodiments, R$_1^2$ is independently -SCH2CH3. In embodiments, R$_1^2$ is independently -SCH2CH2CH3. In embodiments, R$_1^2$ is independently -SCH(CH3)2. In embodiments, R$_1^2$ is independently -SC(CH3)3. In embodiments, R$_1^2$ is independently -CH3. In embodiments, R$_1^2$ is independently substituted cycloalkyl (e.g., C3-C5, C4-C6, or C5-C6). In embodiments, R$_1^2$ is independently substituted alkyl (e.g., tert-butyl), 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 heteroaryl (e.g., 5 to 12, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0266] In embodiments, R$_1^2$ is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C4, or C1-C2). In embodiments, R$_1^2$ is independently substituted alkyl (e.g., C1-C8, C1-C4, or C1-C2). In embodiments, R$_1^2$ is independently unsubstituted alkyl (e.g., C1-C8, C1-C4, or C1-C2). In embodiments, R$_1^2$ is independently unsubstituted methyl. In embodiments, R$_1^2$ is independently unsubstituted ethyl. In embodiments, R$_1^2$ is independently unsubstituted propyl. In embodiments, R$_1^2$ is independently unsubstituted isopropyl. In embodiments, R$_1^2$ is independently unsubstituted tert-butyl. In embodiments, R$_1^2$ 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$_1^2$ 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$_1^2$ is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-G5, or C5-C6). In embodiments, R$_1^2$ is independently substituted cycloalkyl (e.g., C3-C8, C3-G5, C4-C6, or C5-C6). In embodiments,
R\(^{1,2}\) 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\(^{1,2}\) 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\(^{1,2}\) is independently substituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R\(^{1,2}\) is independently unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, R\(^{1,2}\) is independently substituted or unsubstituted aryl (e.g., C\(_6\)-C\(_{12}\), C\(_6\)-C\(_{10}\), or phenyl). In embodiments, R\(^{1,2}\) is independently substituted aryl (e.g., C\(_6\)-C\(_{12}\), C\(_6\)-C\(_{10}\), or phenyl). In embodiments, R\(^{1,2}\) is independently unsubstituted aryl (e.g., C\(_6\)-C\(_{12}\), C\(_6\)-C\(_{10}\), or phenyl). In embodiments, R\(^{1,2}\) is independently 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\(^{1,2}\) is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\(^{1,2}\) is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0267] In embodiments, R\(^{1,2}\) is independently hydrogen, halogen, -CX\(^{\wedge}\), -CHX\(^{\wedge}\), -CH\(_2\)X \(^{\dagger}\), -OCX\(^{\wedge}\), -OCH\(_2\)X \(^{\dagger}\), -OCHX\(^{\wedge}\), -CN, -OH, -NH\(_2\), -COOH, -CONH\(_2\), -NO\(_2\), -SH, -SO\(_3\)H, -SO\(_4\)H, -SO\(_2\)NH\(_2\), -NHNH\(_2\), -ONH\(_2\), -NH\(_2\)=(-NH\(_2\)_)\(_2\), -NHC=(0)NH\(_2\), -NHC=(0)H, -NHC(OH)\(_2\), -NHOH, -OCH\(_3\), R\(_{20}\)-substituted or unsubstituted alkyl (e.g., Ci-Cs, Ci-C\(_6\), C\(_1\)-C\(_4\), or C\(_1\)-C\(_2\)), R\(_{20}\)-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\(_{20}\)-substituted or unsubstituted cycloalkyl (e.g., C\(_3\)-C\(_8\), C\(_3\)-C\(_6\), C\(_4\)-C\(_6\), or C\(_5\)-C\(_6\)), R\(_{20}\)-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\(_{20}\)-substituted or unsubstituted aryl (e.g., C\(_6\)-C\(_{12}\), C\(_6\)-C\(_{10}\), or phenyl), or R\(_{20}\)-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0268] In embodiments, R\(^{1,2}\) is independently hydrogen, halogen, -CX\(^{\wedge}\), -CHX\(^{\wedge}\), -CH\(_2\)X \(^{\dagger}\), -OCX\(^{\wedge}\), -OCH\(_2\)X \(^{\dagger}\), -OCHX\(^{\wedge}\), -CN, -OH, -NH\(_2\), -COOH, -CONH\(_2\), -NO\(_2\), -SH, -SO\(_3\)H, -SO\(_4\)H, -SO\(_2\)NH\(_2\), -NHNH\(_2\), -ONH\(_2\), -NHC=(0)NHNH\(_2\), -NHC=(0)NH\(_2\), -NHC=(0)H, -NHC(OH)\(_2\), -NHOH, unsubstituted alkyl (e.g.,
Ci-C₈, Ci-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, C₅-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-Ci2, C₆-Cio, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹ is independently -F, -Cl, -Br, or -I. In embodiments, R¹² is independently hydrogen. In embodiments, R¹² is independently unsubstituted methyl. In embodiments, R¹² is independently unsubstituted ethyl. In embodiments, R¹² is independently -OCH₃. In embodiments, R¹² is independently -OCH₂CH₃.

In embodiments, R¹³ is independently halogen, -CXⁿ, -CHXⁿ, -CH₂X¹, -OCXS, -OCH₂X¹, -OCHXⁿ, -CN, -SH, -NH₂, -C(ℓ)OH, -C(ℓ)NH₂, -OH, -OCH₃, substituted or unsubstituted Ci-C₈ alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆-Ci₂ aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

In embodiments, R¹³ is independently -CXⁿ. In embodiments, R¹³ is independently -CHXⁿ. In embodiments, R¹³ is independently -CH₂X¹. In embodiments, R¹³ is independently -OCXS. In embodiments, R¹³ is independently -OCH₂X¹. In embodiments, R¹³ is independently -OCHXⁿ. In embodiments, R¹³ is independently -CN. In embodiments, R¹³ is independently -SOₙIR¹ⁿ. In embodiments, R¹³ is independently -SOₙiNR¹ⁿ. In embodiments, R¹³ is independently -N(ℓ)NR¹ⁿ. In embodiments, R¹³ is independently -NR¹ⁿ. In embodiments, R¹³ is independently -C(ℓ)R¹ᶜ. In embodiments, R¹³ is independently -C(ℓ)OR¹ᶜ. In embodiments, R¹³ is independently -C(ℓ)NR¹ⁿ. In embodiments, R¹³ is independently -OR¹ⁿ. In embodiments, R¹³ is independently -NR¹ⁿ.
independently -NR\textsuperscript{1,3}S\textsubscript{0,2}R\textsuperscript{1b}. In embodiments, R\textsuperscript{1,3} is independently -NR\textsuperscript{1,3}C(0)R \textsuperscript{1c}. In embodiments, R\textsuperscript{1,3} is independently -NR\textsuperscript{1,3}C(0)R\textsuperscript{1e}. In embodiments, R\textsuperscript{1,3} is independently -NR\textsuperscript{1,3}A0 R\textsuperscript{1c}. In embodiments, R\textsuperscript{1,3} is independently -OH. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{3}. In embodiments, R\textsuperscript{1,3} is independently -NH\textsubscript{2}. In embodiments, R\textsuperscript{1,3} is independently -COOH. In embodiments, R\textsuperscript{1,3} is independently -CONH\textsubscript{2}. In embodiments, R\textsuperscript{1,3} is independently -N0\textsubscript{2}. In embodiments, R\textsuperscript{1,3} is independently -SH. In embodiments, R\textsuperscript{1,3} is independently halogen. In embodiments, R\textsuperscript{1,3} is independently -F. In embodiments, R\textsuperscript{1,3} is independently -Cl. In embodiments, R\textsuperscript{1,3} is independently -Br. In embodiments, R\textsuperscript{1,3} is independently -I. In embodiments, R\textsuperscript{1,3} is independently -CF\textsubscript{3}. In embodiments, R\textsuperscript{1,3} is independently -CHF\textsubscript{2}. In embodiments, R\textsuperscript{1,3} is independently -CH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F. In embodiments, R\textsuperscript{1,3} is independently -OCH\textsubscript{2}F.
In embodiments, R\textsuperscript{1,2} is independently substituted or unsubstituted alkyl (e.g., C\textsubscript{i}-C\textsubscript{8}, C\textsubscript{i}-C\textsubscript{6}, C\textsubscript{1}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}). In embodiments, R\textsuperscript{1,3} is independently substituted alkyl (e.g., C\textsubscript{i}-C\textsubscript{8}, C\textsubscript{i}-C\textsubscript{6}, C\textsubscript{1}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}). In embodiments, R\textsuperscript{1,3} is independently unsubstituted alkyl (e.g., C\textsubscript{i}-C\textsubscript{8}, C\textsubscript{i}-C\textsubscript{6}, C\textsubscript{1}-C\textsubscript{4}, or C\textsubscript{1}-C\textsubscript{2}). In embodiments, R\textsuperscript{1,3} is independently unsubstituted methyl. In embodiments, R\textsuperscript{1,3} is independently unsubstituted ethyl. In embodiments, R\textsuperscript{1,3} is independently unsubstituted propyl. In embodiments, R\textsuperscript{1,3} is independently unsubstituted isopropyl. In embodiments, R\textsuperscript{1,3} is independently unsubstituted tert-butyl. In embodiments, R\textsuperscript{1,3} 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\textsuperscript{1,3} 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\textsuperscript{1,3} is independently substituted or unsubstituted heterocycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}). In embodiments, R\textsuperscript{1,3} is independently substituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}). In embodiments, R\textsuperscript{1,3} is independently substituted cycloalkyl (e.g., C\textsubscript{3}-C\textsubscript{8}, C\textsubscript{3}-C\textsubscript{6}, C\textsubscript{4}-C\textsubscript{6}, or C\textsubscript{5}-C\textsubscript{6}). In embodiments, R\textsuperscript{1,3} 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\textsuperscript{1,3} 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\textsuperscript{1,3} is independently substituted or unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{12}, C\textsubscript{6}-C\textsubscript{10}, or phenyl). In embodiments, R\textsuperscript{1,3} is independently substituted aryl (e.g., C\textsubscript{6}-C\textsubscript{12}, C\textsubscript{6}-C\textsubscript{10}, or phenyl). In embodiments, R\textsuperscript{1,3} is independently unsubstituted aryl (e.g., C\textsubscript{6}-C\textsubscript{12}, C\textsubscript{6}-C\textsubscript{10}, or phenyl). In embodiments, R\textsuperscript{1,3} is independently 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\textsuperscript{1,3} is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R\textsuperscript{1,3} is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

In embodiments, R\textsuperscript{1,3} is independently hydrogen, halogen, -CX\textsuperscript{a}, -CHX\textsuperscript{a}, -CH2X \textsuperscript{1}, -OCX\textsuperscript{a}, -OCH2X \textsuperscript{1}, -OCHX\textsuperscript{a}, -CN, -OH, -NH\textsubscript{2}, -COOH, -
C=O, NH, COOH, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -HNH₂, -OH, -CH₂O═N═H, -CH₂═NH, -NH₂, -CH₃, 
substituted or unsubstituted alkyl (e.g., C₁-C₈), C₁-C₄, or C₁-C₂), R²₀-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), R²₀-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-
C₆), R²₀-substituted or unsubstituted heterocycloalkyl (e.g., R³₀-substituted or unsubstituted 
aryl (e.g., C₆-C₈, C₆-C₆, or C₆-C₆), R³₀-substituted or unsubstituted heteroaryl (e.g., 5 to 12 
memorized, 5 to 10 membered, 5 to 9 membered, or 5 to 6 
memorized).

[0275] In embodiments, R¹³ is independently hydrogen, halogen, -CX, -CHX, -CH₂X, -OCX, -OCH₂X, -OCHX, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NH₂H₂, -ONH₂, -NHC(0)H, -NH₂(0)H, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 
memorized, 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 
memorized, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₈, C₆-C₆, or C₆-C₆), or unsubstituted heteroaryl (e.g., 5 to 12 
memorized, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹ is independently -F, -Cl, or -I. In embodiments, R¹³ is independently hydrogen. In embodiments, R¹³ is independently unsubstituted methyl. In embodiments, R¹³ is independently unsubstituted ethyl. In embodiments, R¹³ is independently -OCH₃. In embodiments, R¹³ is independently -OCH₂CH₃.

[0276] In embodiments, R¹⁵ is independently halogen, -CX, -CHX, -CH₂X, -OCX, -OCH₂X, -OCHX, -CN, -SH, -NH₂, -C(O)OH, -C(O)NH₂, -OH, -OCH₃, substituted or unsubstituted C₁-C₈ alkyl, or substituted or unsubstituted C₁-C₈ heteroalkyl; substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆-C₁₂ aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0277] In embodiments, R¹⁵ is independently halogen, -CX, -CHX, -CH₂X, -OCX, -OCH₂X, -OCHX, -CN, -SH, -NH₂, -C(O)OH, -C(O)NH₂, -OH, -OCH₃, substituted or
unsubstituted C1-C5 alkyl, or substituted or unsubstituted 2 to 8 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, \( R^{1,5} \) is independently -CXV. In embodiments, \( R^{1,5} \) is independently -CHX. In embodiments, \( R^{1,5} \) is independently -CH2X. In embodiments, \( R^{1,5} \) is independently -OCXS. In embodiments, \( R^{1,5} \) is independently -OCH2X. In embodiments, \( R^{1,5} \) is independently -OCHX. In embodiments, \( R^{1,5} \) is independently -CN. In embodiments, \( R^{1,5} \) is independently -SO_iR^D. In embodiments, \( R^{1,5} \) is independently -SO_iNR^{1A}R^{1B}. In embodiments, \( R^{1,5} \) is independently -NHC(0)NR^{1A}R^{1B}. In embodiments, \( R^{1,5} \) is independently -N(0)_{2i}. In embodiments, \( R^{1,5} \) is independently -N(0)_{2i}. In embodiments, \( R^{1,5} \) is independently -NR^{1A}R^{1B}. In embodiments, \( R^{1,5} \) is independently -C(0)R^{1C}. In embodiments, \( R^{1,5} \) is independently -C(0)-0R^{1C}. In embodiments, \( R^{1,5} \) is independently -C(0)NR^{1A}R^{1B}. In embodiments, \( R^{1,5} \) is independently -OR^D. In embodiments, \( R^{1,5} \) is independently -NR^{1A}SO_{2}R^{1B}. In embodiments, \( R^{1,5} \) is independently -NR^{1A}C(0)R^{1C}. In embodiments, \( R^{1,5} \) is independently -NR^{1A}C(0)OR^{1C}. In embodiments, \( R^{1,5} \) is independently -NR^{1A}OOR^{1C}. In embodiments, \( R^{1,5} \) is independently -OH. In embodiments, \( R^{1,5} \) is independently -OCH3. In embodiments, \( R^{1,5} \) is independently -NH2. In embodiments, \( R^{1,5} \) is independently -COOH. In embodiments, \( R^{1,5} \) is independently -CONH2. In embodiments, \( R^{1,5} \) is independently -NO2. In embodiments, \( R^{1,5} \) is independently -SH. In embodiments, \( R^{1,5} \) is independently halogen. In embodiments, \( R^{1,5} \) is independently -F. In embodiments, \( R^{1,5} \) is independently -Cl. In embodiments, \( R^{1,5} \) is independently -Br. In embodiments, \( R^{1,5} \) is independently -I. In embodiments, \( R^{1,5} \) is independently -CF3. In embodiments, \( R^{1,5} \) is independently -CHF2. In embodiments, \( R^{1,5} \) is independently -CH2F. In embodiments, \( R^{1,5} \) is independently -OCF3. In embodiments, \( R^{1,5} \) is independently -OCHF2. In embodiments, \( R^{1,5} \) is independently -OCH3. In embodiments, \( R^{1,5} \) is independently -OCH2CH3. In embodiments, \( R^{1,5} \) is independently -OCH2CH2CH3. In embodiments, \( R^{1,5} \) is independently -OCH(CH3). In embodiments, \( R^{1,5} \) is independently -OCH(CH3). In embodiments, \( R^{1,5} \) is independently -OCH(CH3). In embodiments, \( R^{1,5} \) is independently -OCH3. In embodiments, \( R^{1,5} \) is independently -SC(CH3). In embodiments, \( R^{1,5} \) is independently -SC(CH3).
independently -CH2CH2CH3. In embodiments, R1.5 is independently -CH (CH3)2. In embodiments, R1.5 is independently -C(CH3)3.

[0279] In embodiments, R1.5 is independently hydrogen, halogen, -CX13, -CHX4, -CH2X5, -OCX7.

5 OCH2X 1, -OCHX^4, -CN, -SOiNR^2, -SOiNR^2, -NHC(0)NR^1A^2, -N(0) m_i, -NR^1A^2, -C(0)R^1C, -C(0)-OR^1C, -C(0)NR^1A^2, -OR^2, -NR^1A^2S^2R^2, -NR^1A^2C(0)R^1C, -N

10 R^1A^2C(0)OR^1C, -NR^1A^2OR^1C, 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-G5, 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-C12, C5-C10, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 12, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

15 [0280] In embodiments, R1.5 is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R1.5 is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R1.5 is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R1.5 is independently unsubstituted methyl. In embodiments, R1.5 is independently unsubstituted ethyl. In embodiments, R1.5 is independently unsubstituted propyl. In embodiments, R1.5 is independently unsubstituted isopropyl. In embodiments, R1.5 is independently unsubstituted tert-butyl. In embodiments, R1.5 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, R1.5 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, R1.5 is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-G5, or C5-C6). In embodiments, R1.5 is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R1.5 is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-G5, or C5-C6). In embodiments, R1.5 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, R1.5 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_{i}^{1,5} 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_{i}^{1,5} is independently substituted or unsubstituted aryl (e.g., C_{6}-C_{12}, C_{6}-Cio, or phenyl). In embodiments, R_{i}^{1,5} is independently substituted aryl (e.g., C_{6}-C_{12}, C_{6}-Cio, or phenyl). In embodiments, R_{i}^{1,5} is independently unsubstituted aryl (e.g., C_{6}-C_{12}, C_{6}-Cio, or phenyl). In embodiments, R_{i}^{1,5} is independently 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_{i}^{1,5} is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R_{i}^{1,5} is independently unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0281] In embodiments, R_{i}^{1,5} is independently hydrogen, halogen, -CX^\alpha, -CHX^\alpha, -CH2X^1, -OCX^\alpha, -OCH2X^1, -OCHX^\alpha, -CN, -OH, -NH_2, -COOH, -CONH_2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NHNNH_2, -OH, -NHC=(O)H, -NHC=(0)H, -NHC=(0)OH, -NHOH, -OCH3, R^{20}-substituted or unsubstituted alkyl (e.g., Ci-C_{8}, Ci-C_{6}, C1-C_{4}, or C1-C_{2}), R^{20}-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^{20}-substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C_{6}), R^{20}-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^{20}-substituted or unsubstituted aryl (e.g., C_{6}-C_{12}, C_{6}-Cio, or phenyl), or R^{20}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0282] In embodiments, R_{i}^{1,5} is independently hydrogen, halogen, -CX^\alpha, -CHX^\alpha, -CH2X^1, -OCX^\alpha, -OCH2X^1, -OCHX^\alpha, -CN, -OH, -NH_2, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NHNNH2, -OH, -NHC=(O)H, -NHC=(0)H, -NHC=(0)OH, -NHOH, unsubstituted alkyl (e.g., Ci-C_{8}, Ci-C_{6}, C1-C_{4}, or C1-C_{2}), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-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., C₆-H₁₂, 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). X¹ is independently -F, -Cl, -Br, or -I. In embodiments, R¹.⁵ is independently hydrogen. In embodiments, R¹.⁵ is independently unsubstituted methyl. In embodiments, R¹.⁵ is independently unsubstituted ethyl. In embodiments, R¹.⁵ is independently -OCH₃. In embodiments, R¹.⁵ is independently -OCH₂CH₃.

[0283] In embodiments, R¹.⁶ is independently halogen, -CX¹, -CHX¹, -CH₂X¹, -OCXS, -OCH₂X¹, -OCHX¹, -CN, -SH, -NH₂, -C(0)OH, -C(0)NH₂, -OH, -OCH₃, substituted or unsubstituted Ci-C₈ alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆-C₁₂ aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0284] In embodiments, R¹.⁶ is independently halogen, -CX¹, -CHX¹, -CH₂X¹, -OCXS, -OCH₂X¹, -OCHX¹, -CN, -SH, -NH₂, -C(0)OH, -C(0)NH₂, -OH, -OCH₃, substituted or unsubstituted Ci-C₈ alkyl, or substituted or unsubstituted 2 to 8 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.

[0285] In embodiments, R¹.⁶ is independently -CXV. In embodiments, R¹.⁶ is independently -CHX¹. In embodiments, R¹.⁶ is independently -OCXS. In embodiments, R¹.⁶ is independently -OCH₂X¹. In embodiments, R¹.⁶ is independently -OCHX¹. In embodiments, R¹.⁶ is independently -CN. In embodiments, R¹.⁶ is independently -SOₙIR¹D. In embodiments, R¹.⁶ is independently -SOₙIR¹B. In embodiments, R¹.⁶ is independently -NH₃(IR¹B). In embodiments, R¹.⁶ is independently -N(0)ₘ⁻. In embodiments, R¹.⁶ is independently -C(0)ₘ⁻. In embodiments, R¹.⁶ is independently -OR¹D. In embodiments, R¹.⁶ is independently -OR¹B. In embodiments, R¹.⁶ is independently -OR¹C. In embodiments, R¹.⁶ is independently -OR¹D. In embodiments, R¹.⁶ is independently -NH₃(IR¹B). In embodiments, R¹.⁶ is independently -NH₃(IR¹B). In embodiments, R¹.⁶ is independently -NH₃(IR¹B). In embodiments, R¹.⁶ is independently -OH. In embodiments, R¹.⁶ is independently -OCH₃. In embodiments, R¹.⁶ is independently -NH₂. In embodiments,
R_{16} is independently -COOH. In embodiments, R_{16} is independently -CONH2. In embodiments, R_{16} is independently -NO2. In embodiments, R_{16} is independently -SH. In embodiments, R_{16} is independently halogen. In embodiments, R_{16} is independently -F. In embodiments, R_{16} is independently -Cl. In embodiments, R_{16} is independently -Br. In embodiments, R_{16} is independently -I. In embodiments, R_{16} is independently -CF3. In embodiments, R_{16} is independently -CHF2. In embodiments, R_{16} is independently -CH2F. In embodiments, R_{16} is independently -OCF3. In embodiments, R_{16} is independently -OCH2F. In embodiments, R_{16} is independently -OCH3. In embodiments, R_{16} is independently -OCH2CH3. In embodiments, R_{16} is independently -OC(H(CH3)2). In embodiments, R_{16} is independently -SCH3. In embodiments, R_{16} is independently -SCH2CH3. In embodiments, R_{16} is independently -OC(CH3)3. In embodiments, R_{16} is independently -SC(CH3)3. In embodiments, R_{16} is independently -CH3. In embodiments, R_{16} is independently -CH2CH3. In embodiments, R_{16} is independently -CH(CH3)2. In embodiments, R_{16} is independently -C(CH3)3.

In embodiments, R_{16} is independently hydrogen, halogen, -CX^1, -CHX^1, -CH2X^1, -OCX^1, -.

OCH2X^1, -OCHX^1, -CN, -SO2NR^1^B, -SC(NR^1^A)^B, -NH C(0) NR^1^A^B, -N(0)_m i, -NR^1^A^B, -C(0)R^1^C, -C(0)-OR^1^C, -C(0)NR^1^A^B, -OR^1^D, -NR^1^A^S^3^R^1^D, -NR^1^A^C(0)R^1^C, -N R^1^A^C(0)OR^1^C, 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-G5, 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-C12, C6-C10, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 12, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

In embodiments, R_{16} is independently substituted or unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R_{16} is independently substituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R_{16} is independently unsubstituted alkyl (e.g., C1-C8, C1-C6, C1-C4, or C1-C2). In embodiments, R_{16} is independently unsubstituted...
methyl. In embodiments, R^{16} is independently unsubstituted ethyl. In embodiments, R^{16} is independently unsubstituted propyl. In embodiments, R^{16} is independently unsubstituted isopropyl. In embodiments, R^{16} is independently unsubstituted tert-butyl. In embodiments, R^{16} 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^{16} 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^{16} is independently substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R^{16} is independently substituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R^{16} is independently unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R^{16} 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^{16} 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^{16} 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^{16} is independently substituted or unsubstituted aryl (e.g., C6-C12, C6-C10, or phenyl). In embodiments, R^{16} is independently substituted aryl (e.g., C6-C12, C6-C10, or phenyl). In embodiments, R^{16} is independently unsubstituted aryl (e.g., C6-C12, C6-C10, or phenyl). In embodiments, R^{16} is independently 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^{16} is independently substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{16} is independently unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4

[0288] In embodiments, R^{16} is independently hydrogen, halogen, -CX^, -CHX^, -CH2X^1, -OCX^, -OCH2X^1, -OCHX^, -CN, -OH, -NH2^, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NH2NH2, -ONH2, -NH=C(0)NH2, -NHC=(0)NH2, -NHSO2H, -NHC=(0)H, -NH(C(0))OH, -NH2OH, -OCH3, R^{30,}-substituted or unsubstituted alkyl (e.g., Ci-Cs, Ci-C6, C1-C4, or C1-C2), R^{20,}-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<sup>20</sup>-substituted or unsubstituted cycloalkyl (e.g., C<sub>3</sub>-C<sub>8</sub>, C<sub>3</sub>-C<sub>6</sub>, C<sub>4</sub>-C<sub>6</sub>, or C<sub>5</sub>-C<sub>6</sub>), R<sup>20</sup>-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<sup>20</sup>-substituted or unsubstituted aryl (e.g., C<sub>6</sub>-C<sub>12</sub>, C<sub>6</sub>-C<sub>10</sub>, or phenyl), or R<sup>20</sup>-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0289] In embodiments, R<sup>16</sup> is independently hydrogen, halogen, -CX<sup>a</sup>, -CHX<sup>a</sup>, -CH2X<sup>a</sup>, -OCX<sup>a</sup>, -OCH2X<sup>a</sup>, -OCHX<sup>a</sup>, -CN, -OH, -NH<sub>2</sub>, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NH2H2, -ONH2, -NH=C(0)NHNH<sub>2</sub>, -NHC=(0)NH<sub>2</sub>, -NHSO2H, -NHC=(0)H, -NHC(0)-OH, -NHOH, unsubstituted alkyl (e.g., C<sub>i</sub>-C<sub>8</sub>, C<sub>i</sub>-C<sub>6</sub>, C<sub>1</sub>-C<sub>4</sub>, or C<sub>1</sub>-C<sub>2</sub>), 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<sub>3</sub>-C<sub>8</sub>, C<sub>3</sub>-C<sub>6</sub>, C<sub>4</sub>-C<sub>6</sub>, or C<sub>5</sub>-C<sub>6</sub>), 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<sub>6</sub>-C<sub>12</sub>, C<sub>6</sub>-C<sub>10</sub>, 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<sup>1</sup> is independently -F, -Cl, -Br, or -I. In embodiments, R<sup>16</sup> is independently hydrogen. In embodiments, R<sup>16</sup> is independently unsubstituted methyl. In embodiments, R<sup>16</sup> is independently unsubstituted ethyl. In embodiments, R<sup>16</sup> is independently -OCH<sub>3</sub>. In embodiments, R<sup>16</sup> is independently -OCH<sub>2</sub>CH<sub>3</sub>.

[0290] In embodiments, two adjacent R<sup>1</sup> substituents (e.g., R<sup>1,1</sup> and R<sup>1,2</sup>) 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 R<sup>1</sup> substituents (e.g., R<sup>1,1</sup> and R<sup>1,2</sup>) are joined to form an unsubstituted cycloalkyl. In embodiments, two adjacent R<sup>1</sup> substituents (e.g., R<sup>1,1</sup> and R<sup>1,2</sup>) are joined to form an unsubstituted C<sub>3</sub>-C<sub>6</sub> cycloalkyl.

[0291] In embodiments, two adjacent R<sup>1</sup> substituents (e.g., R<sup>1,1</sup> and R<sup>1,2</sup>) may optionally be joined to form a substituted or unsubstituted cycloalkyl (e.g., C<sub>3</sub>-C<sub>8</sub>, C<sub>3</sub>-C<sub>6</sub>, C<sub>4</sub>-C<sub>6</sub>, or C<sub>5</sub>-C<sub>6</sub>). In embodiments, two adjacent R<sup>1</sup> substituents (e.g., R<sup>1,1</sup> and R<sup>1,2</sup>) may optionally be joined to form a substituted cycloalkyl (e.g., C<sub>3</sub>-C<sub>8</sub>, C<sub>3</sub>-C<sub>6</sub>, C<sub>4</sub>-C<sub>6</sub>, or C<sub>5</sub>-C<sub>6</sub>). In embodiments, two adjacent R<sup>1</sup>
substituents (e.g., R_1 and R_2) may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered). In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally 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, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally 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). In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form a substituted or unsubstituted aryl (e.g., C_6-Ci2, C_6-Cio, or phenyl). In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form a substituted aryl (e.g., C_6-Ci2, C_6-Cio, or phenyl). In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form an unsubstituted aryl (e.g., C_6-Ci2, C_6-Cio, or phenyl). In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form a 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, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form a substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form an unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0292] In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form a R^{20}-substituted or unsubstituted cycloalkyl (e.g., C_3-C8, C_3-C6, C_4-C6, or C_5-C_6). In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form a R^{20}-substituted cycloalkyl (e.g., C_3-C8, C_3-C6, C_4-C6, or C_5-C_6). In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form an unsubstituted cycloalkyl (e.g., C_3-C8, C_3-C6, C_4-C6, or C_5-C_6). In embodiments, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form a R^{20}-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, two adjacent R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form a R^{20}-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 R^1 substituents (e.g., R_1 and R_2) may optionally be joined to form a R^{20}-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).
and R1,2 may optionally 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). In embodiments, two adjacent R1 substituents (e.g., R1,1 and R1,2) may optionally be joined to form a R20-substituted or unsubstituted aryl (e.g., C6-C12, C6-Cio, or phenyl). In embodiments, two adjacent R1 substituents (e.g., R1,1 and R1,2) may optionally be joined to form an unsubstituted aryl (e.g., C6-Ci2, C6-Cio, or phenyl). In embodiments, two adjacent R1 substituents (e.g., R1,1 and R1,2) may optionally be joined to form a R20-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, two adjacent R1 substituents (e.g., R1,1 and R1,2) may optionally be joined to form a R20-substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, two adjacent R1 substituents (e.g., R1,1 and R1,2) may optionally be joined to form an unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10

[0293] R1,3 and R1,2 may optionally be joined to form a substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, R1,3 and R1,2 are joined to form a substituted or unsubstituted cyclobutyl. In embodiments, R1,3 and R1,2 are joined to form a substituted or unsubstituted cyclopentyl. In embodiments, R1,3 and R1,2 are joined to form a substituted or unsubstituted cyclohexyl. In embodiments, R1,3 and R1,2 are joined to form a substituted cyclobutyl. In embodiments, R1,3 and R1,2 are joined to form a substituted cyclopentyl. In embodiments, R1,3 and R1,2 are joined to form a substituted cyclohexyl. In embodiments, R1,3 and R1,2 are joined to form a substituted cyclohexyl. In embodiments, R1,3 and R1,2 are joined to form an unsubstituted cyclohexyl. In embodiments, R1,3 and R1,2 are joined to form an unsubstituted cyclohexyl. In embodiments, R1,3 and R1,2 are joined to form an unsubstituted cyclohexyl. In embodiments, R1,3 and R1,2 are joined to form an unsubstituted cyclohexyl. In embodiments, R1,3 and R1,2 are joined to form an unsubstituted cyclohexyl.
unsubstituted cyclopentenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted cyclohexenyl.

[0294] $R^{1,3}$ and $R^{1,2}$ may optionally be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted 4 membered heterocycloalkyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted 5 membered heterocycloalkyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted 6 membered heterocycloalkyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted 4 membered heterocycloalkyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted 5 membered heterocycloalkyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted 4 membered heterocycloalkyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted 5 membered heterocycloalkyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted 6 membered heterocycloalkyl. $R^{1,3}$ and $R^{1,2}$ may optionally be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted 4 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted 5 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted 6 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted 4 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted 5 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted 6 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted 5 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted 6 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted 4 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted 5 membered heterocycloalkenyl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted 6 membered heterocycloalkenyl.

[0295] $R^{1,3}$ and $R^{1,2}$ may optionally be joined to form a substituted or unsubstituted $C_6$-$C_{12}$ aryl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted $C_6$ aryl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted $C_6$ aryl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted $C_6$ aryl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted $C_6$ aryl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form a substituted or unsubstituted $C_6$ aryl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted $C_6$ aryl. In embodiments, $R^{1,3}$ and $R^{1,2}$ are joined to form an unsubstituted $C_{12}$ aryl.
[0296] $R^{1.3}$ and $R^{1.2}$ may optionally be joined to form a substituted or unsubstituted 5 to 12 membered heteroaryl. In embodiments, $R^{1.3}$ and $R^{1.2}$ are joined to form a substituted or unsubstituted 5 membered heteroaryl. In embodiments, $R^{1.3}$ and $R^{1.2}$ are joined to form a substituted or unsubstituted 6 membered heteroaryl. In embodiments, $R^{1.3}$ and $R^{1.2}$ are joined to form a substituted or unsubstituted 7 membered heteroaryl. In embodiments, $R^{1.3}$ and $R^{1.2}$ are joined to form a substituted or unsubstituted 8 membered heteroaryl. In embodiments, $R^{1.3}$ and $R^{1.2}$ are joined to form a substituted 5 membered heteroaryl. In embodiments, $R^{1.3}$ and $R^{1.2}$ are joined to form a substituted 6 membered heteroaryl. In embodiments, $R^{1.3}$ and $R^{1.2}$ are joined to form a substituted 7 membered heteroaryl. In embodiments, $R^{1.3}$ and $R^{1.2}$ are joined to form a substituted 8 membered heteroaryl.

[0297] $R^{1.5}$ and $R^{1.6}$ may optionally be joined to form a substituted or unsubstituted cycloalkyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted or unsubstituted cyclobutyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted or unsubstituted cyclopentyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted or unsubstituted cyclohexyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted cyclobutyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted cyclopentyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted cyclohexyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form an unsubstituted cyclohexyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form an unsubstituted cyclopentyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form an unsubstituted cyclohexyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted cycloalkenyl (e.g., C3-C8, C3-C6, C4-C6, or C5-C6). In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted or unsubstituted cyclobutenyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted or unsubstituted cyclopentenyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted or unsubstituted cyclohexenyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted cyclobutenyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted cyclopentenyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form a substituted cyclohexenyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form an unsubstituted cyclobutenyl. In embodiments, $R^{1.5}$ and $R^{1.6}$ are joined to form an
unsubstituted cyclopentenyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted cyclohexenyl.

[0298] R\textsuperscript{1.5} and R\textsuperscript{1.6} may optionally be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form a substituted or unsubstituted 4 membered heterocycloalkyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form a substituted or unsubstituted 5 membered heterocycloalkyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form a substituted or unsubstituted 6 membered heterocycloalkyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form a substituted 4 membered heterocycloalkyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted 4 membered heterocycloalkyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted 5 membered heterocycloalkyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted 6 membered heterocycloalkyl. R\textsuperscript{1.5} and R\textsuperscript{1.6} may optionally be joined to form a substituted or unsubstituted 3 to 8 membered heterocycloalkenyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form a substituted or unsubstituted 4 membered heterocycloalkenyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form a substituted or unsubstituted 5 membered heterocycloalkenyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form a substituted or unsubstituted 6 membered heterocycloalkenyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted 4 membered heterocycloalkenyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted 5 membered heterocycloalkenyl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted 6 membered heterocycloalkenyl.

[0299] R\textsuperscript{1.5} and R\textsuperscript{1.6} may optionally be joined to form a substituted or unsubstituted C\textsubscript{6} aryl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form a substituted or unsubstituted C\textsubscript{6} aryl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted C\textsubscript{6} aryl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted C\textsubscript{12} aryl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted C\textsubscript{6} aryl. In embodiments, R\textsuperscript{1.5} and R\textsuperscript{1.6} are joined to form an unsubstituted C\textsubscript{12} aryl.
[0300] R\textsuperscript{1,5} and R\textsuperscript{1,6} may optionally be joined to form a substituted or unsubstituted 5 to 12 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form a substituted or unsubstituted 5 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form a substituted or unsubstituted 6 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form a substituted or unsubstituted 7 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form a substituted or unsubstituted 8 membered heteroaryl.

5 In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form a substituted or unsubstituted 5 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form a substituted or unsubstituted 6 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form a substituted or unsubstituted 7 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form a substituted or unsubstituted 8 membered heteroaryl.

10 In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form a substituted 5 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form an unsubstituted 5 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form an unsubstituted 6 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form an unsubstituted 7 membered heteroaryl. In embodiments, R\textsuperscript{1,5} and R\textsuperscript{1,6} are joined to form an unsubstituted 8 membered heteroaryl.

15 In embodiments, E is a covalent cysteine modifier moiety.

[0301] In embodiments, E is:

\begin{align*}
\text{O} & \quad \text{O} \\
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

or

\begin{align*}
\text{O} & \quad \text{O} \\
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

In embodiments, E is:

\begin{align*}
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

or

\begin{align*}
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

In embodiments, E is:

\begin{align*}
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

In embodiments, E is:

\begin{align*}
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

[0302] In embodiments, E is:

\begin{align*}
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

or

\begin{align*}
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

In embodiments, E is:

\begin{align*}
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

In embodiments, E is:

\begin{align*}
\text{R}^{15} & \quad \text{R}^{16} \\
\text{R}^{17} & \quad \text{R}^{17}
\end{align*}

[0303] R\textsuperscript{15} is independently hydrogen, halogen, CX\textsuperscript{15}, CH\textsubscript{2}X\textsuperscript{15}, -CN, -SO\textsubscript{2}NR\textsuperscript{15A}R\textsuperscript{15B}, -SO\textsubscript{2}NR\textsuperscript{15A}R\textsuperscript{15B}, -NH\textsubscript{2}NR\textsuperscript{15A}R\textsuperscript{15B}, -ONR\textsuperscript{15A}R\textsuperscript{15B}, -NHC(=0)NR\textsuperscript{15A}R\textsuperscript{15B}, -NHC(=0)NR\textsuperscript{15A}R\textsuperscript{15B}, -N(0)=N(0)=N(0), -NR\textsuperscript{15A}R\textsuperscript{15B}, -R\textsuperscript{15A}R\textsuperscript{15B}, -C(0)R\textsuperscript{15C}, -C(0)-OR\textsuperscript{15C}, -C(0)NR\textsuperscript{15A}R\textsuperscript{15B}, -OR\textsuperscript{15D}, -NR\textsuperscript{15A}SO\textsubscript{2}R\textsuperscript{15D}, -NR\textsuperscript{15A}C(0)R\textsuperscript{15C}, -
NR^{15}A(0)OR^{15C}, -NR^{15A}OR^{15C}, -OCX^{15}, -OCHX^{15}, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
heteroaryl. R^{16} is independently hydrogen, halogen, CX^{16}, -CHX^{16}.
5
CH_{2}X^{16}, -CN, -SO_{i}NR^{16D}, -SO_{i}R^{16D}, -NHR^{16AR^{16B}}, -NHNR^{16AR^{16B}}, -ONR^{16AR^{16B}},
-NHC=(0)NR^{16AR^{16B}}, -NHC(0)NR^{16AR^{16B}}, -N(0)_{i}^{16}, -NR^{16AR^{16B}}, -C(0)R^{16C},
-C(0)-OR^{16C}, -C(0)NR^{16AR^{16B}}, -OR^{16D}, -NR^{16AR^{16B}}SO_{i}^{16D}, -NR^{16AR^{16B}}R^{16D}, -NR^{16AR^{16B}}C(0)R^{16C},
NR^{16AC}(0)OR^{16C}, -NR^{16AR^{16C}}, -OCX^{16}, -OCHX^{16}, 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}, -CHX^{17}.
10
CH_{2}X^{17}, -CN, -SO_{i}NR^{17D}, -SO_{i}vNR^{17AR^{17B}}, -NHR^{17AR^{17B}}, -ONR^{17AR^{17B}},
-NHC=(0)NR^{17AR^{17B}}, -NHC(0)NR^{17AR^{17B}}, -N(0)_{i}^{17}, -NR^{17AR^{17B}}, -C(0)R^{17C},
-C(0)-OR^{17C}, -C(0)NR^{17AR^{17B}}, -OR^{17D}, -NR^{17AR^{17B}}SO_{i}^{17D}, -NR^{17AR^{17B}}R^{17D}, -NR^{17AR^{17B}}C(0)R^{17C},
NR^{17AC}(0)OR^{17C}, -NR^{17AR^{17C}}, -OCX^{17}, -OCHX^{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, -CX^{18}, -CHX^{18}, -CH_{2}X^{18},
15
-C(0)R^{18C}, -C(0)OR^{18C}, -C(0)NR^{18AR^{18B}}, substituted or unsubstituted alkyl, substituted or
unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
heteroaryl.

R^{18B}, R^{18C}, R^{18D}, is independently hydrogen, -CX^{3}, -CN, -COOH, -CONH_{2}, -CHX_{2}, -CH_{2}X,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{15A} and R^{15B} substituents
bonded to the same nitrogen atom may optionally be joined to form a substituted or
unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{16A} and R^{16B}
substituents bonded to the same nitrogen atom may optionally be joined to form a substituted
or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B}
substituents bonded to the same nitrogen atom may optionally be joined to form a substituted
or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B}
substituents bonded to the same nitrogen atom may optionally be joined to form a substituted
or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. Each \( X, X^{15}, X^{16}, X^{17} \) and \( X^{18} \) is independently \(-F, -Cl, -Br, \) or \(-I\). The symbols \( n15, n16, n17, v15, v16, \) and \( v17 \), are independently and integer from \( 0 \) to \( 4 \). The symbols \( ml5, ml6, \) and \( ml7 \) are independently and integer between \( 1 \) and \( 2 \).

[0305] In embodiments, \( E \) is: 

\[
\begin{align*}
\text{and } X^{17} & \text{ is } -Cl. \\
\text{In embodiments, } E & \text{ is: }
\end{align*}
\]

\[
\begin{align*}
\text{In embodiments, } X^{17} & \text{ is } -Cl.
\end{align*}
\]

[0306] In embodiments, \( E \) is: 

\[
\begin{align*}
\text{and } R^{15}, R^{16}, \text{ and } R^{17} & \text{ are independently hydrogen.}
\end{align*}
\]

\[
\begin{align*}
\text{In embodiments, } R^{15}, R^{16}, \text{ and } R^{17} & \text{ are independently hydrogen.}
\end{align*}
\]

[0307] In embodiments, \( E \) is: 

\[
\begin{align*}
\text{R}^{15} & \text{ is independently hydrogen; } R^{16} \text{ is independently hydrogen or } -CH2NR^{16A}R^{16B}; R^{17} \text{ is independently hydrogen; and } R^{16A} \text{ and } R^{16B} \text{ are independently hydrogen or unsubstituted alkyl. In embodiments, } E \text{ is:}
\end{align*}
\]

\[
\begin{align*}
\text{In embodiments, } R^{15} & \text{ is independently hydrogen. In embodiments, } R^{16} \text{ is independently hydrogen or } -CH2NR^{16A}R^{16B}. \text{In embodiments, } R^{17} \text{ is independently hydrogen. In embodiments, } R^{16A} \text{ and } R^{16B} \text{ are independently hydrogen or unsubstituted alkyl. In embodiments, } R^{16A} \text{ and } R^{16B} \text{ are independently unsubstituted methyl.}
\end{align*}
\]
In embodiments, E is: 

In embodiments, E is: 

In embodiments, E is: 

In embodiments, E is: 

[0308]  

In embodiments, E is: 

In embodiments, E is: 

In embodiments, E is: 

In embodiments, E is: 

[0309]  

X may independently be -F. X may independently be -Cl. X may independently be -Br. X may independently be -I. X<sub>15</sub> may independently be -F. X<sub>15</sub> may independently be -Cl. X<sub>15</sub> may independently be -Br. X<sub>15</sub> may independently be -I. X<sub>16</sub> may independently be -F. X<sub>16</sub> may independently be -Cl. X<sub>16</sub> may independently be -Br. X<sub>16</sub> may independently be -I. X<sub>17</sub> may independently be -F. X<sub>17</sub> may independently be -Cl. X<sub>17</sub> may independently be -Br. X<sub>17</sub> may independently be -I. X<sub>18</sub> may independently be -F. X<sub>18</sub> may independently be -Cl. X<sub>18</sub> may independently be -Br. X<sub>18</sub> may independently be -I. nl5 may independently be 0. nl5 may independently be 1. nl5 may independently be 2. nl5 may independently be 3. nl5 may independently be 4. nl6 may independently be 0. nl6 may independently be 1. nl6 may independently be 2. nl6 may independently be 3. nl6 may independently be 4. nl7 may independently be 0. nl7 may independently be 1. nl7 may independently be 2. nl7 may independently be 3. nl7 may independently be 4. vl5 may independently be 0. vl5 may independently be 1. vl5 may independently be 2. vl5 may independently be 3. vl5 may independently be 4. vl6 may independently be 0. vl6 may independently be 1. vl6 may independently be 2. vl6 may independently be 3. vl6 may independently be 4. vl7 may independently be 0. vl7 may independently be 1. vl7 may independently be 2. vl7 may independently be 3. vl7 may independently be 4. ml5 may independently be 1. ml5 may independently be 2. ml5 may independently be 3. ml5 may independently be 4. ml6 may independently be 1. ml6 may independently be 2. ml6 may independently be 3. ml6 may independently be 4. ml7 may independently be 1. ml7 may independently be 2. ml7 may independently be 3. ml7 may independently be 4.
In embodiments, R₁₅ is hydrogen. In embodiments, R₁₅ is halogen. In embodiments, R₁₅ is CX₃. In embodiments, R₁₅ is -CHX₂. In embodiments, R₁₅ is -CH₂X. In embodiments, R₁₅ is -CN. In embodiments, R₁₅ is -SO₃NR₁₅R₁₅B. In embodiments, R₁₅ is -ONR₁₅R₁₅B. In embodiments, R₁₅ is -NHC(0)NR₁₅R₁₅B. In embodiments, R₁₅ is -NH(0)NR₁₅R₁₅B. In embodiments, R₁₅ is -NR₁₅R₁₅B. In embodiments, R₁₅ is -NR₁₅C(0)OR₁₅C. In embodiments, R₁₅ is -NR₁₅AOR₁₅C. In embodiments, R₁₅ is -OCX₃. In embodiments, R₁₅ is -OCHX₂. In embodiments, R₁₅ is substituted or unsubstituted alkyl. In embodiments, R₁₅ is substituted or unsubstituted heteroalkyl. In embodiments, R₁₅ is substituted or unsubstituted cycloalkyl. In embodiments, R₁₅ is substituted or unsubstituted aryl. In embodiments, R₁₅ is substituted or unsubstituted heteroaryl. In embodiments, R₁₅ is substituted or unsubstituted heteroaryl. In embodiments, R₁₅ is substituted heteroalkyl. In embodiments, R₁₅ is substituted cycloalkyl. In embodiments, R₁₅ is substituted heteroaryl. In embodiments, R₁₅ is substituted heteroaryl. In embodiments, R₁₅ is substituted alkyl. In embodiments, R₁₅ is substituted methyl. In embodiments, R₁₅ is substituted ethyl. In embodiments, R₁₅ is substituted propyl. In embodiments, R₁₅ is substituted isopropyl. In embodiments, R₁₅ is unsubstituted butyl. In embodiments, R₁₅ is unsubstituted tert-butyl.

In embodiments, R¹⁵A is hydrogen. In embodiments, R¹⁵A is -CX₃. In embodiments, R¹⁵A is -CN. In embodiments, R¹⁵A is -COOH. In embodiments, R¹⁵A is -CONH₂. In embodiments, R¹⁵A is -CHX₂. In embodiments, R¹⁵A is -CH₂X. In embodiments, R¹⁵A is unsubstituted methyl. In embodiments, R¹⁵A is unsubstituted ethyl. In embodiments, R¹⁵A is unsubstituted propyl. In embodiments, R¹⁵A is unsubstituted isopropyl. In embodiments, R¹⁵A is unsubstituted butyl. In embodiments, R¹⁵A is unsubstituted tert-butyl.
In embodiments, R\textsuperscript{15B} is hydrogen. In embodiments, R\textsuperscript{15B} is -CX\textsubscript{3}. In
embodiments, R\textsuperscript{15B} is -CN. In embodiments, R\textsuperscript{15B} is -COOH. In embodiments, R\textsuperscript{15B}
is -CONHi. In embodiments, R\textsuperscript{15B} is -CH\textsubscript{X\textsubscript{2}}. In embodiments, R\textsuperscript{15B} is -CH\textsubscript{2}X. In
embodiments, R\textsuperscript{15B} is unsubstituted methyl. In embodiments, R\textsuperscript{15B} is unsubstituted ethyl. In
embodiments, R\textsuperscript{15B} is unsubstituted propyl. In embodiments, R\textsuperscript{15B} is unsubstituted isopropyl.
In embodiments, R\textsuperscript{15B} is unsubstituted butyl. In embodiments, R\textsuperscript{15B} is unsubstituted tert-
butyl.

In embodiments, R\textsuperscript{15C} is hydrogen. In embodiments, R\textsuperscript{15C} is -CX\textsubscript{3}. In
embodiments, R\textsuperscript{15C} is -CN. In embodiments, R\textsuperscript{15C} is -COOH. In embodiments, R\textsuperscript{15C}
is -CONH2. In embodiments, R\textsuperscript{15C} is -CH\textsubscript{X\textsubscript{2}}. In embodiments, R\textsuperscript{15C} is -CH\textsubscript{2}X. In
embodiments, R\textsuperscript{15C} is unsubstituted methyl. In embodiments, R\textsuperscript{15C} is unsubstituted ethyl. In
embodiments, R\textsuperscript{15C} is unsubstituted propyl. In embodiments, R\textsuperscript{15C} is unsubstituted isopropyl.
In embodiments, R\textsuperscript{15C} is unsubstituted butyl. In embodiments, R\textsuperscript{15C} is unsubstituted tert-
butyl.

In embodiments, R\textsuperscript{15D} is hydrogen. In embodiments, R\textsuperscript{15D} is -CX\textsubscript{3}. In
embodiments, R\textsuperscript{15D} is -CN. In embodiments, R\textsuperscript{15D} is -COOH. In embodiments, R\textsuperscript{15D}
is -CONH2. In embodiments, R\textsuperscript{15D} is -CH\textsubscript{X\textsubscript{2}}. In embodiments, R\textsuperscript{15D} is -CH\textsubscript{2}X. In
embodiments, R\textsuperscript{15D} is unsubstituted methyl. In embodiments, R\textsuperscript{15D} is unsubstituted ethyl. In
embodiments, R\textsuperscript{15D} is unsubstituted propyl. In embodiments, R\textsuperscript{15D} is unsubstituted isopropyl.
In embodiments, R\textsuperscript{15D} is unsubstituted butyl. In embodiments, R\textsuperscript{15D} is unsubstituted tert-
butyl.

In embodiments, R\textsuperscript{15} is independently hydrogen, oxo,
ahalogen, -CX\textsuperscript{15} \textsubscript{3}, -CH\textsubscript{X\textsubscript{15}} \textsubscript{2}, -OCH\textsubscript{2}X \textsuperscript{15}. -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH2, -NO2, -SH, -S\textsubscript{0} \textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHN\textsubscript{H}2, -ON\textsubscript{H}2, -NHC=(0)NHN\textsubscript{H}2, -NHC=(0)NH 2, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OC\textsubscript{X\textsubscript{15}} \textsubscript{3}, -OCH\textsubscript{X\textsubscript{15}} \textsubscript{2}, R\textsuperscript{72}-substituted or unsubstituted alkyl, R\textsuperscript{72}-substituted or unsubstituted heteroalkyl, R\textsuperscript{72}-substituted or unsubstituted cycloalkyl, R\textsuperscript{72}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{72}-substituted or unsubstituted aryl, or R\textsuperscript{72}-substituted or unsubstituted heteroaryl. X\textsuperscript{15} is halogen. In
embodiments, X\textsuperscript{15} is F.

R\textsuperscript{72} is independently oxo,
ahalogen, -CX\textsuperscript{72} \textsubscript{3}, -CH\textsubscript{X\textsubscript{72}} \textsubscript{2}, -OCH\textsubscript{2}X \textsuperscript{72}, -OCH\textsubscript{X\textsubscript{72}} \textsubscript{2}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH2, -NO2, -SH, -S\textsubscript{0} \textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHN\textsubscript{H}2, -ON\textsubscript{H}2, -NHC=(0)NHN\textsubscript{H}2, -NHC=(0)NH 2.
NHSO₂H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX₃, -OCHX₂, R₁-substituted or unsubstituted alkyl, R₇₃-substituted or unsubstituted heteroalkyl, R₇₃-substituted or unsubstituted cycloalkyl, R₇₃-substituted or unsubstituted heterocycloalkyl, R₇₃-substituted or unsubstituted aryl, or R₇₃-substituted or unsubstituted heteroaryl. X₇₂ is halogen. In embodiments, X₇² is F.

[R0317] R₇₃ is independently oxo, halogen, -CX₇₃, -CHX₇₃, -OCH₂X₇₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHC(0)-OH, -NHOH, -OCX₃, -OCHX₂, R₇₄-substituted or unsubstituted alkyl, R₇₄-substituted or unsubstituted heteroalkyl, R₇₄-substituted or unsubstituted cycloalkyl, R₇₄-substituted or unsubstituted heterocycloalkyl, R₇₄-substituted or unsubstituted aryl, or R₇₄-substituted or unsubstituted heteroaryl. X₇₃ is halogen. In embodiments, X₇₃ is F.

[R0318] In embodiments, R₁⁵A is independently hydrogen, oxo, halogen, -CX₁⁵A₃, -CHX₁⁵A₃, -OCH₂X₁⁵A, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHC(0)-OH, -NHOH, -OCX₁⁵A₃, -OCHX₁⁵A₃, R₇²A-substituted or unsubstituted alkyl, R₇²A-substituted or unsubstituted heteroalkyl, R₇²A-substituted or unsubstituted cycloalkyl, R₇²A-substituted or unsubstituted heterocycloalkyl, R₇²A-substituted or unsubstituted aryl, or R₇²A-substituted or unsubstituted heteroaryl. X₁⁵A is halogen. In embodiments, X₁⁵A is F.

[R0319] R₇²A is independently oxo, halogen, -CX₇²A₃, -CHX₇²A₃, -OCH₂X₇²A, -OCHX₇²A, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHC(0)-OH, -NHOH, -OCX₇²A₃, -OCHX₇²A₃, R₇³A-substituted or unsubstituted alkyl, R₇³A-substituted or unsubstituted heteroalkyl, R₇³A-substituted or unsubstituted cycloalkyl, R₇³A-substituted or unsubstituted heterocycloalkyl, R₇³A-substituted or unsubstituted aryl, or R₇³A-substituted or unsubstituted heteroaryl. X₇²A is halogen. In embodiments, X₇²A is F.

[R0320] R₇³A is independently oxo, halogen, -CX₇³A₃, -CHX₇³A₃, -OCH₂X₇³A, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHC(0)-OH, -NHOH, -OCX₇³A₃, -OCHX₇³A₃, R₇⁴A-substituted or unsubstituted alkyl, R₇⁴A-substituted or unsubstituted heteroalkyl, R₇⁴A-substituted or unsubstituted cycloalkyl, R₇⁴A-substituted or unsubstituted heterocycloalkyl, R₇⁴A-substituted or unsubstituted aryl, or R₇⁴A-substituted or unsubstituted heteroaryl. X₇³A is halogen. In embodiments, X₇³A is F.
NHSO₂H, -NHC=(0)H, -NHOH, -OCX₃₂, -OCH₂X₂, R₄A -substituted or unsubstituted alkyl, R₄A -substituted or unsubstituted heteroalkyl, R₄A -substituted or unsubstituted cycloalkyl, R₄A -substituted or unsubstituted heterocycloalkyl, R₄A -substituted or unsubstituted aryl, or R₄A -substituted or unsubstituted heteroaryl. X₃₂ is halogen. In embodiments, X₃₂ is F.

[0321] In embodiments, R₁⁵B is independently hydrogen, oxo, halogen, -CX₁⁵B₃, -CHX₁⁵B₂, -OCH₂X₁⁵B, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -S₀IH, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NH₂, -NHSO₂H, -NHC=(0)H, -NHOH, -OCX₃₂, -OCH₂, R₇₂B -substituted or unsubstituted alkyl, R₇₂B -substituted or unsubstituted heteroalkyl, R₇₂B -substituted or unsubstituted cycloalkyl, R₇₂B -substituted or unsubstituted heterocycloalkyl, or R₇₂B -substituted or unsubstituted aryl, or R₇₂B -substituted or unsubstituted heteroaryl. X₁⁵B is halogen. In embodiments, X₁⁵B is F.

[0322] R₇₂B is independently oxo, halogen, -CX₇₂B₃, -CHX₇₂B₂, -OCH₂, -OCH₂X₇₂B, -OCX₇₂B, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -S₀IH, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NH₂, -NHSO₂H, -NHC=(0)H, -NHOH, -OCX₇₂B, -OCH₂X₇₂B, R₇₃B -substituted or unsubstituted alkyl, R₇₃B -substituted or unsubstituted heteroalkyl, R₇₃B -substituted or unsubstituted cycloalkyl, R₇₃B -substituted or unsubstituted heterocycloalkyl, R₇₃B -substituted or unsubstituted aryl, or R₇₃B -substituted or unsubstituted heteroaryl. X₇₂B is halogen. In embodiments, X₇₂B is F.

[0323] R₇₃B is independently oxo, halogen, -CX₇₃B₃, -CHX₇₃B₂, -OCH₂X₇₃B, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -S₀IH, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NH₂, -NHSO₂H, -NHC=(0)H, -NHOH, -OCX₇₃B, -OCH₂X₇₃B, R₇₄B -substituted or unsubstituted alkyl, R₇₄B -substituted or unsubstituted heteroalkyl, R₇₄B -substituted or unsubstituted cycloalkyl, R₇₄B -substituted or unsubstituted heterocycloalkyl, or R₇₄B -substituted or unsubstituted aryl, or R₇₄B -substituted or unsubstituted heteroaryl. X₇₃B is halogen. In embodiments, X₇₃B is F.

[0324] In embodiments, R₁⁵C is independently hydrogen, oxo, halogen, -CX₁⁵C₃, -CHX₁⁵C₂, -OCH₂X₁⁵C, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -S₀IH, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NH₂, -NHSO₂H, -NHC=(0)H, -NHOH, -OCX₃₂, -OCH₂, R₇₂B -substituted or unsubstituted alkyl, R₇₂B -substituted or unsubstituted heteroalkyl, R₇₂B -substituted or unsubstituted cycloalkyl, R₇₂B -substituted or unsubstituted heterocycloalkyl, R₇₂B -substituted or unsubstituted aryl, or R₇₂B -substituted or unsubstituted heteroaryl. X₃₂ is halogen. In embodiments, X₃₂ is F.
NHSO₂H, -NHC=(0)H, -NHO₂H, -O₃Cₓ³, -OCHₓ²⁴₂, R²₋₄ substituted or unsubstituted alkyl, R²₋₄ substituted or unsubstituted heteroalkyl, R²₋₄ substituted or unsubstituted cycloalkyl, R²₋₄ substituted or unsubstituted heterocycloalkyl, R²₋₄ substituted or unsubstituted aryl, or R²₋₄ substituted or unsubstituted heteroaryl. X₁⁵C is halogen. In embodiments, X₁⁵C is F.

[R0325] R²₋₄ is independently oxo, halogen, -CX₂₋₄, -CHX₂₋₄, -OCHₓ²⁴₂, -OCHX₂₋₄, -CN, -OH, -NH₂, -COOH, -CONH₂, -N₂₋₄, -SH, -SOₓ₃₋₄, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NHNH₂, -NHOH, -OCX₂₋₄, -OCHX₂₋₄, R³₋₄ substituted or unsubstituted alkyl, R³₋₄ substituted or unsubstituted heteroalkyl, R³₋₄ substituted or unsubstituted cycloalkyl, R³₋₄ substituted or unsubstituted heterocycloalkyl, R³₋₄ substituted or unsubstituted aryl, or R³₋₄ substituted or unsubstituted heteroaryl. X₂₋₄ is halogen. In embodiments, X₂₋₄ is F.

[R0326] R³₋₄ is independently oxo, halogen, -CX₃₋₄, -CHX₃₋₄, -OCHₓ₃₋₄, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SOₓ₂₋₄, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NHNH₂, -NHOH, -OCX₃₋₄, -OCHX₃₋₄, R⁴₋₄ substituted or unsubstituted alkyl, R⁴₋₄ substituted or unsubstituted heteroalkyl, R⁴₋₄ substituted or unsubstituted cycloalkyl, R⁴₋₄ substituted or unsubstituted heterocycloalkyl, R⁴₋₄ substituted or unsubstituted aryl, or R⁴₋₄ substituted or unsubstituted heteroaryl. X₇₋₄ is halogen. In embodiments, X₇₋₄ is F.

[R0327] In embodiments, R⁵₋₄ is independently hydrogen, oxo, halogen, -CX₅₋₄, -CHX₅₋₄, -OCHₓ₅₋₄, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SOₓ₂₋₄, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NHNH₂, -NHOH, -OCX₅₋₄, -OCHX₅₋₄, R⁶₋₄ substituted or unsubstituted alkyl, R⁶₋₄ substituted or unsubstituted heteroalkyl, R⁶₋₄ substituted or unsubstituted cycloalkyl, R⁶₋₄ substituted or unsubstituted heterocycloalkyl, R⁶₋₄ substituted or unsubstituted aryl, or R⁶₋₄ substituted or unsubstituted heteroaryl. X₁⁵D is halogen. In embodiments, X₁⁵D is F.

[R0328] R⁷₋₄ is independently oxo, halogen, -CX₇₋₄, -CHX₇₋₄, -OCHₓ₇₋₄, -OCHX₇₋₄, -CN, -OH, -NH₂, -COOH, -CONH₂, -N₂₋₄, -SH, -SOₓ₂₋₄, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NHNH₂, -NHOH, -OCX₇₋₄, -OCHX₇₋₄, R⁸₋₄ substituted or unsubstituted alkyl, R⁸₋₄ substituted or unsubstituted heteroalkyl, R⁸₋₄ substituted or unsubstituted cycloalkyl, R⁸₋₄ substituted or unsubstituted heterocycloalkyl, R⁸₋₄ substituted or unsubstituted aryl, or R⁸₋₄ substituted or unsubstituted heteroaryl. X₁⁵D is halogen. In embodiments, X₁⁵D is F.
-NHC=(0)NH$_2$, -NHSO$_2$H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX$_{2}$D, -OCHX$_{2}$D$_2$, R$_{3D}$-substituted or unsubstituted alkyl, R$_{3D}$-substituted or unsubstituted heteroalkyl, R$_{3D}$-substituted or unsubstituted cycloalkyl, R$_{3D}$-substituted or unsubstituted heterocycloalkyl, R$_{3D}$-substituted or unsubstituted aryl, or R$_{3D}$-substituted or unsubstituted heteroaryl. X$_{2D}$ is halogen. In embodiments, X$_{2D}$ is F.

[0329] R$_{3D}$ is independently oxo, halogen, -C$_{X_{3D}}$, -CHX$_{2}$, -OCH$_{2}$X$_{3D}$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -NO$_2$, -SH, -SO$_3$H, -SO$_4$H, -SO$_2$NH$_2$, -NH$_2$ - ONH$_2$, - NHC=(0)NHNH$_2$, - NHC=(0)NH$_2$, - NHSO$_2$H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX$_{3D}$, -OCHX$_{3D}$, R$_{4D}$-substituted or unsubstituted alkyl, R$_{4D}$-substituted or unsubstituted heteroalkyl, R$_{4D}$-substituted or unsubstituted cycloalkyl, R$_{4D}$-substituted or unsubstituted heterocycloalkyl, R$_{4D}$-substituted or unsubstituted aryl, or R$_{4D}$-substituted or unsubstituted heteroaryl. X$_{3D}$ is halogen. In embodiments, X$_{3D}$ is F.

[0330] In embodiments, R$_{16}$ is hydrogen. In embodiments, R$_{16}$ is halogen. In embodiments, R$_{16}$ is -CX$_{16}$. In embodiments, R$_{16}$ is -CHX$_{16}$. In embodiments, R$_{16}$ is -CN. In embodiments, R$_{16}$ is -SO$_{i_6}$NR$_{16A}$. In embodiments, R$_{16}$ is -SO$_{i_6}$NR$_{16A}$R$_{16B}$. In embodiments, R$_{16}$ is -ONR$_{16A}$R$_{16B}$. In embodiments, R$_{16}$ is -NHC(0)NR$_{16A}$R$_{16B}$. In embodiments, R$_{16}$ is -NHC(0)(0)NHR$_{16A}$R$_{16B}$. In embodiments, R$_{16}$ is -C(0)R$_{16C}$. In embodiments, R$_{16}$ is -C(0)-OR$_{16C}$. In embodiments, R$_{16}$ is -C(0)NR$_{16AD}$. In embodiments, R$_{16}$ is -OR$_{16D}$. In embodiments, R$_{16}$ is -NR$_{16ASO_2}$R$_{16D}$. In embodiments, R$_{16}$ is -NR$_{16AC}(0)$R$_{16C}$. In embodiments, R$_{16}$ is -NR$_{16AC}(0)$OR$_{16C}$. In embodiments, R$_{16}$ is -OCX$_{16C}$. In embodiments, R$_{16}$ is -OCHX$_{16}$ in embodiments, R$_{16}$ is substituted or unsubstituted alkyl. In embodiments, R$_{16}$ is substituted or unsubstituted heteroalkyl. In embodiments, R$_{16}$ is substituted or unsubstituted heterocycloalkyl. In embodiments, R$_{16}$ is substituted or unsubstituted heterocycloalkyl. In embodiments, R$_{16}$ is substituted or unsubstituted heteroaryl. In embodiments, R$_{16}$ is substituted alkyl. In embodiments, R$_{16}$ is substituted heteroalkyl. In embodiments, R$_{16}$ is substituted heterocycloalkyl. In embodiments, R$_{16}$ is substituted heteroaryl. In embodiments, R$_{16}$ is substituted alkyl. In embodiments, R$_{16}$ is unsubstituted alkyl. In embodiments, R$_{16}$ is unsubstituted heteroalkyl. In embodiments, R$_{16}$ is unsubstituted heterocycloalkyl. In embodiments, R$_{16}$ is unsubstituted heteroaryl. In embodiments, R$_{16}$ is unsubstituted.
cycloalkyl. In embodiments, R_16 is unsubstituted heterocycloalkyl. In embodiments, R_16 is unsubstituted aryl. In embodiments, R_16 is unsubstituted heteroaryl. In embodiments, R_16 is unsubstituted methyl. In embodiments, R_16 is unsubstituted ethyl. In embodiments, R_16 is unsubstituted propyl. In embodiments, R_16 is unsubstituted isopropyl. In embodiments, R_16 is unsubstituted butyl. In embodiments, R_16 is unsubstituted tert-butyl.

[0331] In embodiments, R_16A is hydrogen. In embodiments, R_16A is -CX_3. In embodiments, R_16A is -CN. In embodiments, R_16A is -COOH. In embodiments, R_16A is -CONH_2. In embodiments, R_16A is -CHX_2. In embodiments, R_16A is -CH_2X. In embodiments, R_16A is unsubstituted methyl. In embodiments, R_16A is unsubstituted ethyl. In embodiments, R_16A is unsubstituted propyl. In embodiments, R_16A is unsubstituted isopropyl. In embodiments, R_16A is unsubstituted butyl. In embodiments, R_16A is unsubstituted tert-butyl.

[0332] In embodiments, R_16B is hydrogen. In embodiments, R_16B is -CX_3. In embodiments, R_16B is -CN. In embodiments, R_16B is -COOH. In embodiments, R_16B is -CONH_2. In embodiments, R_16B is -CHX_2. In embodiments, R_16B is -CH_2X. In embodiments, R_16B is unsubstituted methyl. In embodiments, R_16B is unsubstituted ethyl. In embodiments, R_16B is unsubstituted propyl. In embodiments, R_16B is unsubstituted isopropyl. In embodiments, R_16B is unsubstituted butyl. In embodiments, R_16B is unsubstituted tert-butyl.

[0333] In embodiments, R_16C is hydrogen. In embodiments, R_16C is -CX_3. In embodiments, R_16C is -CN. In embodiments, R_16C is -COOH. In embodiments, R_16C is -CONH_2. In embodiments, R_16C is -CHX_2. In embodiments, R_16C is -CH_2X. In embodiments, R_16C is unsubstituted methyl. In embodiments, R_16C is unsubstituted ethyl. In embodiments, R_16C is unsubstituted propyl. In embodiments, R_16C is unsubstituted isopropyl. In embodiments, R_16C is unsubstituted butyl. In embodiments, R_16C is unsubstituted tert-butyl.

In embodiments, R\textsuperscript{16D} is unsubstituted butyl. In embodiments, R\textsuperscript{16D} is unsubstituted tert-butyl.

[0335] In embodiments, R\textsuperscript{16} is independently hydrogen, oxo, halogen, -CX\textsuperscript{16}, -CHX\textsuperscript{16}, -OCX\textsuperscript{16}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}N\textsubscript{2}H\textsubscript{2}, -NHN\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHN\textsubscript{2}, -NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{16}, -OCH\textsuperscript{16}, R\textsuperscript{75}-substituted or unsubstituted alkyl, R\textsuperscript{75}-substituted or unsubstituted heteroalkyl, R\textsuperscript{75}-substituted or unsubstituted cycloalkyl, R\textsuperscript{75}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{75}-substituted or unsubstituted aryl, or R\textsuperscript{75}-substituted or unsubstituted heteroaryl. X\textsuperscript{16} is halogen. In embodiments, X\textsuperscript{16} is F.

[0336] R\textsuperscript{75} is independently oxo,

halogen, -CX\textsuperscript{75}, -CHX\textsuperscript{75}, -OCX\textsuperscript{75}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}N\textsubscript{2}H\textsubscript{2}, -NHN\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHN\textsubscript{2}, -NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{75}, -OCH\textsuperscript{75}, R\textsuperscript{76}-substituted or unsubstituted alkyl, R\textsuperscript{76}-substituted or unsubstituted heteroalkyl, R\textsuperscript{76}-substituted or unsubstituted cycloalkyl, R\textsuperscript{76}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{76}-substituted or unsubstituted aryl, or R\textsuperscript{76}-substituted or unsubstituted heteroaryl. X\textsuperscript{75} is halogen. In embodiments, X\textsuperscript{75} is F.

[0337] R\textsuperscript{76} is independently oxo,

halogen, -CX\textsuperscript{76}, -CHX\textsuperscript{76}, -OCX\textsuperscript{76}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}N\textsubscript{2}H\textsubscript{2}, -NHN\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHN\textsubscript{2}, -NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{76}, -OCH\textsuperscript{76}, R\textsuperscript{77}-substituted or unsubstituted alkyl, R\textsuperscript{77}-substituted or unsubstituted heteroalkyl, R\textsuperscript{77}-substituted or unsubstituted cycloalkyl, R\textsuperscript{77}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{77}-substituted or unsubstituted aryl, or R\textsuperscript{77}-substituted or unsubstituted heteroaryl. X\textsuperscript{76} is halogen. In embodiments, X\textsuperscript{76} is F.

[0338] In embodiments, R\textsuperscript{16A} is independently hydrogen, oxo, halogen, -CX\textsuperscript{16A}, -CHX\textsuperscript{16A}, -OCX\textsuperscript{16A}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}N\textsubscript{2}H\textsubscript{2}, -NHN\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHN\textsubscript{2}, -NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{16A}, -OCH\textsuperscript{16A}, R\textsuperscript{75A}-substituted or unsubstituted alkyl, R\textsuperscript{75A}-substituted or unsubstituted heteroalkyl, R\textsuperscript{75A}-substituted or unsubstituted cycloalkyl, R\textsuperscript{75A}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{75A}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{75A}-substituted or unsubstituted heteroaryl. X\textsuperscript{16A} is halogen. In embodiments, X\textsuperscript{16A} is F.
or unsubstituted aryl, or R\textsuperscript{75A}.-substituted or unsubstituted heteroaryl. X\textsuperscript{16A} is halogen. In embodiments, X\textsuperscript{16A} is F.

[0339] R\textsuperscript{75A} is independently oxo,

halogen, -C\textsubscript{X}\textsuperscript{75A}\textsubscript{3}, -CHX\textsuperscript{75A}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{75A}, -OCHX\textsuperscript{75A}\textsubscript{2}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{0}\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -N\textsubscript{H}C=(0)N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -N\textsubscript{H}C=(0)N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -NHSO\textsubscript{2}H, -N\textsubscript{H}C=(0)H, -N\textsubscript{H}C=(0)OH, -N\textsubscript{H}OH, -OCX\textsuperscript{75A}\textsubscript{3}, -OCHX\textsuperscript{75A}\textsubscript{2}, R\textsuperscript{76A}.-substituted or unsubstituted alkyl, R\textsuperscript{76A}.-substituted or unsubstituted heteroalkyl, R\textsuperscript{76A}.-substituted or unsubstituted cycloalkyl, R\textsuperscript{76A}.-substituted or unsubstituted aryl, or R\textsuperscript{76A}.-substituted or unsubstituted heteroaryl. X\textsuperscript{75A} is halogen. In embodiments, X\textsuperscript{75A} is F.

[0340] R\textsuperscript{76A} is independently oxo,

halogen, -C\textsubscript{X}\textsuperscript{76A}\textsubscript{3}, -CHX\textsuperscript{76A}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{76A}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -S\textsubscript{O}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -N\textsubscript{H}C=(0)N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -N\textsubscript{H}C=(0)N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -NHSO\textsubscript{2}H, -N\textsubscript{H}C=(0)H, -N\textsubscript{H}C=(0)OH, -N\textsubscript{H}OH, -OCX\textsuperscript{76A}\textsubscript{3}, -OCHX\textsuperscript{76A}\textsubscript{2}, R\textsuperscript{77A}.-substituted or unsubstituted alkyl, R\textsuperscript{77A}.-substituted or unsubstituted heteroalkyl, R\textsuperscript{77A}.-substituted or unsubstituted cycloalkyl, R\textsuperscript{77A}.-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{77A}.-substituted or unsubstituted aryl, or R\textsuperscript{77A}.-substituted or unsubstituted heteroaryl. X\textsuperscript{76A} is halogen. In embodiments, X\textsuperscript{76A} is F.

[0341] In embodiments, R\textsuperscript{16B} is independently hydrogen, oxo,

halogen, -C\textsubscript{X}\textsuperscript{16B}\textsubscript{3}, -CHX\textsuperscript{16B}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{16B}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -S\textsubscript{O}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -N\textsubscript{H}C=(0)N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -N\textsubscript{H}C=(0)N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -NHSO\textsubscript{2}H, -N\textsubscript{H}C=(0)H, -N\textsubscript{H}C=(0)OH, -N\textsubscript{H}OH, -OCX\textsuperscript{16B}\textsubscript{3}, -OCHX\textsuperscript{16B}\textsubscript{2}, R\textsuperscript{75B}.-substituted or unsubstituted alkyl, R\textsuperscript{75B}.-substituted or unsubstituted heteroalkyl, R\textsuperscript{75B}.-substituted or unsubstituted cycloalkyl, R\textsuperscript{75B}.-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{75B}.-substituted or unsubstituted aryl, or R\textsuperscript{75B}.-substituted or unsubstituted heteroaryl. X\textsuperscript{16B} is halogen. In embodiments, X\textsuperscript{16B} is F.

[0342] R\textsuperscript{75B} is independently oxo,

halogen, -C\textsubscript{X}\textsuperscript{75B}\textsubscript{3}, -CHX\textsuperscript{75B}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{75B}, -OCHX\textsuperscript{75B}\textsubscript{2}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{0}\textsubscript{2}, -SH, -S\textsubscript{O}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -N\textsubscript{H}C=(0)N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -N\textsubscript{H}C=(0)N\textsubscript{H}N\textsubscript{H}N\textsubscript{2}, -NHSO\textsubscript{2}H, -N\textsubscript{H}C=(0)H, -N\textsubscript{H}C=(0)OH, -N\textsubscript{H}OH, -OCX\textsuperscript{75B}\textsubscript{3}, -OCHX\textsuperscript{75B}\textsubscript{2}, R\textsuperscript{76B}.-substituted or unsubstituted alkyl, R\textsuperscript{76B}.-substituted or unsubstituted heteroalkyl, R\textsuperscript{76B}.-
substituted or unsubstituted cycloalkyl, R^{76b}.-substituted or unsubstituted heterocycloalkyl, R^{76b}.-substituted or unsubstituted aryl, or R^{76b}.-substituted or unsubstituted heteroaryl. X^{75b} is halogen. In embodiments, X^{75b} is F.

[0343] R^{76b} is independently oxo, halogen, -CX^{76b}_{3}, -CHX^{76b}_{2}, -OCH_{2}X^{76b}_{3}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -N0_{2}, -SH, -SO_{3}H, -SO_{4}H, -SO_{2}NH_{2}, -NHNH_{2}, -ONH_{2}, -NHC=(0)NHNH_{2}, -NHC=(0)NH_{2}, -NHSO_{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX^{76b}_{3}, -OCHX^{76b}_{2}, R^{77b}.-substituted or unsubstituted alkyl, R^{77b}.-substituted or unsubstituted heteroaryl, R^{77b}.-substituted or unsubstituted cycloalkyl, R^{77b}.-substituted or unsubstituted heterocycloalkyl, R^{77b}.-substituted or unsubstituted aryl, or R^{77b}.-substituted or unsubstituted heteroaryl. X^{76b} is halogen. In embodiments, X^{76b} is F.

[0344] In embodiments, R^{16c} is independently hydrogen, oxo, halogen, -CX^{16c}_{3}, -CHX^{16c}_{2}, -OCH_{2}X^{16c}_{3}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -NO_{2}, -SH, -SO_{3}H, -SO_{4}H, -SO_{2}NH_{2}, -NHNH_{2}, -ONH_{2}, -NHC=(0)NHNH_{2}, -NHC=(0)NH_{2}, -NHSO_{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX^{16c}_{3}, -OCHX^{16c}_{2}, R^{75c}.-substituted or unsubstituted alkyl, R^{75c}.-substituted or unsubstituted heteroaryl, R^{75c}.-substituted or unsubstituted cycloalkyl, R^{75c}.-substituted or unsubstituted heterocycloalkyl, R^{75c}.-substituted or unsubstituted aryl, or R^{75c}.-substituted or unsubstituted heteroaryl. X^{16c} is halogen. In embodiments, X^{16c} is F.

[0345] R^{75c} is independently oxo, halogen, -CX^{75c}_{3}, -CHX^{75c}_{2}, -OCH_{2}X^{75c}_{3}, -OCX^{75c}_{3}, -OCHX^{75c}_{2}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -N0_{2}, -SH, -SO_{3}H, -SO_{4}H, -SO_{2}NH_{2}, -NHNH_{2}, -ONH_{2}, -NHC=(0)NHNH_{2}, -NHC=(0)NH_{2}, -NHSO_{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX^{75c}_{3}, -OCHX^{75c}_{2}, R^{76c}.-substituted or unsubstituted alkyl, R^{76c}.-substituted or unsubstituted heteroaryl, R^{76c}.-substituted or unsubstituted cycloalkyl, R^{76c}.-substituted or unsubstituted heterocycloalkyl, R^{76c}.-substituted or unsubstituted aryl, or R^{76c}.-substituted or unsubstituted heteroaryl. X^{75c} is halogen. In embodiments, X^{75c} is F.

[0346] R^{76c} is independently oxo, halogen, -CX^{76c}_{3}, -CHX^{76c}_{2}, -OCH_{2}X^{76c}_{3}, -CN, -OH, -NH_{2}, -COOH, -CONH_{2}, -NO_{2}, -SH, -SO_{3}H, -SO_{4}H, -SO_{2}NH_{2}, -NHNH_{2}, -ONH_{2}, -NHC=(0)NHNH_{2}, -NHC=(0)NH_{2}, -NHSO_{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX^{76c}_{3}, -OCHX^{76c}_{2}, R^{77c}.-substituted or
unsubstituted alkyl, R\textsuperscript{77C}-substituted or unsubstituted heteroalkyl, R\textsuperscript{77C}-substituted or unsubstituted cycloalkyl, R\textsuperscript{77C}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{77C}-substituted or unsubstituted aryl, or R\textsuperscript{77C}-substituted or unsubstituted heteroaryl. X\textsuperscript{76C} is halogen. In embodiments, X\textsuperscript{76C} is F.

[0347] In embodiments, R\textsuperscript{16D} is independently hydrogen, oxo, halogen, -CX\textsuperscript{16D}\textsubscript{3}, -CHX\textsuperscript{16D}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{16D}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{0}\textsubscript{2}, -SH, -S\textsubscript{0}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHN\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHN\textsubscript{2}, -NHC=(0)NH, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{16D}\textsubscript{3}, -OCHX\textsuperscript{16D}, R\textsuperscript{75D}-substituted or unsubstituted alkyl, R\textsuperscript{75D}-substituted or unsubstituted heteroalkyl, R\textsuperscript{75D}-substituted or unsubstituted cycloalkyl, R\textsuperscript{75D}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{75D}-substituted or unsubstituted aryl, or R\textsuperscript{75D}-substituted or unsubstituted heteroaryl. X\textsuperscript{16D} is halogen. In embodiments, X\textsuperscript{16D} is F.

[0348] R\textsuperscript{75D} is independently oxo, halogen, -CX\textsuperscript{75D}\textsubscript{3}, -CHX\textsuperscript{75D}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{75D}, -OCHX\textsuperscript{75D}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{0}\textsubscript{2}, -SH, -S\textsubscript{0}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHN\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHN\textsubscript{2}, -NHC=(0)NH, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{75D}\textsubscript{3}, -OCHX\textsuperscript{75D}, R\textsuperscript{76D}-substituted or unsubstituted alkyl, R\textsuperscript{76D}-substituted or unsubstituted heteroalkyl, R\textsuperscript{76D}-substituted or unsubstituted cycloalkyl, R\textsuperscript{76D}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{76D}-substituted or unsubstituted aryl, or R\textsuperscript{76D}-substituted or unsubstituted heteroaryl. X\textsuperscript{75D} is halogen. In embodiments, X\textsuperscript{75D} is F.

[0349] R\textsuperscript{76D} is independently oxo, halogen, -CX\textsuperscript{76D}\textsubscript{3}, -CHX\textsuperscript{76D}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{76D}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{0}\textsubscript{2}, -SH, -S\textsubscript{0}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHN\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHN\textsubscript{2}, -NHC=(0)NH, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{76D}\textsubscript{3}, -OCHX\textsuperscript{76D}, R\textsuperscript{77D}-substituted or unsubstituted alkyl, R\textsuperscript{77D}-substituted or unsubstituted heteroalkyl, R\textsuperscript{77D}-substituted or unsubstituted cycloalkyl, R\textsuperscript{77D}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{77D}-substituted or unsubstituted aryl, or R\textsuperscript{77D}-substituted or unsubstituted heteroaryl. X\textsuperscript{76D} is halogen. In embodiments, X\textsuperscript{76D} is F.

[0350] In embodiments, R\textsuperscript{17} is hydrogen. In embodiments, R\textsuperscript{17} is halogen. In embodiments, R\textsuperscript{17} is CX\textsuperscript{17}. In embodiments, R\textsuperscript{17} is -CHX\textsuperscript{17}. In embodiments, R\textsuperscript{17} is -CH\textsubscript{2}X\textsuperscript{17}. In embodiments, R\textsuperscript{17} is -CN. In embodiments, R\textsuperscript{17} is -SO\textsubscript{nn}R\textsuperscript{17D}. In embodiments, R\textsuperscript{17} is -SO\textsubscript{ov}vNR\textsuperscript{17A}R\textsuperscript{17B}. In embodiments, R\textsuperscript{17} is -NHN\textsubscript{R}\textsuperscript{17A}R\textsuperscript{17B}. In embodiments, R\textsuperscript{17} is
- ONR\textsuperscript{17A}R\textsuperscript{17B}. In embodiments, R\textsuperscript{17} is -NH\textsuperscript{C}≡(0)NHNR\textsuperscript{17A}R\textsuperscript{17B}. In embodiments, R\textsuperscript{17} is -NH(0)NR\textsuperscript{17A}R\textsuperscript{17B}. In embodiments, R\textsuperscript{17} is -N(0)\textsubscript{m}R. In embodiments, R\textsuperscript{17} is -NR\textsuperscript{17A}R\textsuperscript{17B}. In embodiments, R\textsuperscript{17} is -C(0)R\textsuperscript{17C}. In embodiments, R\textsuperscript{17} is -C(0)-OR\textsuperscript{17C}. In embodiments, R\textsuperscript{17} is -C(0)NR\textsuperscript{17A}R\textsuperscript{17B}. In embodiments, R\textsuperscript{17} is -OR\textsuperscript{17D}. In embodiments, R\textsuperscript{17} is -NR\textsuperscript{17A}S\textsubscript{0}R\textsuperscript{17D}. In embodiments, R\textsuperscript{17} is -NR\textsuperscript{17A}C(0)R\textsuperscript{17C}. In embodiments, R\textsuperscript{17} is -NR\textsuperscript{17A}C(0)-OR\textsuperscript{17C}. In embodiments, R\textsuperscript{17} is -OCX\textsuperscript{17F}. In embodiments, R\textsuperscript{17} is -OCHX\textsubscript{2}. In embodiments, R\textsuperscript{17} is substituted or unsubstituted alkyl. In embodiments, R\textsuperscript{17} is substituted or unsubstituted heteroalkyl. In embodiments, R\textsuperscript{17} is substituted or unsubstituted cycloalkyl. In embodiments, R\textsuperscript{17} is substituted or unsubstituted heterocycloalkyl. In embodiments, R\textsuperscript{17} is substituted or unsubstituted aryl. In embodiments, R\textsuperscript{17} is substituted or unsubstituted heteroaryl. In embodiments, R\textsuperscript{17} is substituted alkyl. In embodiments, R\textsuperscript{17} is substituted heteroalkyl. In embodiments, R\textsuperscript{17} is substituted cycloalkyl. In embodiments, R\textsuperscript{17} is substituted heterocycloalkyl. In embodiments, R\textsuperscript{17} is substituted heteroaryl. In embodiments, R\textsuperscript{17} is substituted aryl. In embodiments, R\textsuperscript{17} is unsubstituted heteroalkyl. In embodiments, R\textsuperscript{17} is unsubstituted cycloalkyl. In embodiments, R\textsuperscript{17} is unsubstituted heterocycloalkyl. In embodiments, R\textsuperscript{17} is unsubstituted aryl. In embodiments, R\textsuperscript{17} is unsubstituted heteroaryl. In embodiments, R\textsuperscript{17} is unsubstituted methyl. In embodiments, R\textsuperscript{17} is unsubstituted ethyl. In embodiments, R\textsuperscript{17} is unsubstituted propyl. In embodiments, R\textsuperscript{17} is unsubstituted isopropyl. In embodiments, R\textsuperscript{17} is unsubstituted butyl. In embodiments, R\textsuperscript{17} is unsubstituted tert-butyl.

**[0351]** In embodiments, R\textsuperscript{17A} is hydrogen. In embodiments, R\textsuperscript{17A} is -CX\textsubscript{3}. In embodiments, R\textsuperscript{17A} is -CN. In embodiments, R\textsuperscript{17A} is -COOH. In embodiments, R\textsuperscript{17A} is -CONH\textsubscript{2}. In embodiments, R\textsuperscript{17A} is -CHX\textsubscript{2}. In embodiments, R\textsuperscript{17A} is -CH\textsubscript{2}X. In embodiments, R\textsuperscript{17A} is unsubstituted methyl. In embodiments, R\textsuperscript{17A} is unsubstituted ethyl. In embodiments, R\textsuperscript{17A} is unsubstituted propyl. In embodiments, R\textsuperscript{17A} is unsubstituted isopropyl. In embodiments, R\textsuperscript{17A} is unsubstituted butyl. In embodiments, R\textsuperscript{17A} is unsubstituted tert-butyl.

**[0352]** In embodiments, R\textsuperscript{17B} is hydrogen. In embodiments, R\textsuperscript{17B} is -CX\textsubscript{3}. In embodiments, R\textsuperscript{17B} is -CN. In embodiments, R\textsuperscript{17B} is -COOH. In embodiments, R\textsuperscript{17B} is -CONH\textsubscript{2}. In embodiments, R\textsuperscript{17B} is -CHX\textsubscript{2}. In embodiments, R\textsuperscript{17B} is -CH\textsubscript{2}X. In embodiments, R\textsuperscript{17B} is unsubstituted methyl. In embodiments, R\textsuperscript{17B} is unsubstituted ethyl. In embodiments, R\textsuperscript{17B} is unsubstituted propyl. In embodiments, R\textsuperscript{17B} is unsubstituted isopropyl.
In embodiments, \( R^{17B} \) is unsubstituted butyl. In embodiments, \( R^{17B} \) is unsubstituted tert-butyl.

[0353] In embodiments, \( R^{17C} \) is hydrogen. In embodiments, \( R^{17C} \) is -CX3. In embodiments, \( R^{17C} \) is -CN. In embodiments, \( R^{17C} \) is -COOH. In embodiments, \( R^{17C} \) is -CONHi. In embodiments, \( R^{17C} \) is -CHX2. In embodiments, \( R^{17C} \) is -CH2X. In embodiments, \( R^{17C} \) is unsubstituted methyl. In embodiments, \( R^{17C} \) is unsubstituted ethyl. In embodiments, \( R^{17C} \) is unsubstituted isopropyl. In embodiments, \( R^{17C} \) is unsubstituted butyl. In embodiments, \( R^{17C} \) is unsubstituted tert-butyl.

[0354] In embodiments, \( R^{17D} \) is hydrogen. In embodiments, \( R^{17D} \) is -CX3. In embodiments, \( R^{17D} \) is -CN. In embodiments, \( R^{17D} \) is -COOH. In embodiments, \( R^{17D} \) is -CONH2. In embodiments, \( R^{17D} \) is -CHX2. In embodiments, \( R^{17D} \) is -CH2X. In embodiments, \( R^{17D} \) is unsubstituted methyl. In embodiments, \( R^{17D} \) is unsubstituted ethyl. In embodiments, \( R^{17D} \) is unsubstituted isopropyl. In embodiments, \( R^{17D} \) is unsubstituted butyl. In embodiments, \( R^{17D} \) is unsubstituted tert-butyl.

[0355] In embodiments, \( R^{17} \) is independently hydrogen, oxo, halogen, -CX17, -CHX172, -OCH2X17, -CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -S03H, -SO4H, -SO2NH2, -NHNH2, -ONH2, -NHC=(0)NH2, -NHC=(0)NH 2, -NHSO2H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX17, -OCHX17, R^78-substituted or unsubstituted alkyl, R^78-substituted or unsubstituted heteroalkyl, R^78-substituted or unsubstituted cycloalkyl, R^78-substituted or unsubstituted heterocycloalkyl, R^78-substituted or unsubstituted aryl, or R^78-substituted or unsubstituted heteroaryl. X^17 is halogen. In embodiments, \( X^{17} \) is F.

[0356] R^78 is independently oxo, halogen, -CX78, -CHX782, -OCH2X78, -OCHX78, -CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -S03H, -SO4H, -SO2NH2, -NHNH2, -ONH2, -NHC=(0)NH2, -NHC=(0)NH 2, -NHSO2H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX78, -OCHX78, R^79-substituted or unsubstituted alkyl, R^79-substituted or unsubstituted heteroalkyl, R^79-substituted or unsubstituted cycloalkyl, R^79-substituted or unsubstituted heterocycloalkyl, R^79-substituted or unsubstituted aryl, or R^79-substituted or unsubstituted heteroaryl. X^78 is halogen. In embodiments, \( X^{78} \) is F.
[0357] R⁷⁹ is independently oxo, halogen, -CX⁷⁹ -CHX⁷⁹ -OCH₂X⁷⁹ -CN -OH -NH₂ -COOH -CONH₂ -NO₂ -SH -SO₃H -SO₄H -SO₂NH₂ -NHNH₂ -ONH₂ -NHC=NHNHNH₂ -NHC=(0)NH₂ -NHC=NH₂ -NHSO₂H -NHC=H -NHC(0)-OH -NHOH -OCX⁷⁹ -OCHX⁷⁹ R⁸₀-substituted or unsubstituted alkyl, R⁸₀-substituted or unsubstituted heteroalkyl, R⁸₀-substituted or unsubstituted cycloalkyl, R⁸₀-substituted or unsubstituted heterocycloalkyl, R⁸₀-substituted or unsubstituted aryl, or R⁸₀-substituted or unsubstituted heteroaryl. X⁷⁹ is halogen. In embodiments, X⁷⁹ is F.

[0358] In embodiments, R¹⁷𝑨 is independently hydrogen, oxo, halogen, -CX¹⁷𝑨 -CHX¹⁷𝑨 -OCH₂X¹⁷𝑨 -CN -OH -NH₂ -COOH -CONH₂ -NO₂ -SH -SO₃H -SO₄H -SO₂NH₂ -NHNH₂ -ONH₂ -NHC=NHNHNH₂ -NHC=(0)NH₂ -NHC=H -NHC(0)-OH -NHOH -OCX¹⁷𝑨 -OCHX¹⁷𝑨 R⁷⁸𝑨-substituted or unsubstituted alkyl, R⁷⁸𝑨-substituted or unsubstituted heteroalkyl, R⁷⁸𝑨-substituted or unsubstituted cycloalkyl, R⁷⁸𝑨-substituted or unsubstituted heterocycloalkyl, R⁷⁸𝑨-substituted or unsubstituted aryl, or R⁷⁸𝑨-substituted or unsubstituted heteroaryl. X¹⁷𝑨 is halogen. In embodiments, X¹⁷𝑨 is F.

[0359] R⁷⁸𝑨 is independently oxo, halogen, -CX⁷⁸𝑨 -CHX⁷⁸𝑨 -OCH₂X⁷⁸𝑨 -OCX⁷⁸𝑨 -OCX⁷⁸𝑨 -CN -OH -NH₂ -COOH -CONH₂ -NO₂ -SH -SO₃H -SO₄H -SO₂NH₂ -NHNH₂ -ONH₂ -NHC=NHNHNH₂ -NHC=(0)NH₂ -NHC=H -NHC(0)-OH -NHOH -OCX⁷⁸𝑨 -OCHX⁷⁸𝑨 R⁷⁹𝑨-substituted or unsubstituted alkyl, R⁷⁹𝑨-substituted or unsubstituted heteroalkyl, R⁷⁹𝑨-substituted or unsubstituted cycloalkyl, R⁷⁹𝑨-substituted or unsubstituted heterocycloalkyl, R⁷⁹𝑨-substituted or unsubstituted aryl, or R⁷⁹𝑨-substituted or unsubstituted heteroaryl. X⁷⁸𝑨 is halogen. In embodiments, X⁷⁸𝑨 is F.

[0360] R⁷⁹𝑨 is independently oxo, halogen, -CX⁷⁹𝑨 -CHX⁷⁹𝑨 -OCH₂X⁷⁹𝑨 -CN -OH -NH₂ -COOH -CONH₂ -NO₂ -SH -SO₃H -SO₄H -SO₂NH₂ -NHNH₂ -ONH₂ -NHC=NHNHNH₂ -NHC=(0)NH₂ -NHC=H -NHC(0)-OH -NHOH -OCX⁷⁹𝑨 -OCHX⁷⁹𝑨 R⁸₀𝑨-substituted or unsubstituted alkyl, R⁸₀𝑨-substituted or unsubstituted heteroalkyl, R⁸₀𝑨-substituted or unsubstituted cycloalkyl, R⁸₀𝑨-substituted or unsubstituted heterocycloalkyl, R⁸₀𝑨-substituted or unsubstituted aryl, or R⁸₀𝑨-substituted or unsubstituted heteroaryl. X⁷⁹𝑨 is halogen. In embodiments, X⁷⁹𝑨 is F.
In embodiments, \( R^{17B} \) is independently hydrogen, oxo, halogen, -\( \text{CX}^{17B} \_3 \), -\( \text{CHX}^{17B} \_2 \), -\( \text{OCH}_2 \text{X}^{17B} \_3 \), -\( \text{CN} \), -\( \text{OH} \), -\( \text{NH}_2 \), -\( \text{COOH} \), -\( \text{CONH}_2 \), -\( \text{NO}_2 \), -\( \text{SH} \), -\( \text{SO}_3 \_H \), -\( \text{SO}_4 \_H \), -\( \text{SO}_2 \text{NH}_2 \), -\( \text{NHNH}_2 \), -\( \text{ONH}_2 \), -\( \text{NHC}=(0)\text{NHNH}_2 \_2 \), -\( \text{NHC}=(0)\text{NH}_2 \_2 \), -\( \text{NHSO}_2 \_H \), -\( \text{NHC}=(0)\text{H} \), -\( \text{NHC}(0)\text{-OH} \), -\( \text{NHOH} \), -\( \text{OCX}^{17B} \_3 \), -\( \text{OCHX}^{17B} \_2 \), \( R^{78B} \)-substituted or unsubstituted alkyl, \( R^{78B} \)-substituted or unsubstituted cycloalkyl, \( R^{78B} \)-substituted or unsubstituted heteroalkyl, \( R^{78B} \)-substituted or unsubstituted heteroaryl.

In embodiments, \( X^{17B} \) is halogen. In embodiments, \( X^{17B} \) is \( F \).

\( R^{78B} \) is independently oxo,

halogen, -\( \text{CX}^{78B} \_3 \), -\( \text{CHX}^{78B} \_2 \), -\( \text{OCH}_2 \text{X}^{78B} \_3 \), -\( \text{OCHX}^{78B} \_2 \), -\( \text{CN} \), -\( \text{OH} \), -\( \text{NH}_2 \), -\( \text{COOH} \), -\( \text{CONH}_2 \), -\( \text{NO}_2 \), -\( \text{SH} \), -\( \text{SO}_3 \_H \), -\( \text{SO}_4 \_H \), -\( \text{SO}_2 \text{NH}_2 \), -\( \text{NHNH}_2 \), -\( \text{ONH}_2 \), -\( \text{NHC}=(0)\text{NHNH}_2 \_2 \), -\( \text{NHC}=(0)\text{NH}_2 \_2 \), -\( \text{NHSO}_2 \_H \), -\( \text{NHC}=(0)\text{H} \), -\( \text{NHC}(0)\text{-OH} \), -\( \text{NHOH} \), -\( \text{OCX}^{78B} \_3 \), -\( \text{OCHX}^{78B} \_2 \), \( R^{79B} \)-substituted or unsubstituted alkyl, \( R^{79B} \)-substituted or unsubstituted heteroalkyl, \( R^{79B} \)-substituted or unsubstituted cycloalkyl, \( R^{79B} \)-substituted or unsubstituted heterocycloalkyl, \( R^{79B} \)-substituted or unsubstituted aryl, or \( R^{79B} \)-substituted or unsubstituted heteroaryl.

In embodiments, \( X^{78B} \) is halogen. In embodiments, \( X^{78B} \) is \( F \).

\( R^{79B} \) is independently oxo,

halogen, -\( \text{CX}^{79B} \_3 \), -\( \text{CHX}^{79B} \_2 \), -\( \text{OCH}_2 \text{X}^{79B} \_3 \), -\( \text{OCHX}^{79B} \_2 \), -\( \text{CN} \), -\( \text{OH} \), -\( \text{NH}_2 \), -\( \text{COOH} \), -\( \text{CONH}_2 \), -\( \text{NO}_2 \), -\( \text{SH} \), -\( \text{SO}_3 \_H \), -\( \text{SO}_4 \_H \), -\( \text{SO}_2 \text{NH}_2 \), -\( \text{NHNH}_2 \), -\( \text{ONH}_2 \), -\( \text{NHC}=(0)\text{NHNH}_2 \_2 \), -\( \text{NHC}=(0)\text{NH}_2 \_2 \), -\( \text{NHSO}_2 \_H \), -\( \text{NHC}=(0)\text{H} \), -\( \text{NHC}(0)\text{-OH} \), -\( \text{NHOH} \), -\( \text{OCX}^{79B} \_3 \), -\( \text{OCHX}^{79B} \_2 \), \( R^{80B} \)-substituted or unsubstituted alkyl, \( R^{80B} \)-substituted or unsubstituted heteroalkyl, \( R^{80B} \)-substituted or unsubstituted cycloalkyl, \( R^{80B} \)-substituted or unsubstituted heterocycloalkyl, \( R^{80B} \)-substituted or unsubstituted aryl, or \( R^{80B} \)-substituted or unsubstituted heteroaryl.

In embodiments, \( X^{79B} \) is halogen. In embodiments, \( X^{79B} \) is \( F \).

In embodiments, \( R^{17C} \) is independently hydrogen, oxo,

halogen, -\( \text{CX}^{17C} \_3 \), -\( \text{CHX}^{17C} \_2 \), -\( \text{OCH}_2 \text{X}^{17C} \_3 \), -\( \text{CN} \), -\( \text{OH} \), -\( \text{NH}_2 \), -\( \text{COOH} \), -\( \text{CONH}_2 \), -\( \text{NO}_2 \), -\( \text{SH} \), -\( \text{SO}_3 \_H \), -\( \text{SO}_4 \_H \), -\( \text{SO}_2 \text{NH}_2 \), -\( \text{NHNH}_2 \), -\( \text{ONH}_2 \), -\( \text{NHC}=(0)\text{NHNH}_2 \_2 \), -\( \text{NHC}=(0)\text{NH}_2 \_2 \), -\( \text{NHSO}_2 \_H \), -\( \text{NHC}=(0)\text{H} \), -\( \text{NHC}(0)\text{-OH} \), -\( \text{NHOH} \), -\( \text{OCX}^{17C} \_3 \), -\( \text{OCHX}^{17C} \_2 \), \( R^{78C} \)-substituted or unsubstituted alkyl, \( R^{78C} \)-substituted or unsubstituted heteroalkyl, \( R^{78C} \)-substituted or unsubstituted cycloalkyl, \( R^{78C} \)-substituted or unsubstituted heterocycloalkyl, \( R^{78C} \)-substituted or unsubstituted aryl, or \( R^{78C} \)-substituted or unsubstituted heteroaryl.

In embodiments, \( X^{17C} \) is halogen. In embodiments, \( X^{17C} \) is \( F \).
[0365] R\textsuperscript{78C} is independently o xo, halogen, -CX\textsuperscript{78C}\textsubscript{3}, -CHX\textsuperscript{78C}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{78C}, -OCHX\textsuperscript{78C}\textsubscript{2}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{0}\textsubscript{2}, -SH, -S\textsubscript{0}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHNH\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHNH\textsubscript{2}, -NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{78C}\textsubscript{3}, -OCHX\textsuperscript{78C}\textsubscript{2}, X\textsuperscript{78C} in embodiments, X\textsuperscript{78C} is F.

[0366] R\textsuperscript{79C} is independently o xo, halogen, -CX\textsuperscript{79C}\textsubscript{3}, -CHX\textsuperscript{79C}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{79C}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -S\textsubscript{0}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHNH\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHNH\textsubscript{2}, -NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{79C}\textsubscript{3}, -OCHX\textsuperscript{79C} 15 in embodiments, X\textsuperscript{79C} is F.

[0367] In embodiments, R\textsuperscript{17D} is independently hydrogen, o xo, halogen, -CX\textsuperscript{17D}\textsubscript{3}, -CHX\textsuperscript{17D}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{17D}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -NO\textsubscript{2}, -SH, -S\textsubscript{0}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHNH\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHNH\textsubscript{2}, -NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{17D}\textsubscript{3}, -OCHX\textsuperscript{17D} 20 in embodiments, X\textsuperscript{17D} is F.

[0368] R\textsuperscript{78D} is independently o xo, halogen, -CX\textsuperscript{78D}\textsubscript{3}, -CHX\textsuperscript{78D}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{78D}, -OCHX\textsuperscript{78D}\textsubscript{2}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{0}\textsubscript{2}, -SH, -S\textsubscript{0}\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NHNH\textsubscript{2}, -ONH\textsubscript{2}, -NHC=(0)NHNH\textsubscript{2}, -NHC=(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX\textsuperscript{78D}\textsubscript{3}, -OCHX\textsuperscript{78D} 30 in embodiments, X\textsuperscript{78D} is F.
[0369] R<sup>79D</sup> is independently oxo, halogen, -CX<sup>79D</sup>, -CHX<sup>79D</sup>, -OCH<sub>2</sub>X<sup>79D</sup>, -CN, -OH, -NH<sub>2</sub>, -COOH, -CONH<sub>2</sub>, -N<sub>0</sub>, -SH, -S<sub>0</sub>2H, -SO<sub>4</sub>H, -SO<sub>2</sub>NH<sub>2</sub>, -NH NH<sub>2</sub>, - ONH<sub>2</sub>, - NH<sub>3</sub>, -NHC=(0)NH<sub>2</sub>, - NHC=(0)NH<sub>2</sub>, -NHS<sub>0</sub>2H, -NHC=(0)H, -NHC(0)-OH, -NH OH, -OCX<sup>79D</sup>, -OCHX<sup>79D</sup>, R<sup>80D</sup>-substituted or unsubstituted alkyl, R<sup>80D</sup>-substituted or unsubstituted heteroalkyl, R<sup>80D</sup>-substituted or unsubstituted cycloalkyl, R<sup>80D</sup>-substituted or unsubstituted heterocycloalkyl, R<sup>80D</sup>-substituted or unsubstituted aryl, or R<sup>80D</sup>-substituted or unsubstituted heteroaryl. X<sup>79D</sup> is halogen. In embodiments, X<sup>79D</sup> is F.

[0370] In embodiments, R<sup>18</sup> is hydrogen. In embodiments, R<sup>18</sup> is halogen. In embodiments, R<sup>18</sup> is CH<sub>2</sub>X<sup>18</sup>. In embodiments, R<sup>18</sup> is CN. In embodiments, R<sup>18</sup> is SO<sub>2</sub>i<sub>8</sub>R<sup>18D</sup>. In embodiments, R<sup>18</sup> is -SO<sub>2</sub>i<sub>8</sub>N R<sup>18A</sup>R<sup>18B</sup>. In embodiments, R<sup>18</sup> is -ONR<sup>18A</sup>R<sup>18B</sup>. In embodiments, R<sup>18</sup> is -NHC=(0)NR<sup>18A</sup>R<sup>18B</sup>. In embodiments, R<sup>18</sup> is -NHC=(0)NH<sub>2</sub>. In embodiments, R<sup>18</sup> is -NHC(0)-H. In embodiments, R<sup>18</sup> is -NHC(0)-OH. In embodiments, R<sup>18</sup> is -NH<sub>2</sub>, - COOH, -CONH<sub>2</sub>, -N<sub>0</sub>, -SH, -S<sub>0</sub>2H, -SO<sub>4</sub>H, -SO<sub>2</sub>NH<sub>2</sub>, -NH NH<sub>2</sub>, - ONH<sub>2</sub>, - NH<sub>3</sub>, -NHC=(0)NH<sub>2</sub>, - NHC=(0)NH<sub>2</sub>, -NHS<sub>0</sub>2H, -NHC=(0)H, -NHC(0)-OH, -NH OH, -OCX<sup>79D</sup>, -OCHX<sup>79D</sup>, R<sup>80D</sup>-substituted or unsubstituted alkyl, R<sup>80D</sup>-substituted or unsubstituted heteroalkyl, R<sup>80D</sup>-substituted or unsubstituted cycloalkyl, R<sup>80D</sup>-substituted or unsubstituted heterocycloalkyl, R<sup>80D</sup>-substituted or unsubstituted aryl, or R<sup>80D</sup>-substituted or unsubstituted heteroaryl. X<sup>79D</sup> is halogen. In embodiments, X<sup>79D</sup> is F.
In embodiments, $R^{1A}$ is hydrogen. In embodiments, $R^{1A}$ is -CX3. In embodiments, $R^{1A}$ is -CN. In embodiments, $R^{1A}$ is -COOH. In embodiments, $R^{1A}$ is -CONH2. In embodiments, $R^{1A}$ is -CHX2. In embodiments, $R^{1A}$ is -CH2X. In embodiments, $R^{1A}$ is unsubstituted methyl. In embodiments, $R^{1A}$ is unsubstituted ethyl. In embodiments, $R^{1A}$ is unsubstituted propyl. In embodiments, $R^{1A}$ is unsubstituted butyl. In embodiments, $R^{1A}$ is unsubstituted tert-butyl.

In embodiments, $R^{1B}$ is hydrogen. In embodiments, $R^{1B}$ is -CX3. In embodiments, $R^{1B}$ is -CN. In embodiments, $R^{1B}$ is -COOH. In embodiments, $R^{1B}$ is -CONH2. In embodiments, $R^{1B}$ is -CHX2. In embodiments, $R^{1B}$ is -CH2X. In embodiments, $R^{1B}$ is unsubstituted methyl. In embodiments, $R^{1B}$ is unsubstituted ethyl. In embodiments, $R^{1B}$ is unsubstituted propyl. In embodiments, $R^{1B}$ is unsubstituted isopropyl. In embodiments, $R^{1B}$ is unsubstituted butyl. In embodiments, $R^{1B}$ is unsubstituted tert-butyl.

In embodiments, $R^{1C}$ is hydrogen. In embodiments, $R^{1C}$ is -CX3. In embodiments, $R^{1C}$ is -CN. In embodiments, $R^{1C}$ is -COOH. In embodiments, $R^{1C}$ is -CONH2. In embodiments, $R^{1C}$ is -CHX2. In embodiments, $R^{1C}$ is -CH2X. In embodiments, $R^{1C}$ is unsubstituted methyl. In embodiments, $R^{1C}$ is unsubstituted ethyl. In embodiments, $R^{1C}$ is unsubstituted propyl. In embodiments, $R^{1C}$ is unsubstituted isopropyl. In embodiments, $R^{1C}$ is unsubstituted butyl. In embodiments, $R^{1C}$ is unsubstituted tert-butyl.

In embodiments, $R^{1D}$ is hydrogen. In embodiments, $R^{1D}$ is -CX3. In embodiments, $R^{1D}$ is -CN. In embodiments, $R^{1D}$ is -COOH. In embodiments, $R^{1D}$ is -CONH2. In embodiments, $R^{1D}$ is -CHX2. In embodiments, $R^{1D}$ is -CH2X. In embodiments, $R^{1D}$ is unsubstituted methyl. In embodiments, $R^{1D}$ is unsubstituted ethyl. In embodiments, $R^{1D}$ is unsubstituted propyl. In embodiments, $R^{1D}$ is unsubstituted isopropyl. In embodiments, $R^{1D}$ is unsubstituted butyl. In embodiments, $R^{1D}$ is unsubstituted tert-butyl.

In embodiments, $R^{18}$ is independently hydrogen, oxo, halogen, -CX3, -CHX2, -OCH2X, -CN, -OH, -NH2, -COOH, -CONH2, -NO2, -SH, -SO3H, -SO4H, -SO2NH2, -NHNH2, -ONH2, -NHC -(0 )NHNH2, -NHC -(0 )NH2, -NHSO2H, -NHC -(0 )H, -NHC -(0 )OH, -NHOH, -OCX3, -OCHX2, $R^{81}$-substituted or
unsubstituted alkyl, R^8₁-substituted or unsubstituted heteroalkyl, R^8₁-substituted or unsubstituted cycloalkyl, R^8₁-substituted or unsubstituted heterocycloalkyl, R^8₁-substituted or unsubstituted aryl, or R^8₁-substituted or unsubstituted heteroaryl. X^1₈ is halogen. In embodiments, X^1₈ is F.

5 [0376] R^8₁ is independently oxo,
halogen, -CX^8₁₃, -CHX^8₂, -OCH₂X^8₁₈, -OCHX^R₈₁, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₃, -ONH₂, -NHC=(0)NH₂, -NHSO₂H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX^R₈₂, -OCHX^R₈₂, R^8₂-substituted or unsubstituted alkyl, R^8₂-substituted or unsubstituted heteroalkyl, R^8₂-substituted or unsubstituted cycloalkyl, R^8₂-substituted or unsubstituted heterocycloalkyl, R^8₂-substituted or unsubstituted aryl, or R^8₂-substituted or unsubstituted heteroaryl. X^8₁ is halogen. In embodiments, X^8₁ is F.

10 [0377] R^8₂ is independently oxo,
halogen, -CX^R₈₃, -CHX^R₈₂, -OCH₂X^R₈₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NH₂, -NH₂, -NHSO₂H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX^R₈₃, -OCHX^R₈₃, R^8₃-substituted or unsubstituted alkyl, R^8₃-substituted or unsubstituted heteroalkyl, R^8₃-substituted or unsubstituted cycloalkyl, R^8₃-substituted or unsubstituted heterocycloalkyl, R^8₃-substituted or unsubstituted aryl, or R^8₃-substituted or unsubstituted heteroaryl. X^8₂ is halogen. In embodiments, X^8₂ is F.

20 [0378] In embodiments, R^{1₈A} is independently hydrogen, oxo,
halogen, -CX^{1₈A₃}, -CHX^{1₈A₂}, -OCH₂X^{1₈A₂}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NH₂, -NH₂, -NHSO₂H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX^{1₈A₃}, -OCHX^{1₈A₃}, R^{1₈A₁}-substituted or unsubstituted alkyl, R^{1₈A₁}-substituted or unsubstituted heteroalkyl, R^{1₈A₁}-substituted or unsubstituted cycloalkyl, R^{1₈A₁}-substituted or unsubstituted heterocycloalkyl, R^{1₈A₁}-substituted or unsubstituted aryl, or R^{1₈A₁}-substituted or unsubstituted heteroaryl. X^{1₈A} is halogen. In embodiments, X^{1₈A} is F.

25 [0379] R^{1₈A₁} is independently oxo,
halogen, -CX^{1₈A₁₃}, -CHX^{1₈A₁₂}, -OCH₂X^{1₈A₁₂}, -OCHX^{1₈A₁₂}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -ONH₂, -NHC=(0)NH₂, -NH₂, -NHSO₂H, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX^{1₈A₁₃}, -OCHX^{1₈A₁₃},
R\textsuperscript{82A}-substituted or unsubstituted alkyl, R\textsuperscript{82A}-substituted or unsubstituted heteroalkyl, R\textsuperscript{82A}-substituted or unsubstituted cycloalkyl, R\textsuperscript{82A}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{82A}-substituted or unsubstituted aryl, or R\textsuperscript{82A}-substituted or unsubstituted heteroaryl. X\textsuperscript{81A} is halogen. In embodiments, X\textsuperscript{81A} is F.

[0380] R\textsuperscript{82A} is independently oxo, halogen, -CX\textsuperscript{82A}\textsubscript{3}, -CHX\textsuperscript{82A}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{82A}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{2}O, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NH\textsubscript{2}NH\textsubscript{2}, -NHC\textsubscript{2}(0)N\textsubscript{H}N\textsubscript{H}\textsubscript{2}, -NHC\textsubscript{2}(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC\textsubscript{2}(0)H, -NHC\textsubscript{2}(0)-OH, -NHOH, -OCX\textsuperscript{82A}\textsubscript{3}, -OCHX\textsuperscript{82A}\textsubscript{2}, R\textsuperscript{83A}-substituted or unsubstituted alkyl, R\textsuperscript{83A}-substituted or unsubstituted heteroalkyl, R\textsuperscript{83A}-substituted or unsubstituted cycloalkyl, R\textsuperscript{83A}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{83A}-substituted or unsubstituted aryl, or R\textsuperscript{83A}-substituted or unsubstituted heteroaryl. X\textsuperscript{82A} is halogen. In embodiments, X\textsuperscript{82A} is F.

[0381] In embodiments, R\textsuperscript{18B} is independently hydrogen, oxo, halogen, -CX\textsuperscript{18B}\textsubscript{3}, -CHX\textsuperscript{18B}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{18B}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{2}O, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NH\textsubscript{2}NH\textsubscript{2}, -NHC\textsubscript{2}(0)N\textsubscript{H}N\textsubscript{H}\textsubscript{2}, -NHC\textsubscript{2}(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC\textsubscript{2}(0)H, -NHC\textsubscript{2}(0)-OH, -NHOH, -OCX\textsuperscript{18B}\textsubscript{3}, -OCHX\textsuperscript{18B}\textsubscript{2}, R\textsuperscript{81B}-substituted or unsubstituted alkyl, R\textsuperscript{81B}-substituted or unsubstituted heteroalkyl, R\textsuperscript{81B}-substituted or unsubstituted cycloalkyl, R\textsuperscript{81B}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{81B}-substituted or unsubstituted aryl, or R\textsuperscript{81B}-substituted or unsubstituted heteroaryl. X\textsuperscript{18B} is halogen. In embodiments, X\textsuperscript{18B} is F.

[0382] R\textsuperscript{81B} is independently oxo, halogen, -CX\textsuperscript{81B}\textsubscript{3}, -CHX\textsuperscript{81B}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{81B}, -OCX\textsuperscript{81B}\textsubscript{2}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{2}O\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NH\textsubscript{2}NH\textsubscript{2}, -NHC\textsubscript{2}(0)N\textsubscript{H}N\textsubscript{H}\textsubscript{2}, -NHC\textsubscript{2}(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC\textsubscript{2}(0)H, -NHC\textsubscript{2}(0)-OH, -NHOH, -OCX\textsuperscript{81B}\textsubscript{3}, -OCHX\textsuperscript{81B}\textsubscript{2}, R\textsuperscript{82B}-substituted or unsubstituted alkyl, R\textsuperscript{82B}-substituted or unsubstituted heteroalkyl, R\textsuperscript{82B}-substituted or unsubstituted cycloalkyl, R\textsuperscript{82B}-substituted or unsubstituted heterocycloalkyl, R\textsuperscript{82B}-substituted or unsubstituted aryl, or R\textsuperscript{82B}-substituted or unsubstituted heteroaryl. X\textsuperscript{81B} is halogen. In embodiments, X\textsuperscript{81B} is F.

[0383] R\textsuperscript{82B} is independently oxo, halogen, -CX\textsuperscript{82B}\textsubscript{3}, -CHX\textsuperscript{82B}\textsubscript{2}, -OCH\textsubscript{2}X\textsuperscript{82B}, -CN, -OH, -NH\textsubscript{2}, -COOH, -CONH\textsubscript{2}, -N\textsubscript{2}O\textsubscript{2}, -SH, -SO\textsubscript{3}H, -SO\textsubscript{4}H, -SO\textsubscript{2}NH\textsubscript{2}, -NH\textsubscript{2}NH\textsubscript{2}, -NHC\textsubscript{2}(0)N\textsubscript{H}N\textsubscript{H}\textsubscript{2}, -NHC\textsubscript{2}(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC\textsubscript{2}(0)H, -NHC\textsubscript{2}(0)-OH, -NHOH, -OCX\textsuperscript{82B}\textsubscript{3}, -OCHX\textsuperscript{82B}\textsubscript{2}, -NHC\textsubscript{2}(0)N\textsubscript{H}N\textsubscript{H}\textsubscript{2}, -NHC\textsubscript{2}(0)NH\textsubscript{2}, -NHSO\textsubscript{2}H, -NHC\textsubscript{2}(0)H, -NHC\textsubscript{2}(0)-OH, -NHOH, -OCX\textsuperscript{82B}\textsubscript{3}, -OCHX\textsuperscript{82B}\textsubscript{2},
NHSO2H, -NHC(0)=H, -NHOH, -OCX 3B 2, -OCHX 3B 2, R 83B -substituted or unsubstituted alkyl, R 83B -substituted or unsubstituted heteroalkyl, R 83B -substituted or unsubstituted cycloalkyl, R 83B -substituted or unsubstituted heterocycloalkyl, R 83B -substituted or unsubstituted aryl, or R 83B -substituted or unsubstituted heteroaryl. X 83B is halogen. In embodiments, X 82B is F.

[0384] In embodiments, R 18C is independently hydrogen, oxo, halogen, -CX 18C 3, -CHX 18C 2, -OCH 3X 18C, -CN, -OH, -NH 2, -COOH, -CONH2, -NO2, -SH, -SO 3H, -SO4H, -SO2NH2, -ONH2, -NHC=(0)NHNH 2, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX 18C 3, -OCHX 18C 2, R 81C -substituted or unsubstituted alkyl, R 81C -substituted or unsubstituted heteroalkyl, R 81C -substituted or unsubstituted cycloalkyl, R 81C -substituted or unsubstituted heterocycloalkyl, R 81C -substituted or unsubstituted aryl, or R 81C -substituted or unsubstituted heteroaryl. X 18C is halogen. In embodiments, X 18C is F.

[0385] R 81C is independently oxo,
halogen, -CX 81C 3, -CHX 81C 2, -OCH 3X 81C, -OCHX 81C 2, -CN, -OH, -NH 2, -COOH, -CONH2, -NO2, -SH, -SO 3H, -SO4H, -SO2NH2, -ONH2, -NHC=(0)NHNH 2, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX 81C 3, -OCHX 81C 2, R 82C -substituted or unsubstituted alkyl, R 82C -substituted or unsubstituted heteroalkyl, R 82C -substituted or unsubstituted cycloalkyl, R 82C -substituted or unsubstituted heterocycloalkyl, R 82C -substituted or unsubstituted aryl, or R 82C -substituted or unsubstituted heteroaryl. X 81C is halogen. In embodiments, X 81C is F.

[0386] R 82C is independently oxo,
halogen, -CX 82C 3, -CHX 82C 2, -OCH 3X 82C, -CN, -OH, -NH 2, -COOH, -CONH2, -NO2, -SH, -SO 3H, -SO4H, -SO2NH2, -ONH2, -NHC=(0)NHNH 2, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX 82C 3, -OCHX 82C 2, R 83C -substituted or unsubstituted alkyl, R 83C -substituted or unsubstituted heteroalkyl, R 83C -substituted or unsubstituted cycloalkyl, R 83C -substituted or unsubstituted heterocycloalkyl, R 83C -substituted or unsubstituted aryl, or R 83C -substituted or unsubstituted heteroaryl. X 82C is halogen. In embodiments, X 82C is F.

[0387] In embodiments, R 18D is independently hydrogen, oxo,
algon, -CX 18D 3, -CHX 18D 2, -OCH 3X 18D, -CN, -OH, -NH 2, -COOH, -CONH2, -NO2, -SH, -SO 3H, -SO4H, -SO2NH2, -ONH2, -NHC=(0)NHNH 2, -NHC=(0)H, -NHC(0)-OH, -NHOH, -OCX 18D 3, -OCHX 18D 2, R 83D -substituted or unsubstituted alkyl, R 83D -substituted or unsubstituted heteroalkyl, R 83D -substituted or unsubstituted cycloalkyl, R 83D -substituted or unsubstituted heterocycloalkyl, R 83D -substituted or unsubstituted aryl, or R 83D -substituted or unsubstituted heteroaryl. X 83D is halogen. In embodiments, X 83D is F.
NHSO₂H, -NHC(=O)H, -NHC(=O)-OH, -NHOH, -OCX₃₂, -OCHX₃₂, R₁D-substituted or unsubstituted alkyl, R₁D-substituted or unsubstituted heteroalkyl, R₁D-substituted or unsubstituted cycloalkyl, R₁D-substituted or unsubstituted heterocycloalkyl, R₁D-substituted or unsubstituted aryl, or R₁D-substituted or unsubstituted heteroaryl. X¹B₈ is halogen. In embodiments, X¹B₈ is F.

[0388] R₁D is independently oxo,
halogen, -CX₁B₃, -CHX₁B₂, -OCH₂X₁B₂, -OCHX₁B₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NH, -NHC(=O)NHNH₂, -NHSO₂H, -NHC(=O)H, -NHC(=O)-OH, -NHOH, -OCX₁B₃, -OCHX₁B₂, R¹D-substituted or unsubstituted alkyl, R¹D-substituted or unsubstituted heteroalkyl, R¹D-substituted or unsubstituted cycloalkyl, R¹D-substituted or unsubstituted heterocycloalkyl, R¹D-substituted or unsubstituted aryl, or R¹D-substituted or unsubstituted heteroaryl. X¹D is halogen. In embodiments, X¹D is F.

[0389] R¹D is independently oxo,
halogen, -CX¹D₃, -CHX¹D₂, -OCH₂X¹D₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NH, -NHC(=O)NHNH₂, -NHSO₂H, -NHC(=O)H, -NHC(=O)-OH, -NHOH, -OCX¹D₃, -OCHX¹D₂, R¹D-substituted or unsubstituted alkyl, R¹D-substituted or unsubstituted heteroalkyl, R¹D-substituted or unsubstituted cycloalkyl, R¹D-substituted or unsubstituted heterocycloalkyl, R¹D-substituted or unsubstituted aryl, or R¹D-substituted or unsubstituted heteroaryl. X¹D is halogen. In embodiments, X¹D is F.

cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. In embodiments, $R_4$, $R_5$, ... is a compound described herein (e.g., in an aspect, embodiment, example, claim, table, scheme, drawing, or figure).

In embodiments, $R_4$, $R_5$, ... is a compound described herein (e.g., in an aspect, embodiment, example, claim, table, scheme, drawing, or figure).

$R$ variables

For unsubstituted group in multiple instances, $R$ is assumed to be hydrogen.

- halogen, -CF$_3$, -CN, -OH, -NH$_2$, -COOH, -CONH$_2$, -N0$_2$, -SH, -SO$_3$H, -SO$_4$H, -SO$_2$NH$_2$, $\text{H}_2\text{NHN}_2$, -ONH$_2$, -NHC(0)NH$_2$, -NHC(0)NH$_2$, -NHSO$_2$H, -NHC(0)H, -NHC(0)OH, -NHOH, -OCF$_3$, -OCHF$_2$, unsubstituted Ci-Cs alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted C$_3$-C$_8$ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0391] In embodiments, $R^{15}$, $R^{16}$, $R^{17}$, and $R^{18}$ are hydrogen.

[0392] In embodiments, $E$ is: $\text{N}$.

In embodiments, $E$ is: $\text{N}$.

In embodiments, $E$ is: $\text{N}$.

In embodiments, $E$ is: $\text{N}$.

In embodiments, $E$ is: $\text{N}$.

[0393] In some embodiments, a compound as described herein may include multiple instances of $R^1$ or $R^2$, and/or other variables. In such embodiments, each variable may optional be different and be appropriately labeled to distinguish each group for greater clarity. For example, where each $R^1$ and/or $R^2$, is different, they may be referred to, for example, as $R^{1,1}$, $R^{1,2}$, $R^{1,3}$, $R^{1,4}$, $R^{1,5}$, $R^{2,1}$, $R^{2,2}$, $R^{2,3}$, or $R^{2,4}$, respectively, wherein the definition of $R^1$ is assumed by $R^{1,1}$, $R^{1,2}$, $R^{1,3}$, $R^{1,4}$, $R^{1,5}$; and/or $R^2$ is assumed by $R^{2,1}$, $R^{2,2}$, $R^{2,3}$, $R^{2,4}$. The variables used within a definition of $R^1$ and/or $R^2$, and/or other variables that appear at multiple instances and are different may similarly be appropriately labeled to distinguish each group for greater clarity. In some embodiments, the compound is a compound described herein (e.g., in an aspect, embodiment, example, claim, table, scheme, drawing, or figure).
In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a single stereoisomer. In embodiments, unless otherwise indicated, a compound described herein is a single enantiomer. In embodiments, the compound is a compound described herein (e.g., in an aspect, embodiment, example, figure, table, scheme, or claim).

In embodiments, the compound has the formula:

In embodiments, the compound has the formula:

In embodiments, the compound has the formula:

In embodiments, the compound has the formula:
In embodiments, the compound has the formula:

In embodiments, the compound is described herein, including in an aspect, embodiment, example, table, figure, claim, or scheme.

In embodiments, the compound has the formula:
III. Pharmaceutical compositions

[0403] In an aspect is provided a pharmaceutical composition including a Ubiquitin-like modifier activating enzyme 5 (UBA5) inhibitor and a pharmaceutically acceptable excipient. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is a compound described herein. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), protein (e.g., antibody, anti-Ubiquitin-like modifier activating enzyme 5 antibody, anti-Ubiquitin-like modifier activating enzyme 5 binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is included in a therapeutically effective amount.

[0404] In an aspect is provided a pharmaceutical composition including a compound described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
[0405] In embodiments of the pharmaceutical compositions, the compound, or pharmaceutically acceptable salt thereof, is included in a therapeutically effective amount.

[0406] In embodiments of the pharmaceutical compositions, the pharmaceutical composition includes a second agent (e.g., a therapeutic agent). In embodiments of the pharmaceutical compositions, the pharmaceutical composition includes a second agent (e.g. therapeutic agent) in a therapeutically effective amount. In embodiments of the pharmaceutical compositions, the second agent is an agent for treating cancer. In embodiments, the second agent is an anti-cancer agent. In embodiments, the second agent is a chemotherapeutic.

IV. Methods of Treatment

[0407] In an aspect is provided a method of treating cancer, the method including administering to a subject in need thereof an effective amount of a Ubiquitin-like modifier activating enzyme 5 inhibitor. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is a compound described herein. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), protein (e.g., antibody, anti-Ubiquitin-like modifier activating enzyme 5 antibody, anti-Ubiquitin-like modifier activating enzyme 5 binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is included in a therapeutically effective amount.

[0408] In an aspect is provided a method of treating cancer including administering to a subject in need thereof an effective amount of a compound described herein. In embodiments, the cancer is pancreatic cancer. In embodiments, the cancer is a pancreatic neuroendocrine tumor. In embodiments, the cancer is an exocrine tumor (e.g., pancreas ductal adenocarcinoma). In embodiments, the cancer is an adenocarcinoma, acinar cell carcinoma, intraductal papillary-mucinous neoplasm, or mucinous cystadenocarcinoma. In embodiments, the cancer is pancreas ductal adenocarcinoma. In embodiments, the cancer is intermediate grade (moderately differentiated) pancreatic cancer. In embodiments, the cancer is high grade (poorly differentiated) pancreatic cancer. In embodiments, the cancer is stage 0 pancreatic cancer. In embodiments, the cancer is stage I pancreatic cancer. In embodiments, the cancer is stage II pancreatic cancer. In embodiments, the cancer is stage III pancreatic cancer. In embodiments, the cancer is stage IV pancreatic cancer. In embodiments, the cancer is breast cancer.
cancer. In embodiments, the cancer is estrogen receptor (ER) negative breast cancer. In embodiments, the cancer is tamoxifen resistant breast cancer. In embodiments, the cancer is HER2 negative breast cancer. In embodiments, the cancer is HER2 positive breast cancer. In embodiments, the cancer is low grade (well differentiated) breast cancer. In embodiments, the cancer is intermediate grade (moderately differentiated) breast cancer. In embodiments, the cancer is high grade (poorly differentiated) breast cancer. In embodiments, the cancer is stage 0 breast cancer. In embodiments, the cancer is stage I breast cancer. In embodiments, the cancer is stage II breast cancer. In embodiments, the cancer is stage III breast cancer. In embodiments, the cancer is stage IV breast cancer. In embodiments, the cancer is triple negative breast cancer.

[0409] In an aspect is provided a method of treating a disease associated with ubiquitin-like modifier activating enzyme 5 activity including administering to a subject in need thereof an effective amount of a Ubiquitin-like modifier activating enzyme 5 inhibitor. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is a compound described herein. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), protein (e.g., antibody, anti-Ubiquitin-like modifier activating enzyme 5 antibody, anti-Ubiquitin-like modifier activating enzyme 5 binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the disease is associated with aberrant ubiquitin-like modifier activating enzyme 5 activity.

[0410] In embodiments, the method includes administering a second agent (e.g. therapeutic agent). In embodiments, the method includes administering a second agent (e.g. therapeutic agent) in a therapeutically effective amount. In embodiments, the second agent is an agent for treating cancer. In embodiments, the second agent is an anti-cancer agent. In embodiments, the second agent is a chemotherapeutic.

V. Methods of Inhibition

[0411] In an aspect is provided a method of inhibiting ubiquitin-like modifier activating enzyme 5 activity including contacting the ubiquitin-like modifier activating enzyme 5 with a Ubiquitin-like modifier activating enzyme 5 inhibitor. In embodiments, the ubiquitin-like modifier activating enzyme 5 is a human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is a compound described herein. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), antisense nucleic acid, protein (e.g.,
antibody, anti-Ubiquitin-like modifier activating enzyme 5 antibody, anti-Ubiquitin-like modifier activating enzyme 5 binding antibody fragment), or compound (e.g., compound described herein). In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is provided in a therapeutically effective amount.

In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts one or more amino acids corresponding to C250, N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5.

In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor covalently binds an amino acid corresponding to C250 in human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to N210 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to C250 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to E209 of human ubiquitin-like modifier activating enzyme 5.

In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to L254 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to S253 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to A251 of human ubiquitin-like modifier activating enzyme 5.

In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts one or more amino acids corresponding to C250, N210, E209, L254, S253, and A251 of SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts one or more amino acids corresponding to C250, N210, E209, L254, S253, and A251 of SEQ ID NO:337.
covalently binds an amino acid corresponding to C250 in SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to N210, E209, L254, S253, and A251 of SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to N210 of SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to C250 of SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to E209 of SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to L254 of SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to S253 of SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to A251 of SEQ ID NO:337. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to C250 of SEQ ID NO:337.

[0414] In an aspect is provided a method of inhibiting ubiquitin-like modifier activating enzyme 5 activity including contacting the ubiquitin-like modifier activating enzyme 5 with a compound described herein. In embodiments, the ubiquitin-like modifier activating enzyme 5 is a human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound is provided in an effective amount. In embodiments, the compound is provided in a therapeutically effective amount. In embodiments, the method includes contacting the ubiquitin-like modifier activating enzyme 5 protein with an effective amount of a compound described herein.

[0415] In embodiments, compound is covalently bonded to the amino acid corresponding to C250 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts one or more amino acids corresponding to C250, N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound covalently binds an amino acid corresponding to C250 in human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to N210 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an
amino acids corresponding to C250 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to E209 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to L254 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to S253 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to C250 of human ubiquitin-like modifier activating enzyme 5.

[0416] In embodiments, compound is covalently bonded to the amino acid corresponding to C250 of SEQ ID NO:337. In embodiments, the compound contacts one or more amino acids corresponding to C250, N210, E209, L254, S253, and A251 of SEQ ID NO:337. In embodiments, the compound contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of SEQ ID NO:337. In embodiments, the compound covalently binds an amino acid corresponding to C250 in SEQ ID NO:337. In embodiments, the compound contacts an amino acids corresponding to N210, E209, L254, S253, and A251 of SEQ ID NO:337. In embodiments, the compound contacts an amino acids corresponding to N210 of SEQ ID NO:337. In embodiments, the compound contacts an amino acids corresponding to C250 of SEQ ID NO:337. In embodiments, the compound contacts an amino acids corresponding to E209 of SEQ ID NO:337. In embodiments, the compound contacts an amino acids corresponding to L254 of SEQ ID NO:337. In embodiments, the compound contacts an amino acids corresponding to S253 of SEQ ID NO:337. In embodiments, the compound contacts an amino acids corresponding to A251 of SEQ ID NO:337. In embodiments, the compound contacts an amino acids corresponding to C250 of SEQ ID NO:337.

[0417] In embodiments, the inhibition is competitive inhibition. In embodiments, the inhibition is irreversible. In embodiments, the compound covalently binds to the ubiquitin-like modifier activating enzyme 5 protein.

[0418] Where the compound covalently binds to the ubiquitin-like modifier activating enzyme 5 a ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5) covalently bonded to a ubiquitin-like modifier activating enzyme 5 inhibitor is formed (also referred to herein as a "ubiquitin-like modifier activating...
enzyme 5-compound adduct”), as described below. In embodiments, the resulting covalent bond is reversible. Where the resulting covalent bond is reversible, the bonding reverses upon denaturation of the protein. Thus, in embodiments, the reversibility of a covalent bond between the compound and the ubiquitin-like modifier activating enzyme 5 upon denaturation of the ubiquitin-like modifier activating enzyme 5 avoids or decreases autoimmune response in a subject subsequent to administration of the compound (relative to irreversibility). Moreover, in embodiments, the reversibility of a covalent bond between the compound and the ubiquitin-like modifier activating enzyme 5 upon denaturation of the ubiquitin-like modifier activating enzyme 5 avoids or decreases the toxicity (e.g. liver toxicity) of the compound in a subject (relative to irreversibility).

[0419] In an aspect is provided a method of inhibiting cell division (e.g., cancer cell division, cancer proliferation), the method including contacting a cell (e.g., cancer cell) with an effective amount of a Ubiquitin-like modifier activating enzyme 5 inhibitor. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is a compound described herein. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), protein (e.g., antibody, anti-Ubiquitin-like modifier activating enzyme 5 antibody, anti-Ubiquitin-like modifier activating enzyme 5 binding antibody fragment), or compound (e.g., compound described herein including embodiments).

[0420] In an aspect is provided a method of inhibiting cell division (e.g., cancer cell division, cancer proliferation) including contacting a cell (e.g., cancer cell) with an effective amount of a compound described herein, including embodiments.

VI. Ubiquitin-like Modifier activating enzyme 5 protein

[0421] In an aspect is provided a ubiquitin-like modifier activating enzyme 5 protein covalently bonded to a Ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., a ubiquitin-like modifier activating enzyme 5 protein-ubiquitin-like modifier activating enzyme 5 inhibitor complex). In embodiments, the ubiquitin-like modifier activating enzyme 5 is a human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is a compound described herein. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is an oligonucleotide (e.g., DNA, RNA, or siRNA), protein (e.g., antibody, anti-Ubiquitin-like modifier activating enzyme 5 antibody, anti-Ubiquitin-like modifier activating enzyme 5 binding antibody fragment), or compound
(e.g., compound described herein). In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor is provided in a therapeutically effective amount.

[0422] In embodiments, a UBA5 protein covalently bonded to a compound as described herein, including embodiments, through the reacted residue of the electrophilic moiety of the compound, thereby forming a ubiquitin-like modifier activating enzyme 5 protein-ubiquitin-like modifier activating enzyme 5 inhibitor complex. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts one or more amino acids corresponding to C250, N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts one or more amino acids corresponding to C250 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to C250 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to N210 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to E209 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to L254 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to S253 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the Ubiquitin-like modifier activating enzyme 5 inhibitor contacts an amino acids corresponding to C250 of human ubiquitin-like modifier activating enzyme 5.

[0423] In an aspect is provided a ubiquitin-like modifier activating enzyme 5 protein covalently bonded to a compound described herein through the reacted residue of the electrophilic moiety. In embodiments, compound is covalently bonded to the amino acid corresponding to C250 of human ubiquitin-like modifier activating enzyme 5. In
embodiments, the compound contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound covalently binds an amino acid corresponding to C250 in human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to N210 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to C250 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to E209 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to S253 of human ubiquitin-like modifier activating enzyme 5. In embodiments, the compound contacts an amino acids corresponding to A251 of human ubiquitin-like modifier activating enzyme 5.

[0424] In embodiments, the compound is bonded to a cysteine residue of the ubiquitin-like modifier activating enzyme 5 protein through the reacted residue of the electrophilic moiety of the compound. In embodiments, the compound is covalently bonded to a cysteine residue of the ubiquitin-like modifier activating enzyme 5 protein. In embodiments, the compound is reversibly covalently bonded to a cysteine residue of the ubiquitin-like modifier activating enzyme 5 protein. In embodiments, the compound is irreversibly covalently bonded to a cysteine residue of the ubiquitin-like modifier activating enzyme 5 protein. In embodiments, the cysteine residue corresponds to C250 of human ubiquitin-like modifier activating enzyme 5.

[0425] In an embodiment, the ubiquitin-like modifier activating enzyme 5 protein is covalently bonded (e.g., reversibly or irreversibly) to a portion of a compound described herein (e.g., portion of a ubiquitin-like modifier activating enzyme 5 inhibitor or portion of a compound described herein).

[0426] In an aspect is provided a ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5) covalently bonded to a ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., ubiquitin-like modifier activating enzyme 5 inhibitor, compound described herein, or a portion of a compound described herein).
In embodiments, the ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5) is covalently bonded to a ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., compound described herein or a portion of a compound described herein). In embodiments, the ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5) is irreversibly covalently bonded to a ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., compound described herein or a portion of a compound described herein). In embodiments, the ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5) is reversibly covalently bonded to a ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., compound described herein or a portion of a compound described herein). In embodiments, the ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5) is covalently bonded to a portion of a ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., compound described herein). In embodiments, the ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5) is reversibly covalently bonded to a portion of a ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., compound described herein). In embodiments, the ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5) is irreversibly covalently bonded to a portion of a ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., compound described herein). In embodiments, the ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5) is reversibly covalently bonded to a portion of a ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., compound described herein). In embodiments, the ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., compound described herein) is bonded to a cysteine residue (e.g., Cys250 of human ubiquitin-like modifier activating enzyme 5 or cysteine corresponding to Cys250 of human ubiquitin-like modifier activating enzyme 5) of the ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5). In embodiments, the portion of a ubiquitin-like modifier activating enzyme 5 inhibitor (e.g., compound described herein) is bonded to a cysteine residue (e.g., Cys250 of human ubiquitin-like modifier activating enzyme 5 or cysteine corresponding to Cys250 of human ubiquitin-like modifier activating enzyme 5) of the ubiquitin-like modifier activating enzyme 5 protein (e.g., human ubiquitin-like modifier activating enzyme 5).

In embodiments, the UBA5 protein covalently bonded to a UBA5 inhibitor or compound described herein is the product of a reaction between the UBA5 protein and a UBA5 inhibitor or compound described herein. It will be understood that the covalently bonded UBA5 protein and UBA5 inhibitor (e.g., compound described herein) are the
remnants of the reactant UBA5 protein and UBA5 inhibitor or compound, wherein each reactant now participates in the covalent bond between the UBA5 protein and UBA5 inhibitor or compound. In embodiments of the covalently bonded UBA5 protein and compound described herein, the remnant of the E substituent is a linker including a covalent bond between the UBA5 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 UBA5 protein is covalently bonded to a UBA5 inhibitor (e.g., compound described herein), the UBA5 inhibitor (e.g., compound described herein) forms a remnant of the pre-reacted UBA5 inhibitor (e.g., compound described herein) wherein a bond connects the remnant of the UBA5 inhibitor (e.g., compound described herein) to the remnant of the UBA5 protein (e.g., cysteine sulfur, sulfur of amino acid corresponding to C250 of human UBA5, sulfur of C250 of human UBA5). The remnant of the UBA5 inhibitor (compound described herein) may also be called a portion of the UBA5 inhibitor. In embodiments, the remnant of the E substituent is a linker selected from a bond, \(-\text{S}(0)\_2\), \(-\text{NH}_2\), \(-\text{O}\_2\), \(-\text{S}\), \(-\text{C(0)}\_\text{NH}\), \(-\text{NHC(O)}\_\text{O}\),

\(-\text{NHC(0)}\_\text{NH}\), \(-\text{NHC(0)}\_\text{NH}\), \(-\text{C(0)}\_\text{O}\), \(-\text{OC(O)}\), \(-\text{CH}_2\_\text{NH}\), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted alkylene (e.g., \text{C}_1-\text{C}_6, \text{C}_1-\text{C}_4, \text{C}_1-\text{C}_2), substituted (e.g., substituted with a substituent group, a 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 a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted cycloalkylene (e.g., \text{C}_3-\text{C}_8, \text{C}_3-\text{C}_6, \text{C}_4-\text{C}_6, \text{or} \text{C}_5-\text{C}_6), substituted (e.g., substituted with a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted 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 a substituent group, a size-limited substituent group, or lower substituent group) or unsubstituted arylene (e.g., \text{C}_6-\text{Cio} or phenyl), or substituted (e.g., substituted with a substituent group, a 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). As a non-limiting example, the UBA5 protein covalently bonded to a UBA5 inhibitor may have the formula:
wherein $S_i$ is the sulfur of a ubiquitin-like modifier activating enzyme 5 protein cysteine (e.g., corresponding to C250 of human ubiquitin-like modifier activating enzyme 5), which is bonded to the remainder of the ubiquitin-like modifier activating enzyme 5 protein and wherein $R^1, L^1, L^2,$ and $z_1$ are as described herein.

As a non-limiting example, the UBA5 protein covalently bonded to a UBA5 inhibitor may have the formula:

$$(R^1)_{z_1}$$

wherein $S_i$ is the sulfur of a ubiquitin-like modifier activating enzyme 5 protein cysteine (e.g., corresponding to C250 of human ubiquitin-like modifier activating enzyme 5), which is bonded to the remainder of the ubiquitin-like modifier activating enzyme 5 protein and wherein $R^1, L^1, L^2,$ and $z_1$ are as described herein.

As a non-limiting example, the ubiquin UBA5 protein covalently bonded to a UBA5 inhibitor may have the formula:

$$(R^{1,2})_{z_1}$$

wherein $S_i$ is the sulfur of a ubiquitin-like modifier activating enzyme 5 protein cysteine (e.g., corresponding to C250 of human ubiquitin-like modifier activating enzyme 5), which is bonded to the remainder of the ubiquitin-like modifier activating enzyme 5 protein and wherein $R^{1,1}, R^{1,2}, L^1,$ and $L^2$ are as described herein. As a non-limiting example, the ubiquin UBA5 protein covalently bonded to a UBA5 inhibitor may have the formula:

$$(R^{1,2})_{z_1}$$

wherein $S_i$ is the sulfur of a ubiquitin-like modifier activating enzyme 5 protein cysteine (e.g., corresponding to C250 of human ubiquitin-like modifier activating enzyme 5), which is bonded to the remainder of the ubiquitin-like modifier activating enzyme 5 protein and wherein $R^{1,1}, R^{1,2}, L^1, L^2, R^{15}, R^{16},$ and $R^{17}$ are as described herein.
EMBODIMENTS

[0429] Embodiment P1. A compound having the formula:

\[
\begin{align*}
\text{R}^1 & \text{ is independently halogen, } -\text{CX}^\Lambda, -\text{CHX}^\Lambda, -\text{CHX}^2, -\text{OCX}^\Lambda, \\
\text{OCHX}^1, -\text{OCHX}^2, -\text{CN}, -\text{SO}^\text{NR}^\text{AB}, -\text{SO}^\text{NR}^\text{AB}, -\text{NHC}(0)NR^\text{AB}, -N(0)_m, -NR^\text{AB}, \\
& -C(0)R^\text{IC}, -C(0)-OR^\text{IC}, -C(0)NR^\text{AB}, -OR^\text{IB}, -NR^\text{AB}S_2R^\text{IB}, -NR^\text{AB}C(0)R^\text{IC}, -NR^\text{AB}C(0)R^\text{IC}, \\
& \text{R}^\text{IC}, -NR^\text{AB}0R^\text{IC}, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,} \\
& \text{substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,} \\
& \text{substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent } \text{R}^1 \\
& \text{substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl,} \\
& \text{substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted} \\
& \text{or unsubstituted heteroaryl;} \\

z_l \text{ is an integer from 0 to 5;}
\end{align*}
\]

[0429] L^1 \text{ is a bond, } -S(0)_2, -NR^\text{F}, -O-, -S-, -C(0)-, -C(0)NR^\text{F}, -NR^\text{F}C(0)-, \\
& -NR^\text{F}C(0)NH-, -NHC(0)NR^\text{F}, -C(0)0-, -OC(0)-, -CH2NR^\text{F}, \text{substituted or unsubstituted} \\
& \text{alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted} \\
& \text{cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted} \\
& \text{arylene, or substituted or unsubstituted heteroarylene;}

[0429] R^4 \text{ is hydrogen, } -\text{CX}^3, -\text{CHX}^3, -\text{CHX}^2, -\text{OCX}^3, -\text{OCX}^2, \\
& -\text{OCHX}^3, -\text{CN}, -C(0)R^\text{IC}, -C(0)-OR^\text{IC}, -C(0)NR^\text{AB}, -OR^\text{IB}, -NR^\text{AB}S_2R^\text{IB}, \\
& -NR^\text{AB}C(0)R^\text{IC}, -NR^\text{AB}C(0)R^\text{IC}, \text{substituted or unsubstituted} \\
& \text{alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,} \\
& \text{substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted} \\
& \text{or unsubstituted heteroaryl;}

[0429] L^2 \text{ is a bond, } -S(0)_2, -NR^\text{F}, -O-, -S-, -C(0)-, -C(0)NR^\text{F}, -NR^\text{F}C(0)-, \\
& -NR^\text{F}C(0)NH-, -NHC(0)NR^\text{F}, -C(0)0-, -OC(0)-, -CH2NR^\text{F}, \text{substituted or unsubstituted} \\
& \text{alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted} \\
& \text{cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted} \\
& \text{arylene, or substituted or unsubstituted heteroarylene;}

[0429] R^5 \text{ is hydrogen, } -\text{CX}^3, -\text{CHX}^3, -\text{CHX}^2, -\text{OCX}^3, -\text{OCX}^2, \\
& -\text{OCHX}^3, -\text{CN}, -C(0)R^\text{IC}, -C(0)-OR^\text{IC}, -C(0)NR^\text{AB}, -OR^\text{IB}, -NR^\text{AB}S_2R^\text{IB}, \\
& -NR^\text{AB}C(0)R^\text{IC}, -NR^\text{AB}C(0)R^\text{IC}, \text{substituted or unsubstituted} 

unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

\[ \text{E is an electrophilic moiety;} \]

Each \( R^1A, R^1B, R^1C, R^1D, R^4A, R^4B, R^4C, R^4D, R^5A, R^5B, R^5C, \) and \( R^5D \) is independently hydrogen, -CX\(_3\), -CN, -COOH, -CONH\(_2\), -CH\(_X\)_2, -CH\(_2\)X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; \( R^1A \) and \( R^1B \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^4A \) and \( R^4B \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^5A \) and \( R^5B \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

Each \( X, X^1, X^4, \) and \( X^5 \) is independently -F, -Cl, -Br, or -I;

n\(_{l}, n^4, \) and n\(_5 \) are independently an integer from 0 to 4; and

m\(_{l}, m^4, m^5, v_l, v^4, \) and v\(_5 \) are independently an integer from 1 to 2.

[0430] Embodiment P2. The compound of embodiment P1 having the formula:

![Formula Image](image)

(R\(_1\))^z1

(Ia).

[0431] Embodiment P3. The compound of embodiment P1 having the formula:

![Formula Image](image)

(R\(_1\))^z1

(Ib).

[0432] Embodiment P4. The compound of embodiment P1 having the formula:

![Formula Image](image)

(R\(_1\))

(II).
Embodiment P5. The compound of embodiment PI having the formula:

(IIa).

Embodiment P6. The compound of embodiment PI having the formula:

(IIb).

Embodiment P7. The compound of one of embodiments PI to P6, wherein R^1 is independently halogen, -CX^1_3, -CHX^1_2, -CH2X^1, -OCXS, -OCH2X^1, -OCHXS, -CN, -SR^{1d}, -NR^{1a}R^{1b}, -C(0)R^{1c}, -C(0)OR^{1c}, -C(0)NR^{1a}R^{1b}, -OR^{1d}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

Embodiment P8. The compound of one of embodiments PI to P6, wherein R^1 is independently halogen, -CX^1_3, -CHX^1_2, -CH2X^1, -OCXS, -OCH2X^1, -OCHXS, -CN, -SH, -NH_2, -C(0)OH, -C(0)NH_2, -OH, -OCH_3, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C3-C8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C6-C12 cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

Embodiment P9. The compound of one of embodiments PI to P6, wherein R^1 is independently halogen, -CX^1_3, -CHX^1_2, -CH2X^1, -OCXS, -OCH2X^1, -OCHXS, -CN, -SH, -NH_2, -C(0)OH, -C(0)NH_2, -OH, -OCH3, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 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.

Embodiment P10. The compound of one of embodiments PI to P6, wherein R^1 is independently -OR^{1d}. 

178
Embodiment P11. The compound of one of embodiments PI to P6, wherein $R^1$ is independently -OCH3.

Embodiment P12. The compound of embodiment PI, wherein $z1$ is 0.

Embodiment P13. The compound of embodiment PI having the formula:

$$\text{(III)},$$

wherein

$R^{1,1}$ and $R^{1,2}$ are independently hydrogen, halogen, -CX^, -CHX^, -CH2X^1, -OCX^1, -OCH2X^1, -OCX^12, -CN, -SONiR_{1D}, -SO_iNR_{1A}R_{1B}, -NH(C(0))NR_{1A}R_{1B}, -N(0)mi, -NR_{1A}R_{1B}, -C((0))OR_{1C}, -C(0)NR_{1A}R_{1B}, -OR_{1B}, -NR_{1A}SO_{2R_{1D}}, -NR_{1A}C(0)R_{1C}, -NR_{1A}C(0)OR_{1C}, -NR_{1A}OR_{1C},$ substituted 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 $R^{1,1}$ and $R^{1,2}$ may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

Embodiment P14. The compound of embodiment P13 having the formula:

$$\text{(IIIa)}.$$  

Embodiment P15. The compound of embodiment P13 having the formula:

$$\text{(IIIb)}.$$  

Embodiment P16. The compound of one of embodiments P13 to P15, wherein $R^{1,1}$ and $R^{1,2}$ are independently halogen, -CX^, -CHX^, -CH2X^1, -OCX^, -OCH2X^1, -OCX^1, -CN, -SR_{1D}, -NR_{1A}R_{1B}, -C((0))OR_{1C}, -C((0))OR_{1C}, -C(0)NR_{1A}R_{1B}, -OR_{1D},$ substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
Embodiment P17. The compound of one of embodiments P13 to P15, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently halogen, -CX\textsuperscript{1}, -CHX\textsuperscript{1}, -CH2X\textsuperscript{1}, -OCX\textsuperscript{1}, -OCH\textsubscript{2}X\textsuperscript{1}, -OCHX\textsuperscript{1}, -CN, -SH, -NH\textsubscript{2}, -C (\varnothing )OH, -C (\varnothing )NH\textsubscript{2}, -OH, -OCH\textsubscript{3}, substituted or unsubstituted Ci-C\textsubscript{8} alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\textsubscript{5}-C\textsubscript{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C\textsubscript{6}-C\textsubscript{12} cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

Embodiment P18. The compound of one of embodiments P13 to P15, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently halogen, -CX\textsuperscript{1}, -CHX\textsuperscript{1}, -CH2X\textsuperscript{1}, -OCX\textsuperscript{1}, -OCH\textsubscript{2}X\textsuperscript{1}, -OCHX\textsuperscript{1}, or substituted or unsubstituted Ci-C\textsubscript{8} alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\textsubscript{5}-C\textsubscript{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered heteroaryl.

Embodiment P19. The compound of one of embodiments P13 to P15, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently -OR\textsuperscript{1D}.

Embodiment P20. The compound of one of embodiments P13 to P15, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently -OCH\textsubscript{3}.

Embodiment P21. The compound of one of embodiments P1 to P20, wherein L\textsuperscript{1} is a bond, substituted or unsubstituted Ci-C\textsubscript{8} alkyne, substituted or unsubstituted 2 to 8 membered heteroalkyne, substituted or unsubstituted C\textsubscript{5}-C\textsubscript{8} cycloalkyne, substituted or unsubstituted 3 to 8 membered heterocycloalkyne, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

Embodiment P22. The compound of one of embodiments P1, P4, P7 to P13, and P16 to P20, wherein L\textsuperscript{1} is a bond.

Embodiment P23. The compound of one of embodiments P1, P4, P7 to P13, and P16 to P20, wherein L\textsuperscript{1} is -CH\textsubscript{2}NR\textsuperscript{4}.

Embodiment P24. The compound of one of embodiments P1, P2, P4, P5, P7 to P14, and P16 to P22, wherein L\textsuperscript{2} is -NR\textsuperscript{5}.
Embodiment P25. The compound of embodiment P24, wherein R\textsuperscript{5} is hydrogen, substituted or unsubstituted \textit{C}_{1}-\textit{C}_{6} alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

Embodiment P26. The compound of embodiment P24, wherein R\textsuperscript{5} is hydrogen or unsubstituted \textit{C}_{1}-\textit{C}_{3} alkyl.

Embodiment P27. The compound of embodiment P24, wherein R\textsuperscript{5} is hydrogen, unsubstituted methyl, unsubstituted ethyl, unsubstituted hexyl, or unsubstituted benzyl.

Embodiment P28. The compound of embodiment P24, wherein R\textsuperscript{5} is hydrogen.

Embodiment P29. The compound of one of embodiments P1 to P28, wherein E is a covalent cysteine modifier moiety.

Embodiment P30. The compound of one of embodiments P1 to P28, wherein E is:

\[
\begin{align*}
\text{CH}_{2}X_{15}^- & , -CN , -\text{SO}_{\text{R}16}\text{NR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , -\text{NHNC}(0)\text{NR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , -\text{NHR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , -\text{ONR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , \\
-NHC & = (0)\text{NHNR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , -\text{NHC}(0)\text{NR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , -\text{NHR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , -\text{NHR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , -\text{NHR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , -\text{NHR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , \\
-C(0) & -\text{OR}_{\text{R}15C}^- , -\text{C}(0)\text{NR}_{\text{R}15A}\text{R}_{\text{R}15B}^- , -\text{OR}_{\text{R}15D}^- , -\text{NR}_{\text{R}15A}\text{C}(0)\text{R}_{\text{R}15C}^- , -
\end{align*}
\]

\[
\begin{align*}
\text{NR}_{\text{R}15A}\text{C}(0)\text{OR}_{\text{R}15C}^- , -\text{NR}_{\text{R}15A}\text{OR}_{\text{R}15C}^- , -\text{OCX}_{15}^- , -\text{OCHX}_{15}^- , \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;}
\end{align*}
\]

\[
\begin{align*}
\text{R}_{\text{R}16} & \text{is independently hydrogen, halogen, } \text{CX}_{16}^- , -\text{CHX}_{16}^- , -
\end{align*}
\]

\[
\begin{align*}
\text{CH}_{2}X_{16}^- , -\text{CN} , -\text{SO}_{\text{R}16}\text{NR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , -\text{NHNR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , -\text{ONR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , \\
-NHC & = (0)\text{NHNR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , -\text{NHC}(0)\text{NR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , -\text{NHR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , -\text{NHR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , -\text{NHR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , -\text{NHR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , \\
-C(0) & -\text{OR}_{\text{R}16C}^- , -\text{C}(0)\text{NR}_{\text{R}16A}\text{R}_{\text{R}16B}^- , -\text{OR}_{\text{R}16D}^- , -\text{NR}_{\text{R}16A}\text{SO}_{2}\text{R}_{\text{R}16D}^- , -\text{NR}_{\text{R}16A}\text{C}(0)\text{R}_{\text{R}16C}^- , -
\end{align*}
\]
NR^{16A}C(0)OR^{16C}, -NR^{16A}OR^{16C}, -OCX^{16}_3,
-OCHX^{16}_2, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R^{17} is independently hydrogen, halogen, CX^{17}_3, -CHX^{17}_2, -
CH_2X^{17}, -CN, -SONivR^{17D}, -SOv-NR^{17A}R^{17B}, - NHR^{17A}R^{17B}, - ONR^{17A}R^{17B},
-NHC=(O)NHNR^{17A}R^{17B}, - NHC(NH)NR^{17A}R^{17B}, -N(NH)_m^{17}, -NR^{17A}R^{17B}, -C(0)R^{17C},
-C(0)-OR^{17C}, -C(O)NR^{17A}R^{17B}, -OR^{17D}, -NR^{17A}S_n^{17D}, -NR^{17A}C(0)R^{17C},
NR^{17A}C(0)OR^{17C}, -NR^{17A}OR^{17C}, -OCX^{17}_3, -OCHX^{17}_2, substituted or unsubstituted alkyl,

R^{18} is independently hydrogen, -CX^{18}_3, -CHX^{18}_2, -
CH_2X^{18}, -C(0)R^{18C}, -C(0)OR^{18C}, -C(0)NR^{18A}R^{18B}, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R^{18B}, R^{18C}, R^{18D}, are independently hydrogen, -CX_3, -CN, -COOH, -CONH2, -CHX_2, -CH_2X,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, or unsubstituted heteroaryl; R^{15A} and R^{15B} substituents
bonded to the same nitrogen atom may optionally be joined to form a substituted or
unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{16A} and R^{16B}
substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or
unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B}
substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or
unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B}
substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or
unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X^{15}, X^{16}, X^{17} and X^{18} is independently -F, -Cl, -Br, or -I;

n_{l5}, n_{l6}, n_{l7}, v_{l5}, v_{l6}, and v_{l7}, are independently an integer from 0 to 4; and
m\textsubscript{15}, m\textsubscript{16}, and m\textsubscript{17} are independently and integer from 1 to 2.

[0459] Embodiment P31. The compound of embodiment P30, wherein R\textsuperscript{15}, R\textsuperscript{16}, R\textsuperscript{17}, and R\textsuperscript{18} are hydrogen.

[0460] Embodiment P32. The compound of one of embodiments P30 to P31, wherein E is:

\begin{center}
\begin{tikzpicture}
\node at (0,0) {O} edge [bend left=10, line width=1pt] (0,-0.5) edge [bend right=10, line width=1pt] (0,-0.5) edge [bend left=10, line width=1pt] (0.5,-0.5) edge [bend right=10, line width=1pt] (0.5,-0.5);
\node at (0.5,0) {R\textsuperscript{15}} edge [bend right=10, line width=1pt] (0.5+0.5,-0.5) edge [bend left=10, line width=1pt] (0.5+0.5,-0.5) edge [bend right=10, line width=1pt] (1,-0.5) edge [bend left=10, line width=1pt] (1,-0.5);
\node at (1,0) {R\textsuperscript{16}} edge [bend right=10, line width=1pt] (1.5,-0.5) edge [bend left=10, line width=1pt] (1.5,-0.5) edge [bend right=10, line width=1pt] (2,-0.5) edge [bend left=10, line width=1pt] (2,-0.5);
\node at (2,0) {R\textsuperscript{17}} edge [bend right=10, line width=1pt] (2.5,-0.5) edge [bend left=10, line width=1pt] (2.5,-0.5) edge [bend right=10, line width=1pt] (3,-0.5) edge [bend left=10, line width=1pt] (3,-0.5);
\end{tikzpicture}
\end{center}

[0461] Embodiment P33. The compound of embodiment P30, wherein E is:

\begin{center}
\begin{tikzpicture}
\node at (0,0) {O} edge [bend left=10, line width=1pt] (0,-0.5) edge [bend right=10, line width=1pt] (0,-0.5) edge [bend left=10, line width=1pt] (0.5,-0.5) edge [bend right=10, line width=1pt] (0.5,-0.5);
\node at (0.5,0) {x\textsuperscript{17}} edge [bend right=10, line width=1pt] (0.5+0.5,-0.5) edge [bend left=10, line width=1pt] (0.5+0.5,-0.5) edge [bend right=10, line width=1pt] (1,-0.5) edge [bend left=10, line width=1pt] (1,-0.5);
\end{tikzpicture}
\end{center}


[0463] Embodiment P35. A pharmaceutical composition comprising a compound of one of embodiments P30 to P33 and a pharmaceutically acceptable excipient.


[0465] Embodiment P37. The method of embodiment P36, wherein the UBA5 inhibitor is an siRNA, antibody, or compound.

[0466] Embodiment P38. The method of embodiment P37, wherein the UBA5 inhibitor contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of human UBA5.


[0468] Embodiment P40. The method of embodiment P39, wherein the compound is covalently bonded to the amino acid corresponding to C250 of human UBA5.
[0469] Embodiment P41. The method of embodiment P39, wherein the compound contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of human UBA5.

[0470] Embodiment P42. A method of treating cancer, said method comprising administering to a subject in need thereof an effective amount of a compound of one of embodiments P1 to P33.

[0471] Embodiment P43. The method of embodiment P42, wherein the cancer is pancreatic cancer.

[0472] Embodiment P44. A UBA5 protein covalently bonded to a compound of one of embodiments P1 to P33 through the reacted residue of said electrophilic moiety.

[0473] Embodiment P45. The UBA5 protein of embodiment P44, wherein the compound is bonded to a cysteine residue of the protein.

[0474] Embodiment P46. The UBA5 protein of embodiment P44, covalently bonded to a portion of a compound of one of embodiments P1 to P33.

[0475] Embodiment P47. The UBA5 protein of embodiment P44, irreversibly covalently bonded to a portion of a compound of one of embodiments P1 to P33.

[0476] Embodiment P48. The UBA5 protein of one of embodiments P44 to P47, wherein the compound or portion of the compound is covalently bonded to an amino acid corresponding to C250 of human UBA5.

20 Additional Embodiments

[0477] Embodiment 1. A method of treating cancer, said method comprising administer ng to a subject in need thereof an effective amount of a compound having the formula: 

\[ \text{(I)} \]

wherein,

- \( R^1 \) is independently halogen, -CX\(^a\), -CHX\(^a\), -CH2X\(^1\), -OCX\(^1\), -
- OCH2X\(^1\), -OCHX\(^1\), -CN, -SONH\(^\text{R}1\), -SO\(^\text{R}1\), -NH\( 2 \)C(0)\( \text{R}1\), -NR\(^1\)\( \text{R}2\), -N(0)\( m \), -NR\(^1\)\( \text{R}1\), -
- C(0)R\(^1\), -C(0)-OR\(^1\), -C(0)NR\(^1\)\( \text{R}1\), -OR\(^\text{R}1\), -NR\(^1\)\( \text{R}1\), -NR\(^1\)\( \text{R}2\), -NR\(^1\)\( \text{R}1\), -NR\(^1\)\( \text{R}3\), 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; two adjacent R
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 an integer from 0 to 5;

L1 is a bond, -S(0)2-, -NR4-, -0-, -S-, -C(O)-, -C(0)NR 4-, -NR4C(0)-,
-NR4C(0)NH-, -NHC(0)NR 4-, -C(0)0-, -OC(O)-, -CH2NR4-, substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted
aryl, or substituted or unsubstituted heteroarylene;

R4 is hydrogen, -CX43, -CHX42, -CH2X4, -O CX43, -OCH2X4,
-OCHX42, -CN, -C(0)R 4C, -C(0)-OR 4C, -C(0)NR 4A-R4b, -OR4D, substituted or unsubstituted
alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
or unsubstituted heteroaryl;

L2 is a bond, -S(0)2-, -NR5-, -0-, -S-, -C(O)-, -C(0)NR 5-, -NR5C(0)-,
-NR5C(0)NH-, -NHC(0)NR 5-, -C(0)0-, -OC(O)-, -CH2NR5-, substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted
aryl, or substituted or unsubstituted heteroarylene;

R5 is hydrogen, -CX53, -CHX52, -CH2X5, -O CX53, -OCH2X5,
-OCHX52, -CN, -C(0)R 5C, -C(0)-OR 5C, -C(0)NR 5A-R5b, -OR5D, substituted or unsubstituted
alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

Each R1A, R1B, R1C, R1D, R1A, R1B, R1C, R1D, R5A, R5B, R5C, and R5D is
independently hydrogen, -CX3, -CN, -COOH, -CONH2, -CHX2, -CH2X, substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl; R1A and R1B substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; R4A and R4B substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5a} and R^{5b} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

5

each X, X^1, X^4, and X^5 is independently -F, -Cl, -Br, or -I;

tl, n4, and n5 are independently an integer from 0 to 4; and

ml, m4, m5, v1, v4, and v5 are independently an integer from 1 to 2.

[0478] Embodiment 2. The method of embodiment 1, wherein the compound has the

formula: (R^1)_{x1} (Ia).

[0479] Embodiment 3. The method of embodiment 1, wherein the compound has the

formula: (R^1)_{x1} (Ib).

[0480] Embodiment 4. The method of embodiment 1, wherein the compound has the

formula: R^1 (II).

[0481] Embodiment 5. The method of embodiment 1, wherein the compound has the

formula: R^1 (IIa).

[0482] Embodiment 6. The method of embodiment 1, wherein the compound has the

formula: R^1 (IIb).

[0483] Embodiment 7. The method of one of embodiments 1 to 6, wherein R^1 is independently halogen, -CX^A, -CHX^A, -CH_2X^1, -OCXS, -

OCHX^A, -CN, -SR^{1b}, -NR^{1a}R^{1b},

-C(0)R^{1c}, -C(0)OR^{1c}, -C(0)NR^{1a}R^{1b}, -OR^{1b}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0484] Embodiment 8. The method of one of embodiments 1 to 6, wherein R¹ is independently halogen, -CX³, -CHX¹₂, -CH₂X¹, -OCXS, -

5 OCH₂X¹, -OCHXS, -CN, -SH, -NH₂,
-C(0)OH, -C(0)NH₂, -OH, -OCH₃, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆-C₁₂ cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0485] Embodiment 9. The method of one of embodiments 1 to 6, wherein R¹ is independently halogen, -CX³, -CHX¹₂, -CH₂X¹, -OCXS, -

OCH₂X¹, -OCHXS, -CN, -SH, -NH₂,
-C(0)OH, -C(0)NH₂, -OH, -OCH₃, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 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.

[0486] Embodiment 10. The method of one of embodiments 1 to 6, wherein R¹ is independently -OR¹b.

[0487] Embodiment 11. The method of one of embodiments 1 to 6, wherein R¹ is independently -OCH₃.

[0488] Embodiment 12. The method of embodiment 1, wherein z₁ is 0.

[0489] Embodiment 13. The method of embodiment 1, wherein the compound has the

formula: R¹²

(III), wherein

R¹¹ and R¹² are independently hydrogen, halogen, -CX³, -CHX¹₂,

-CH₂X¹, -OCXS, -OCH₂X¹, -OCHXS, -CN, -SO₃R¹b, -SO₂NR¹bR¹b, -NHC(0)NR¹bR¹b,
-N(0)mi, -NR¹bR¹b, -C(0)R¹c, -C(0)-OR¹c, -C(0)NR¹bR¹b, -OR¹b, -NR¹bSO₂R¹b, -NR¹bC(0)R¹c, -NR¹bC(0)OR¹c, substituted 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 R\textsuperscript{1,1} and R\textsuperscript{1,2} may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0490] Embodiment 14. The method of embodiment 13, wherein the compound has the formula: R\textsuperscript{1,1} \textsuperscript{12} E

[0491] Embodiment 15. The method of embodiment 13, wherein the compound has the formula: R\textsuperscript{1,1} \textsuperscript{12} E

[0492] Embodiment 16. The method of one of embodiments 13 to 15, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently halogen, -CX\textsuperscript{a}, -CHX\textsuperscript{a}, -CH2X\textsuperscript{1}, -OCX\textsuperscript{a}, -OCH\textsuperscript{a}, -OCH\textsuperscript{a}, -CN, -SR\textsuperscript{id}, -NR\textsuperscript{1a}R\textsuperscript{1b}, -C(\textsubscript{a})\textsuperscript{1c}, -C(\textsubscript{a})\textsuperscript{1c}OR\textsuperscript{1d}, -C(\textsubscript{a})\textsuperscript{1c}NR\textsuperscript{1a}R\textsuperscript{1b}, -OR\textsuperscript{1d}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0493] Embodiment 17. The method of one of embodiments 13 to 15, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently halogen, -CX\textsuperscript{a}, -CHX\textsuperscript{a}, -CH2X\textsuperscript{1}, -OCX\textsuperscript{a}, -OCH2X\textsuperscript{1}, -OCHX\textsuperscript{a}, -CN, -SH, -NH\textsubscript{2}, -C(\textsubscript{a})OH, -C(\textsubscript{a})\textsubscript{2}NH\textsubscript{2}, -OH, -OCH\textsubscript{3}, substituted or unsubstituted Ci-C\textsubscript{8} alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\textsubscript{3}-C\textsubscript{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C\textsubscript{6}-C\textsubscript{8} cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0494] Embodiment 18. The method of one of embodiments 13 to 15, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently halogen, -CX\textsuperscript{a}, -CHX\textsuperscript{a}, -CH2X\textsuperscript{1}, -OCX\textsuperscript{a}, -OCH2X\textsuperscript{1}, -OCHX\textsuperscript{a}, -NH\textsubscript{2}, -C(\textsubscript{a})OH, -C(\textsubscript{a})\textsubscript{2}NH\textsubscript{2}, -OH, -OCH\textsubscript{3}, substituted or unsubstituted Ci-C\textsubscript{8} alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\textsubscript{3}-C\textsubscript{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.
Embodiment 19. The method of one of embodiments 13 to 15, wherein $R^1$ and $R^2$ are independently -OR.

Embodiment 20. The method of one of embodiments 13 to 15, wherein $R^1$ and $R^2$ are independently -OCH3.

Embodiment 21. The method of one of embodiments 1 to 20, wherein $L^1$ is a bond, substituted or unsubstituted Ci-Cs alkylene, substituted or unsubstituted 2 to 8 membered heteroalkylene, substituted or unsubstituted C3-C8 cycloalkylene, substituted or unsubstituted 3 to 8 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

Embodiment 22. The method of one of embodiments 1, 4, 7 to 13, and 16 to 20, wherein $L^1$ is a bond.

Embodiment 23. The method of one of embodiments 1, 4, 7 to 13, and 16 to 20, wherein $L^1$ is -CH2NR4.

Embodiment 24. The method of one of embodiments 1, 2, 4, 5, 7 to 14, and 16 to 22, wherein $L^2$ is -NR5.

Embodiment 25. The method of embodiment 24, wherein $R^5$ is hydrogen, substituted or unsubstituted Ci-C6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

Embodiment 26. The method of embodiment 24, wherein $R^5$ is hydrogen or unsubstituted C1-C3 alkyl.

Embodiment 27. The method of embodiment 24, wherein $R^5$ is hydrogen, unsubstituted methyl, unsubstituted ethyl, unsubstituted hexyl, or unsubstituted benzyl.

Embodiment 28. The method of embodiment 24, wherein $R^5$ is hydrogen.

Embodiment 29. The method of one of embodiments 1 to 28, wherein $E$ is a covalent cysteine modifier moiety.

Embodiment 30. The method of one of embodiments 1 to 28, wherein $E$ is:
$R^{15}$ is independently hydrogen, halogen, $X^{15}_3$, $-CHX^{15}_2$, $-CH_2X^{15}$, $-CN$, $-SO_{17}NR^{15AR}X^{15}_3$, $-NHR^{15AR}X^{15}_3$, $-ONR^{15AR}X^{15}_3$, $-NH(0)NR^{15AR}X^{15}_3$, $-N(0)NR^{15AR}X^{15}_3$, $-NR^{15AR}X^{15}_3$, $-C(0)R^{15C}$, $-C(0)OR^{15C}$, $-C(0)NR^{15AR}X^{15}_3$, $-OR^{15D}$, $-NR^{15A SO_2 R^{15D}_2}$, $-NR^{15A C(0)R^{15C}}$, $-NR^{15A C(0)OR^{15C}}$, $-NR^{15A OR^{15C}}$, $-OCHX^{15}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

$R^{16}$ is independently hydrogen, halogen, $X^{16}_3$, $-CHX^{16}_2$, $-CH_2X^{16}$, $-CN$, $-SO_{17}NR^{16AR}X^{16}_3$, $-NHR^{16AR}X^{16}_3$, $-ONR^{16AR}X^{16}_3$, $-NH(0)NHNR^{16AR}X^{16}_3$, $-NHC(0)NR^{16AR}X^{16}_3$, $-N(0)NR^{16AR}X^{16}_3$, $-NR^{16AR}X^{16}_3$, $-C(0)R^{16C}$, $-C(0)OR^{16C}$, $-C(0)NR^{16AR}X^{16}_3$, $-OR^{16D}$, $-NR^{16A SO_2 R^{16D}_2}$, $-NR^{16A C(0)R^{16C}}$, $-NR^{16A C(0)OR^{16C}}$, $-NR^{16A OR^{16C}}$, $-OCHX^{16}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

$R^{17}$ is independently hydrogen, halogen, $X^{17}_3$, $-CHX^{17}_2$.

$R^{18}$ is independently hydrogen, halogen, $X^{18}_3$, $-CHX^{18}_2$, $-NH(0)NHNR^{17AR}X^{17}_3$, $-NH(0)NR^{17AR}X^{17}_3$, $-N(0)NR^{17AR}X^{17}_3$, $-NR^{17AR}X^{17}_3$, $-C(0)R^{17C}$, $-C(0)OR^{17C}$, $-C(0)NR^{17AR}X^{17}_3$, $-OR^{17D}$, $-NR^{17A SO_2 R^{17D}_2}$, $-NR^{17A C(0)R^{17C}}$, $-NR^{17A C(0)OR^{17C}}$, $-NR^{17A OR^{17C}}$, $-OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

$R^{19}$ is independently hydrogen, halogen, $X^{19}_3$, $-CHX^{19}_2$, $-NH(0)NHNR^{18AR}X^{18}_3$, $-NH(0)NR^{18AR}X^{18}_3$, $-N(0)NR^{18AR}X^{18}_3$, $-NR^{18AR}X^{18}_3$, $-C(0)R^{18C}$, $-C(0)OR^{18C}$, $-C(0)NR^{18AR}X^{18}_3$, $-OR^{18D}$, $-NR^{18A SO_2 R^{18D}_2}$, $-NR^{18A C(0)R^{18C}}$, $-NR^{18A C(0)OR^{18C}}$, $-NR^{18A OR^{18C}}$, $-OCHX^{18}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; 


are independently hydrogen, -CX₃, -CN, -COOH, -CONH₂, -CHX₂, -CH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{15A} and R^{15B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X^{15}, X^{16}, X^{17} and X^{18} is independently -F, -Cl, -Br, or -I;

n_{l5}, n_{l6}, n_{l7}, v_{l5}, v_{l6}, and v_{l7}, are independently an integer from 0 to 4; and

m_{l5}, m_{l6}, and m_{l7} are independently an integer from 1 to 2.


[0508] Embodiment 32. The method of one of embodiments 30 to 31, wherein E is:

\[
\text{[Diagram]} \]

[0509] Embodiment 33. The method of embodiment 30, wherein E is:

\[
\text{[Diagram]} \]
Embodiment 34. The method of embodiment 1, wherein the compound has the formula:
Embodiment 35. The method of embodiment 1 wherein the compound has the formula:

Embodiment 36. The method of one of embodiments 1 to 35, wherein the cancer is pancreatic cancer.

Embodiment 37. The use of a compound for the preparation of a medicament for the treatment of cancer, wherein the compound has the formula: 

$$\text{(I)}$$

wherein,

- \( R^1 \) is independently halogen, \(-\text{CX}^\text{\textsuperscript{\textit{a}}}, -\text{CHX}^\text{\textsuperscript{\textit{a}}}, -\text{CH2X}^\text{\textsuperscript{\textit{b}}}, -\text{OCX}^\text{\textsuperscript{\textit{a}}} \), \(-\text{OCH2X}^\text{\textsuperscript{\textit{b}}}, -\text{OCHX}^\text{\textsuperscript{\textit{b}}} \), \(-\text{CN} \), \(-\text{SO} i \text{R}^\text{\textsuperscript{\textit{b}}}, -\text{SO} vi \text{NR}^\text{\textsuperscript{\textit{a}}} R^\text{\textsuperscript{\textit{b}}}, -\text{NHC}(0)\text{NR}^\text{\textsuperscript{\textit{a}}} R^\text{\textsuperscript{\textit{b}}}, -\text{N}(0)_m i, -\text{NR}^\text{\textsuperscript{\textit{a}}} R^\text{\textsuperscript{\textit{b}}} \), \(-\text{C} (0) R^\text{\textsuperscript{\textit{c}}}, -\text{C} (0) -\text{OR}^\text{\textsuperscript{\textit{c}}}, -\text{C} (0) \text{NR}^\text{\textsuperscript{\textit{a}}} R^\text{\textsuperscript{\textit{b}}}, -\text{OR}^\text{\textsuperscript{\textit{d}}}, -\text{NR}^\text{\textsuperscript{\textit{a}}} S_2 R^\text{\textsuperscript{\textit{d}}}, -\text{NR}^\text{\textsuperscript{\textit{a}}} C(0) R^\text{\textsuperscript{\textit{e}}}, -\text{NR}^\text{\textsuperscript{\textit{a}}} C(0) 0 R^\text{\textsuperscript{\textit{e}}}, -\text{NR}^\text{\textsuperscript{\textit{a}}} O R^\text{\textsuperscript{\textit{d}}} \), substituted 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;

- \( z_1 \) is an integer from 0 to 5;
L is a bond, -S(0) 2 -, -NR 4 -, -O-, -S-, -C(O)-, -NR 4 C(0)-, -NR 4 C(0)NH-, -NHC(0)NR 4 -, -C(0)0-, -CH 2 NR 4 -, substituted or unsubstituted alkenylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R 4 is hydrogen, -CX 4 3 -, -CHX 4 2 -, -CH 2 X 4, -OCHX 4 2, -CN, -C(0)R 4 C, -C(0)-OR 4 C, -C(0)NR 4 R 4 B, -OR 4 D, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L is a bond, -S(0) 2 -, -NR 5 -, -O-, -S-, -C(O)-, -C(0)NR 5 -, -NR 5 C(0)-, -NR 5 C(0)NH-, -NHC(0)NR 5 -, -C(0)0-, -CH 2 NR 5 -, substituted or unsubstituted alkenylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R 5 is hydrogen, -CX 5 3, -CHX 5 2, -CH 2 X 5, -OCHX 5 2, -OCHX 5, -CN, -C(0)R 5 C, -C(0)-OR 5 C, -C(0)NR 5 R 5 B, -OR 5 D, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

Each R 1A, R 1B, R 1C, R 1D, R 4A, R 4B, R 4C, R 4D, R 5A, R 5B, R 5C, and R 5D is independently hydrogen, -CX 3, -CN, -COOH, -CONH 2, -CHX 2, -CH 2 X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R 1A and R 1B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R 4A and R 4B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R 5A and R 5B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X 1, X 4, and X 5 is independently -F, -Cl, -Br, or -I,
nl, n4, and n5 are independently an integer from 0 to 4; and
ml, m4, m5, vl, v4, and v5 are independently an integer from 1 to 2.

[0514] Embodiment 38. The compound of embodiment 37, wherein the compound has
the formula: (R'1)2

[0515] Embodiment 39. The compound of embodiment 37, wherein the compound has
the formula: (R'1)2

[0516] Embodiment 40. The compound of embodiment 37, wherein the compound has
the formula: R'

[0517] Embodiment 41. The compound of embodiment 37, wherein the compound has
the formula: R'

[0518] Embodiment 42. The compound of embodiment 37, wherein the compound has
the formula: R'

[0519] Embodiment 43. The compound of one of embodiments 37 to 42, wherein R' is
independently halogen, -CX'3, -CHX'2, -CH2X', -OCXS, -

[0520] Embodiment 44. The compound of one of embodiments 37 to 42, wherein R' is
independently halogen, -CX'3, -CHX'2, -CH2X', -OCXS, -
OCH2X₁, -OCHXS, -CN, -SH, -NH₂,
-C(0)OH, -C(0)NH₂, -OH, -OCH3, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C3-C8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted c₆-C₁₂ cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0521] Embodiment 45. The compound of one of embodiments 37 to 42, wherein R₁ is independently halogen, -CX₁³, -CHX₁², -CH₂X₁, -OCXS, -OCH₂X₁, -OCHXS, -CN, -SH, -NH₂,
-C(0)OH, -C(0)NH₂, -OH, -OCH3, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 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.

[0522] Embodiment 46. The compound of one of embodiments 37 to 42, wherein R₁ is independently -OR₁°.

[0523] Embodiment 47. The compound of one of embodiments 37 to 42, wherein R₁ is independently -OCH₃.

[0524] Embodiment 48. The compound of embodiment 37, wherein z₁ is 0.

[0525] Embodiment 49. The compound of embodiment 37, wherein the compound has

\[ \text{the formula: } R^{1,2}_1 \quad \text{L}^1 \quad \text{L}^2 \quad \text{E} \] (III), wherein

R₁° and R₁² are independently hydrogen, halogen, -CX₁³, -CHX₁²,
-CH₂X₁, -OCXS₁³, -OCH₂X₁, -OCHXS₁, -CN, -SONiR₁°₁, -SO₂NiR₁°₁, -NHC(0)NR₁º₁R₁°₂, -N(0)ni, -NR₁º₁R₁°₂, -C(0)R₁°₁, -C(0)-OR₁°₁, -C(0)NR₁º₁R₁°₂, -OR₁°₁, -NR₁º₁SO₂R₁°₂, -NR₁º₁C(0)R₁°₁, -NR₁º₁C(0)OR₁°₁, -NR₁º₁OR₁°₁, substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and R₁° and R₁² may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
Embodiment 50. The compound of embodiment 49, wherein the compound has the formula: \[ R_{1}^{1} \]

\[ (\text{IIIa}). \]

Embodiment 51. The compound of embodiment 49, wherein the compound has the formula: \[ R_{1}^{1} \]

\[ (\text{IIIb}). \]

Embodiment 52. The compound of one of embodiments 49 to 51, wherein \( R_{1}^{11} \) and \( R_{1}^{12} \) are independently halogen, \(-\text{CX}^{1}, \text{-CHX}^{\wedge}, -\text{CH}_{2}X^{1}, -\text{OCX}^{\wedge}, -\text{OCH}_{2}X^{1}, -\text{OCHX}^{\wedge}, -\text{CN}, -\text{SH}, -\text{NH}_{2}, -\text{C}(0)\text{OH}, -\text{C}(0)\text{NH}_{2}, -\text{OH}, -\text{CH}_{2}X^{1}, \) substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

Embodiment 53. The compound of one of embodiments 49 to 51, wherein \( R_{1}^{11} \) and \( R_{1}^{12} \) are independently halogen, \(-\text{CX}^{1}, -\text{CHX}^{\wedge}, \text{-CH}_{2}X^{1}, -\text{OCX}^{\wedge}, \text{-OCH}_{2}X^{1}, -\text{OCHX}^{\wedge}, -\text{CN}, -\text{SH}, -\text{NH}_{2}, -\text{C}(0)\text{OH}, -\text{C}(0)\text{NH}_{2}, -\text{OH}, -\text{CH}_{2}X^{1}, \) substituted or unsubstituted Ci-C_{6} alkyl, or substituted or unsubstituted C_{3}-C_{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C_{6}-C_{12} cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

Embodiment 54. The compound of one of embodiments 49 to 51, wherein \( R_{1}^{11} \) and \( R_{1}^{12} \) are independently halogen, \(-\text{CX}^{1}, -\text{CHX}^{\wedge}, -\text{CH}_{2}X^{1}, -\text{OCX}^{\wedge}, -\text{OCH}_{2}X^{1}, -\text{OCHX}^{\wedge}, -\text{CN}, -\text{SH}, -\text{NH}_{2}, -\text{C}(0)\text{OH}, -\text{C}(0)\text{NH}_{2}, -\text{OH}, -\text{OCH}_{3}, \) substituted or unsubstituted Ci-C_{8} alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C_{3}-C_{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C_{6}-C_{12} cycloalkyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

Embodiment 55. The compound of one of embodiments 49 to 51, wherein \( R_{1}^{11} \) and \( R_{1}^{12} \) are independently halogen, \(-\text{CX}^{1}, -\text{CHX}^{\wedge}, -\text{CH}_{2}X^{1}, -\text{OCX}^{\wedge}, -\text{OCH}_{2}X^{1}, -\text{OCHX}^{\wedge}, -\text{CN}, -\text{SH}, -\text{NH}_{2}, -\text{C}(0)\text{OH}, -\text{C}(0)\text{NH}_{2}, -\text{OH}, -\text{OCH}_{3}, \) substituted or unsubstituted Ci-C_{8} alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C_{3}-C_{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

Embodiment 56. The compound of one of embodiments 49 to 51, wherein \( R_{1}^{11} \) and \( R_{1}^{12} \) are independently halogen, 

- \( -\text{OCH}_{3} \).
Embodiment 57. The compound of one of embodiments 37 to 56, wherein L\(^1\) is a bond, substituted or unsubstituted Ci-Cs alkylene, substituted or unsubstituted 2 to 8 membered heteroalkylene, substituted or unsubstituted C3-C8 cycloalkylene, substituted or unsubstituted 3 to 8 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

Embodiment 58. The compound of one of embodiments 37, 40, 43 to 49, and 52 to 56, wherein L\(^1\) is a bond.

Embodiment 59. The compound of one of embodiments 37, 40, 43 to 49, and 52 to 56, wherein L\(^1\) is \(-\text{CH}_2\text{NR}^4\).

Embodiment 60. The compound of one of embodiments 37, 40, 43 to 49, and 52 to 56, wherein L\(^2\) is \(-\text{NR}^5\).

Embodiment 61. The compound of embodiment 60, wherein R\(^5\) is hydrogen, substituted or unsubstituted Ci-C\(_6\) alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

Embodiment 62. The compound of embodiment 60, wherein R\(^5\) is hydrogen or unsubstituted C1-C3 alkyl.

Embodiment 63. The compound of embodiment 60, wherein R\(^5\) is hydrogen, unsubstituted methyl, unsubstituted ethyl, unsubstituted hexyl, or unsubstituted benzyl.

Embodiment 64. The compound of embodiment 60, wherein R\(^5\) is hydrogen.

Embodiment 65. The compound of one of embodiments 37 to 64, wherein E is a covalent cysteine modifier moiety.

Embodiment 66. The compound of one of embodiments 37 to 64, wherein E is:
R\(^{15}\) is independently hydrogen, halogen, CX\(^{15}\), -CHX\(^{15}\), -

CH\(_2\)X\(^{15}\), -CN, -SO\(_{ni}\)R\(^{15D}\), -SO\(_{vi}\)NR\(^{15A}R\(^{15B}\), - NHNR \(^{15A}R\(^{15B}\), - ONR \(^{15A}R\(^{15B}\),

-NHC=(0)NHNR \(^{15A}R\(^{15B}\), - NHNC(0)NR \(^{15A}R\(^{15B}\), -N(0) \(_{ni}\), -NR \(^{15A}R\(^{15B}\), -C(0)R \(^{15C}\),

-C(0)-OR \(^{15C}\), -C(0)NR \(^{15A}R\(^{15B}\), -OR \(^{15p}\), -NR \(^{15A}SO\(_{2}\)R\(^{15D}\), -NR \(^{15A}C(0)R\(^{15C}\), -

NR \(^{15A}C(0)OR\(^{15C}\), -NR \(^{15A}OR\(^{15C}\), -OCX\(^{15}\), -OCHX\(^{15}\), substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R\(^{16}\) is independently hydrogen, halogen, CX\(^{16}\), -CHX\(^{16}\), -

CH\(_2\)X\(^{16}\), -CN, -SO\(_{ni}e\)R\(^{16D}\), -SO\(_{vi}\)NR\(^{16A}R\(^{16B}\), -NHNR \(^{16A}R\(^{16B}\), - ONR \(^{16A}R\(^{16B}\),

-NHC=(0)NHNR \(^{16A}R\(^{16B}\), - NHNC(0)NR \(^{16A}R\(^{16B}\), -N(0) \(_{ni}\), -NR \(^{16A}R\(^{16B}\),

-C(0)R \(^{16C}\), -C(0)-OR \(^{16C}\), -C(0)NR \(^{16A}R\(^{16B}\), -OR \(^{16D}\), -NR \(^{16A}SO\(_{2}\)R\(^{16D}\), -NR \(^{16A}C(0)R\(^{16C}\), -

NR \(^{16A}C(0)OR\(^{16C}\), -NR \(^{16A}OR\(^{16C}\), -OCX\(^{16}\), -OCHX\(^{16}\), 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\(^{17}\), -CHX\(^{17}\), -

CH\(_2\)X\(^{17}\), -CN, -SO\(_{ni}e\)R\(^{17D}\), -SO\(_{vi}\)NR\(^{17A}R\(^{17B}\), -NHNR \(^{17A}R\(^{17B}\), - ONR \(^{17A}R\(^{17B}\),

-NHC=(0)NHNR \(^{17A}R\(^{17B}\), - NHNC(0)NR \(^{17A}R\(^{17B}\), -N(0) \(_{ni}\), -NR \(^{17A}R\(^{17B}\), -C(0)R \(^{17C}\),

-C(0)-OR \(^{17C}\), -C(0)NR \(^{17A}R\(^{17B}\), -OR \(^{17D}\), -NR \(^{17A}SO\(_{2}\)R\(^{17D}\), -NR \(^{17A}C(0)R\(^{17C}\), -

NR \(^{17A}C(0)OR\(^{17C}\), -NR \(^{17A}OR\(^{17C}\), -OCX\(^{17}\), -OCHX\(^{17}\), 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, -CX\(^{18}\), -CHX\(^{18}\), -

CH\(_2\)X\(^{18}\), -C(0)R \(^{18C}\), -C(0)OR \(^{18C}\), -C(0)NR \(^{18A}R\(^{18B}\), substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R\(^{15A}\), R\(^{15B}\), R\(^{15D}\), R\(^{16A}\), R\(^{16B}\), R\(^{16C}\), R\(^{16D}\), R\(^{17A}\), R\(^{17B}\), R\(^{17C}\), R\(^{17D}\), R\(^{18A}\),
R\(^{18B}\), R\(^{18C}\), R\(^{18D}\), are independently hydrogen, -CX\(^{3}\), -CN, -COOH, -CONH\(_{2}\), -CHX\(^{2}\), -CH\(_2\)X,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl;
unsubstituted aryl, or substituted or unsubstituted heteroaryl; \( R^{15A} \) and \( R^{15B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^{16A} \) and \( R^{16B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^{17A} \) and \( R^{17B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^{18A} \) and \( R^{18B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

\[
each X, X^{15}, X^{16}, X^{17} \text{ and } X^{18} \text{ is independently } -F, -Cl, -Br, \text{ or } -I; \\
\text{nl5, nl6, nl7, vl5, vl6, and vl7, are independently an integer from 0 to 4; and} \\
\text{m15, m16, and m17 are independently and integer from 1 to 2.} \\
\]

[0543] Embodiment 67. The compound of embodiment 66, wherein \( R^{5}, R^{6}, R^{7}, \text{ and } R \) are hydrogen.

[0544] Embodiment 68. The compound of one of embodiments 66 to 67, wherein \( E \) is:

![Chemical Structure](image1)

[0545] Embodiment 69. The compound of embodiment 66, wherein \( E \) is:

![Chemical Structure](image2)

[0546] Embodiment 70. The compound of embodiment 1, wherein the compound has the formula:

![Chemical Structure](image3)
Embodiment 71. The compound of embodiment 1, wherein the compound has the formula:

![Chemical structure]

or

![Chemical structure]

Embodiment 72. A pharmaceutical composition comprising a Ubiquitin-like modifier activating enzyme 5 (UBA5) inhibitor and a pharmaceutically acceptable excipient.

Embodiment 73. The pharmaceutical composition of embodiment 72, wherein the Ubiquitin-like modifier activating enzyme 5 (UBA5) inhibitor has the formula:

![Chemical structure]

(I), wherein,

- \( R^1 \) is independently halogen, -CX^, -CHX^, -CH2X^, -OCX^, -OCH2X^, -OCHX^, -CN, -SONiR^2, -SOviNR^1R^2, -NHCl(0)NR^1A^R^2, -N(0)_m^, -NR^1A^R^2, -C(0)R^IC, -C(0)-OR^IC, -C(0)NR^1A^R^2, -OR^1C, -NR^1A^S0^2R^1D, -NR^1A^C(0)R^IC, -NR^1A^C(0)R^1C, -NR^1A^0^1R^1C, substituted 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;

- \( z1 \) is an integer from 0 to 5;

- \( L^1 \) is a bond, -S(0)_2^, -NR^4^, -O-, -S-, -C(0)-, -C(0)NR^4^, -NR^4^C(0)-, -NR^4^C(0)NH-, -NHC(0)NR^4^, -C(0)0-, -OC(O)-, -CH2NR^4^, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted heteroalkyl ene, substituted or unsubstituted
cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

\[ R^4 \text{ is hydrogen, } -\text{CX}_3, -\text{CHX}_2, -\text{CH}_2X, -\text{OCHX}_2, -\text{CN}, -\text{C(O)}R^4C, -\text{C(O)}-\text{OR}^4C, -\text{C(O)}NR^4R^4B, -\text{OR}^4D, \text{ substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl}; \]

\[ L^2 \text{ is a bond, } -\text{S(O)}_2-, -\text{NR}^5, -\text{C(O)}-, -\text{C(O)}NR^5-, -\text{NR}^5\text{C(O)}-, -\text{NHC(O)NR}^5, -\text{C(O)}NR^5, -\text{OC(O)}-, -\text{CH}_2NR^5, \text{ substituted or unsubstituted cycloalkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene}; \]

\[ R^5 \text{ is hydrogen, } -\text{CX}_5, -\text{CHX}_5, -\text{CH}_2X, -\text{OCHX}_5, -\text{CN}, -\text{C(O)}R^5C, -\text{C(O)}-\text{OR}^5C, -\text{C(O)}NR^5R^5B, -\text{OR}^5D, \text{ substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl}; \]

\[ E \text{ is an electrophilic moiety}; \]

Each \( R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C}, \text{ and } R^{5D} \) is independently hydrogen, -CX, -CN, -COOH, -CONH, -CHX, -CHX, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^{4A} \) and \( R^{4B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; \( R^{5A} \) and \( R^{5B} \) substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

\[ \text{each } X, X^1, X^4, \text{ and } X^5 \text{ is independently } -\text{F, -Cl, -Br, or -I}; \]

\[ n_1, n_4, \text{ and } n_5 \text{ are independently an integer from } 0 \text{ to } 4; \text{ and } \]

\[ m_1, m_4, m_5, v_1, v_4, \text{ and } v_5 \text{ are independently an integer from } 1 \text{ to } 2. \]
[0550] Embodiment 74. A method of inhibiting ubiquitin-like modifier activating enzyme 5 protein (UBA5) activity, said method comprising contacting a UBA5 protein with an effective amount of a UBA5 inhibitor, wherein the UBA5 inhibitor contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of SEQ ID NO:337.

[0551] Embodiment 75. The method of embodiment 74, wherein the UBA5 inhibitor is an antisense nucleic acid, antibody, or compound.

[0552] Embodiment 76. The method of embodiment 74 or 75, said method comprising contacting a UBA5 protein with an effective amount of a compound having the formula:

![Chemical Structure](image)

(1), wherein,

- $R^1$ is independently halogen, -$CX^1$, -$CHX^1$, -$CH2X^1$, -$OCX^1$, -$OCH2X^1$, -$OCHX^1$, -$CN$, -$SO_n R^1$, -$SO_{2n} R^1$, -$NH C(0) NR^1 R^{1b}$, -$N(0)_m l$, -$NR^1 R^{1b}$, -$OCH(0)$-$OR^{1c}$, -$C(0)$-$NR^1 R^{1b}$, -$OR^1$, -$NR^1 S(0) R^{1b}$, -$NR^1 C(0) R^{1c}$, -$NR^1 C(0) l$, substituted 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;

- $z1$ is an integer from 0 to 5;

- $L^1$ is a bond, -$S(0)$-$2l$, -$NR^4 l$, -$0 l$, -$S l$, -$C(0) l$, -$C(0)NR^4 l$, -$NR^4 C(0) l$, -$NR^4 C(0)NH l$, -$NH C(0) NR^4 l$, -$C(0) l$, -$OC(0) l$, -$CH 2NR^4 l$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

- $R^4$ is hydrogen, -$CX^4 l$, -$CHX^4 l$, -$CH2X^4 l$, -$OCX^4 l$, -$OCH2X^4 l$, -$OCHX^4 l$, -$CN$, -$C(0) R^{4c}$, -$C(0) OR^{4c}$, -$C(0) NR^{4a} R^{4b}$, -$OR^{4d}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
L2 is a bond, -S(0) 2 -, -NR 5 -, -0-, -S-, -C(O)-, -C(0)NR 5 -, -C(0)0-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylenes, or substituted or unsubstituted heteroarylene;

R5 is hydrogen, -CX 5 -,-CHX 5 -,-CH 2 X 5 -,-OCX 5 -,-OCH X 5 -,-CN, -C(0)R 3C, -C(0)-OR 3c, -C(0)NR 5A R 5B, -OR 5d, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

Each R 1A, R 1B, R 1C, R 1D, R 4A, R 4B, R 4C, R 4D, R 5A, R 5B, R 5C, and R 5D is independently hydrogen, -CX 3 -, -CN, -COOH, -CONH 2 , -CHX 2 , -CH 2 X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R 1A and R 1B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R 4A and R 4B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R 5A and R 5B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X 1 , X 4 , and X 5 is independently -F, -Cl, -Br, or -I;

n 4 , n 5 are independently an integer from 0 to 4; and

m 4 , m 5 , v 1 , v 4 , and v 5 are independently an integer from 1 to 2.

[0553] Embodiment 77. The method of embodiment 76, wherein the compound is covalently bonded to the amino acid corresponding to C250 of SEQ ID NO:337.

[0554] Embodiment 78. The method of embodiment 76, wherein the compound contacts one or more amino acids corresponding to N210, E209, L254, S253, and A251 of SEQ ID NO:337.
Embodiment 79. A UBA5 protein covalently bonded to a compound having the formula: (I), wherein,

\[ R^1 \text{ is independently halogen, } -\text{CX}^\Lambda, -\text{CHX}^\Lambda, -\text{CH2X}^\Lambda, -\text{OCX}^\Lambda, -\text{OCH2X}^\Lambda, -\text{OCHX}^\Lambda, -\text{CN}, -\text{SONiR}^D, -\text{SOviNR}^\Lambda R^\Lambda, -\text{NHC(0)NR}^\Lambda R^\Lambda, -\text{N(0)}_m, -\text{NR}^\Lambda R^\Lambda, -\text{C(0)R}^\Lambda C(0)R^\Lambda, -\text{C(0)-OR}^\Lambda, -\text{C(0)NR}^\Lambda R^\Lambda, -\text{OR}^\Lambda, -\text{NR}^\Lambda S_2 R^\Lambda, -\text{NR}^\Lambda C(0)R^\Lambda, -\text{NR}^\Lambda C(0)R^\Lambda, -\text{NR}^\Lambda R^\Lambda, -\text{SR}^\Lambda, -\text{NR}^\Lambda R^\Lambda, -\text{NR}^\Lambda A_0 R^\Lambda, \text{ substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arenyl or substituted or unsubstituted heteroarylen; two adjacent } R^1 \text{ substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arenyl, or substituted or unsubstituted heteroarylen; } \]

\[ z^1 \text{ is an integer from 0 to 5; } \]

\[ L^1 \text{ is a bond, } -\text{S(0)}_2, -\text{NR}^4, -\text{O}, -\text{S}, -\text{C(O)}, -\text{C(0)NR}^4, -\text{NR}^4 C(0), -\text{NR}^4 C(0)NH-, -\text{NHC(0)NR}^4, -\text{C(0)O}, -\text{OC(O)}, -\text{CH2NR}^4, \text{ substituted or unsubstituted alkylen, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; } \]

\[ R^4 \text{ is hydrogen, } -\text{CX}^4, -\text{CHX}^4, -\text{CH2X}^4, -\text{OCX}^4, -\text{OCH2X}^4, -\text{OCHX}^4, -\text{CN}, -\text{C(O)R}^4, -\text{C(O)-OR}^4, -\text{C(O)NR}^4 A_0 R^4 B, -\text{OR}^4 D, \text{ substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arenyl, or substituted or unsubstituted heteroarylen; } \]

\[ L^2 \text{ is a bond, } -\text{S(0)}_2, -\text{NR}^5, -\text{O}, -\text{S}, -\text{C(O)}, -\text{C(0)NR}^5, -\text{NR}^5 C(0), -\text{NR}^5 C(0)NH-, -\text{NHC(0)NR}^5, -\text{C(0)O}, -\text{OC(O)}, -\text{CH2NR}^5, \text{ substituted or unsubstituted alkylen, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; } \]

\[ R^5 \text{ is hydrogen, } -\text{CX}^5, -\text{CHX}^5, -\text{CH2X}^5, -\text{OCX}^5, -\text{OCH2X}^5, -\text{OCHX}^5, -\text{CN}, -\text{C(O)R}^5, -\text{C(O)-OR}^5, -\text{C(O)NR}^5 A_0 R^5 B, -\text{OR}^5 D, \text{ substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted arenyl, or substituted or unsubstituted heteroarylen; } \]
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

Each $R^{1A}$, $R^{1B}$, $R^{1C}$, $R^{1D}$, $R^{1A}$, $R^{1B}$, $R^{1C}$, $R^{1D}$, $R^{5A}$, $R^{5B}$, $R^{5C}$, and $R^{5D}$ is independently hydrogen, -CN, -COOH, -CONH$_2$, -CH$_2$X, substituted or unsubstituted alkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; $R^{1A}$ and $R^{1B}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; $R^{4A}$ and $R^{4B}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; $R^{5A}$ and $R^{5B}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each $X$, $X^1$, $X^4$, and $X^5$ is independently -F, -Cl, -Br, or -I;

$n_l$, $n_4$, and $n_5$ are independently an integer from 0 to 4; and $m_l$, $m_4$, $m_5$, $v_l$, $v_4$, and $v_5$ are independently an integer from 1 to 2; wherein the UBA5 protein is covalently bonded to the compound through the reacted residue of said electrophilic moiety.

[0556] Embodiment 80. The UBA5 protein of embodiment 79, wherein the compound is bonded to a cysteine residue of the protein.


[0558] Embodiment 82. The UBA5 protein of one of embodiments 79 to 81, wherein the compound is covalently bonded to an amino acid corresponding to C250 of SEQ ID NO:337.

[0559] Embodiment 83. A compound having the formula: (R$^1$)$_{21}$ (I),

wherein, $R^1$ is independently halogen, -CX$^A$, -CHX$^A$, -CH$_2$X$^1$, -OCX$^A$, -OCH$_2$X$^1$, -OCHX$^A$, -CN, -SO$_2$NR$^{1A}$R$^{1B}$, -SO$_2$NR$^{1A}$R$^{1B}$, -NHC(0)NR$^{1A}$R$^{1B}$, -N(0)$_m$i, -NR$^{1A}$R$^{1B}$, -C(0)R$^{1C}$, -C(0)-OR$^{1C}$, -C(0)NR$^{1A}$R$^{1B}$, -OR$^{1B}$, -NR$^{1A}$S$_2$R$^{1D}$, -NR$^{1A}$C(0)R$^{1C}$, -NR$^{1A}$C(0)R$^{1C}$.
R^1C, -NR^1AOR^1C, substituted 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; R^A and R^B substituents bonded to the same nitrogen

z1 is an integer from 0 to 5;

L^1 is a bond, -S(0)_{2-}, -NR^4, -0-, -S-, -C(O)-, -C(0)NR^4, -NR^4C(0)NH-, -NHC(0)NR^4, -C(0)O-, -OC(O)-, -CH_2NR^4, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^4 is hydrogen, -CX^4, -CHX^4, -CH_2X^4, -OCX^4, -OCH_2X^4, -OCHX^4, -CN, -C(0)R^4C, -C(0)-OR^4C, -C(0)NR^4AOR^4B, -OR^4D, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

L^2 is a bond, -S(0)_{2-}, -NR^5, -0-, -S-, -C(O)-, -C(0)NR^5, -NR^5C(0)NH-, -NHC(0)NR^5, -C(0)O-, -OC(O)-, -CH_2NR^5, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^5 is hydrogen, -CX^5, -CHX^5, -CH_2X^5, -OCX^5, -OCH_2X^5, -OCHX^5, -CN, -C(0)R^5C, -C(0)-OR^5C, -C(0)NR^5AOR^5B, -OR^5D, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

Each R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C}, and R^{5D} is independently hydrogen, -CX^3, -CN, -COOH, -CONH_2, -CHX^2, -CH_2X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; \( R^{4a} \) and \( R^{4b} \) substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; \( R^{5a} \) and \( R^{5b} \) substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl;

\[
\text{each } X, X^1, X^4, \text{ and } X^5 \text{ is independently } -F, -Cl, -Br, \text{ or } -I; \\
\text{nl, } n^4, \text{ and } n^5 \text{ are independently an integer from } 0 \text{ to } 4; \text{ and} \\
\text{ml, } m^4, m^5, v^1, v^4, \text{ and } v^5 \text{ are independently an integer from } 1 \text{ to } 2.
\]

10  [0560] Embodiment 84. The compound of embodiment 83, wherein the compound has

\[
\text{the formula: } (R^1)_{2} \text{ (Ia).}
\]

11  [0561] Embodiment 85. The compound of embodiment 83, wherein the compound has

\[
\text{the formula: } (R^1)_{2} \text{ (Ib).}
\]

12  [0562] Embodiment 86. The compound of embodiment 83, wherein the compound has

\[
\text{the formula: } R^1 \text{ (II).}
\]

13  [0563] Embodiment 87. The compound of embodiment 83, wherein the compound has

\[
\text{the formula: } R^1 \text{ (Ila).}
\]

14  [0564] Embodiment 88. The compound of embodiment 83, wherein the compound has

\[
\text{the formula: } R^1 \text{ (lib).}
\]

15  [0565] Embodiment 89. The compound of one of embodiments 83 to 88, wherein \( R^1 \) is
independently halogen, -CX^A, -CHX^1, -CH2X^1, -OCXS, -OCH2X^1, -OCHX^1, -CN, -SR^D, -NR^1AR^1B,
-C(0)R\textsuperscript{1C}, -C(0)OR\textsuperscript{1C}, -C(0)NR\textsuperscript{1A}R\textsuperscript{1B}, -OR\textsuperscript{1p}, substituted 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 [0566] Embodiment 90. The compound of one of embodiments 83 to 88, wherein R\textsubscript{1} is independently halogen, -CX\textsubscript{1}, -CHX\textsubscript{1}, -CH\textsubscript{2}X\textsubscript{1}, -OCXS, -OCH\textsubscript{2}X\textsubscript{1}, -OCHXS, -CN, -SH, -NH\textsubscript{2}, -C(0)OH, -C(0)NH\textsubscript{2}, -OH, -OCH\textsubscript{3}, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\textsubscript{5}-C\textsubscript{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C\textsubscript{6}-Cl\textsubscript{2} cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

8 [0567] Embodiment 91. The compound of one of embodiments 83 to 88, wherein R\textsubscript{1} is independently halogen, -CX\textsubscript{1}, -CHX\textsubscript{1}, -CH\textsubscript{2}X\textsubscript{1}, -OCXS, -OCH\textsubscript{2}X\textsubscript{1}, -OCHXS, -CN, -SH, -NH\textsubscript{2}, -C(0)OH, -C(0)NH\textsubscript{2}, -OH, -OCH\textsubscript{3}, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\textsubscript{5}-C\textsubscript{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

10 [0568] Embodiment 92. The compound of one of embodiments 83 to 88, wherein R\textsubscript{1} is independently -OR\textsuperscript{1p}.

13 [0569] Embodiment 93. The compound of one of embodiments 83 to 88, wherein R\textsubscript{1} is independently -OCH\textsubscript{3}.

15 [0570] Embodiment 94. The compound of embodiment 83, wherein z\textsubscript{1} is 0.

18 [0571] Embodiment 95. The compound of embodiment 83, wherein the compound has the formula: $\text{R}^{1,2}L^{1}\text{L}^{2}\text{E}$ (III), wherein

$$\text{R}^{1,1} \text{ and } \text{R}^{1,2} \text{ are independently hydrogen, halogen, } -\text{CX}^{1,3}, -\text{CHX}^{1,2}, -\text{CH}^{2}X^{1}, -\text{OCXS}, -\text{OCH}^{2}X^{1}, -\text{OCHXS}, -\text{CN}, -\text{SO}^{i}i\text{R}^{1p}, -\text{SO}^{i}i\text{NR}^{1A}R^{1B}, -\text{NHC}(0)\text{NR}^{1A}R^{1B}, -\text{N}(0)mi, -\text{NR}^{1A}R^{1B}, -\text{C}(0)R^{1C}, -\text{C}(0)OR^{1C}, -\text{C}(0)NR^{1A}R^{1B}, -\text{OR}^{1p}, -\text{NR}^{1A}S0^{2}R^{1p}, -\text{NR}^{1A}C(0)R^{1C}, -\text{NR}^{1A}C(0)OR^{1C}, -\text{NR}^{1A}OR^{1C}, \text{ substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.}$$
unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and R\textsuperscript{1,2} may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0572] Embodiment 96. The compound of embodiment 95, wherein the compound has the formula: (IIIa).

[0573] Embodiment 97. The compound of embodiment 95, wherein the compound has the formula: (IIIb).

[0574] Embodiment 98. The compound of one of embodiments 95 to 97, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently halogen, \(-\text{CX}^1_3\), \(-\text{CH}^X\), \(-\text{CH}_2\text{X}^1\), \(-\text{OCX}^X\), \(-\text{OCH}_2\text{X}^1\), \(-\text{OCH}^X\), \(-\text{CN}\), \(-\text{SR}^1\text{b}\), \(-\text{NR}^1\text{AR}^1\text{b}\), \(-\text{C(0)R}^1\text{C}\), \(-\text{C(0)OR}^1\text{C}\), \(-\text{C(0)NR}^1\text{AR}^1\text{b}\), \(-\text{OR}^1\text{b}\), substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0575] Embodiment 99. The compound of one of embodiments 95 to 97, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently halogen, \(-\text{CX}^1_3\), \(-\text{CH}^X\), \(-\text{CH}_2\text{X}^1\), \(-\text{OCX}^X\), \(-\text{OCH}_2\text{X}^1\), \(-\text{OCH}^X\), \(-\text{CN}\), \(-\text{SH}\), \(-\text{NH}_2\), \(-\text{C(0)OH}\), \(-\text{C(0)NH}_2\), \(-\text{OH}\), \(-\text{OCH}_3\), substituted or unsubstituted C\textsubscript{1}-C\textsubscript{8} alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\textsubscript{5}-C\textsubscript{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C\textsubscript{6}-C\textsubscript{12} cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0576] Embodiment 100. The compound of one of embodiments 95 to 97, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently halogen, \(-\text{CX}_S\), \(-\text{CH}^X\), \(-\text{CH}_2\text{X}^1\), \(-\text{OCX}^X\), \(-\text{OCH}_2\text{X}^1\), \(-\text{OCH}^X\), \(-\text{NH}_2\), \(-\text{C(0)OH}\), \(-\text{C(0)NH}_2\), \(-\text{OH}\), \(-\text{OCH}_3\), substituted or unsubstituted C\textsubscript{1}-C\textsubscript{8} alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C\textsubscript{5}-C\textsubscript{8} cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.
Embodiment 101. The compound of one of embodiments 95 to 97, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently -OR\textsuperscript{D}.

Embodiment 102. The compound of one of embodiments 95 to 97, wherein R\textsuperscript{1,1} and R\textsuperscript{1,2} are independently -OCH\textsubscript{3}.

Embodiment 103. The compound of one of embodiments 83 to 102, wherein L\textsuperscript{1} is a bond, substituted or unsubstituted Ci-Cs alkylene, substituted or unsubstituted 2 to 8 membered heteroalkylene, substituted or unsubstituted C3-C8 cycloalkylene, substituted or unsubstituted 3 to 8 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

Embodiment 104. The compound of one of embodiments 83, 86, 89 to 95, and 98 to 102, wherein L\textsuperscript{1} is a bond.

Embodiment 105. The compound of one of embodiments 83, 86, 89 to 95, and 98 to 102, wherein L\textsuperscript{1} is -CH\textsubscript{2}NR\textsubscript{4}-. 

Embodiment 106. The compound of one of embodiments 83, 86, 89 to 95, and 98 to 105, wherein L\textsuperscript{2} is -NR\textsubscript{5}-. 

Embodiment 107. The compound of embodiment 106, wherein R\textsuperscript{5} is hydrogen, substituted or unsubstituted Ci-C\textsubscript{6} alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

Embodiment 108. The compound of embodiment 106, wherein R\textsuperscript{5} is hydrogen or unsubstituted C1-C3 alkyl.

Embodiment 109. The compound of embodiment 106, wherein R\textsuperscript{5} is hydrogen, unsubstituted methyl, unsubstituted ethyl, unsubstituted hexyl, or unsubstituted benzyl.

Embodiment 110. The compound of embodiment 106, wherein R\textsuperscript{5} is hydrogen.

Embodiment 111. The compound of one of embodiments 83 to 110, wherein E is a covalent cysteine modifier moiety.

Embodiment 112. The compound of one of embodiments 83 to 110, wherein E is:
R₁⁵ is independently hydrogen, halogen, Cₓ₁⁵, -CHₓ₁⁵, -CH₂ₓ₁⁵, -CN, -SOₙ₁⁵ˢᴿ₅₁⁵, -SOvi₅ᴿ₅₁⁵, -NHNR₁₅ᴿ¹⁵ᴮ, -ONR₁₅ᴿ¹⁵ᴮ, -NHC(₀)NR₁⁵ᴿ¹⁵ᴮ, -C(₀)R₁⁵Ｃ, -C(₀)-OR¹⁵Ｃ, -C(₀)NR₁⁵ᴿ¹⁵ᴮ, -OR¹⁵ᴰ, -NR₁⁵ᴬΣΟ₂ᴿ¹⁵ᴰ, -NR₁⁵ᴮC(₀)R₁⁵ᶜ, -NR₁⁵ᴬC(₀)OR¹⁵ᶜ, -NR₁⁵ᴬOR¹⁵ᶜ, -OCTX₁⁵, -OCHX₁⁵, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R₁⁶ is independently hydrogen, halogen, Cₓ₁⁶, -CHₓ₁⁶, -CH₂ₓ₁⁶, -CN, -SOₙ₁⁶ˢᴿ₆₁⁶, -SOvi₆ᴿ₆₁⁶, -NHNR₁₆ᴿ¹⁶ᴮ, -ONR₁₆ᴿ¹⁶ᴮ, -NHC(₀)NHNR₁⁶ᴿ¹⁶ᴮ, -NHC(₀)NR₁⁶ᴿ¹⁶ᴮ, -N(₀)ᵣ₁⁶, -NR₁⁶ᴬR₁⁶ᴮ, -C(₀)R₁⁶ᶜ, -C(₀)-OR¹⁶ᶜ, -C(₀)NR₁⁶ᴿ¹⁶ᴮ, -OR¹⁶ᴰ, -NR₁⁶ᴬΣΟ₂ᴿ¹⁶ᴰ, -NR₁⁶ᴮC(₀)R₁⁶ᶜ, -NR₁⁶ᴬC(₀)OR¹⁶ᶜ, -NR₁⁶ᴬOR¹⁶ᶜ, -OCX₁⁶, -OCHX₁⁶, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R₁⁷ is independently hydrogen, halogen, Cₓ₁⁷, -CHₓ₁⁷, -CH₂ₓ₁⁷, -CN, -SOₙ₁⁷ˢᴿ₇₁⁷, -SOvi₇ᴿ₇₁⁷, -NHNR₁⁷ᴿ¹⁷ᴮ, -ONR₁⁷ᴿ¹⁷ᴮ, -NHC(₀)NHNR₁⁷ᴿ¹⁷ᴮ, -NHC(₀)NR₁⁷ᴿ¹⁷ᴮ, -N(₀)ᵣ₁⁷, -NR₁⁷ᴿ¹⁷ᴮ, -C(₀)R₁⁷ᶜ, -C(₀)-OR¹⁷ᶜ, -C(₀)NR₁⁷ᴿ¹⁷ᴮ, -OR¹⁷ᴰ, -NR₁⁷ᴬΣΟ₂ᴿ¹⁷ᴰ, -NR₁⁷ᴮC(₀)R₁⁷ᶜ, -NR₁⁷ᴬC(₀)OR¹⁷ᶜ, -NR₁⁷ᴬOR¹⁷ᶜ, -OCX₁⁷, -OCHX₁⁷, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

R₁⁸ is independently hydrogen, halogen, Cₓ₁⁸, -CHₓ₁⁸, -CH₂ₓ₁⁸, -CN, -SOₙ₁⁸ˢᴿ₈₁⁸, -SOvi₈ᴿ₈₁⁸, -NHNR₁⁸ᴿ¹⁸ᴮ, -ONR₁⁸ᴿ¹⁸ᴮ, -NHC(₀)NHNR₁⁸ᴿ¹⁸ᴮ, -NHC(₀)NR₁⁸ᴿ¹⁸ᴮ, -N(₀)ᵣ₁⁸, -NR₁⁸ᴿ¹⁸ᴮ, -C(₀)R₁⁸ᶜ, -C(₀)-OR¹⁸ᶜ, -C(₀)NR₁⁸ᴿ¹⁸ᴮ, -OR¹⁸ᴰ, -NR₁⁸ᴬΣΟ₂ᴿ¹⁸ᴰ, -NR₁⁸ᴮC(₀)R₁⁸ᶜ, -NR₁⁸ᴬC(₀)OR¹⁸ᶜ, -NR₁⁸ᴬOR¹⁸ᶜ, 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 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;


R₁₈₈, R₁₈C, R₁₈D, are independently hydrogen, -CX₃, -CN, -COOH, -CONH₂, -CHX₂, -CH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R₁₅₈ and R₁₅₉ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R₁₆₈A and R₁₆₈B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R₁₆₈₈A and R₁₆₈₈B 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, X₁₅, X₁₆, X₁₇ and X₁₈ is independently -F, -Cl, -Br, or -I;

nl₅, nl₆, nl₇, vl₅, vl₆, and vl₇, are independently an integer from 0 to 4;

and ml₅, ml₆, and ml₇ are independently an integer from 1 to 2.

[0589] Embodiment 113. The compound of embodiment 112, wherein R₁₅, R₁₆, R₁₇, and R₁₈ are hydrogen.

[0590] Embodiment 114. The compound of one of embodiments 112 to 113, wherein E is:

[0591] Embodiment 115. The compound of embodiment 112, wherein E is:
Embodiment 116. The compound of embodiment 83, wherein the compound has the formula:
Example 1 - Chemoproteomic Screening of Covalent Ligands Reveals UBA5 as a Novel Pancreatic Cancer Target

Chemical genetic screening of small-molecules libraries has been a promising strategy for discovering unique and novel therapeutic compounds. However, identifying the targets of lead molecules that arise from these screens has remained a major bottleneck in understanding mechanism of action of these compounds. Here, we have coupled the screening of a cysteine-reactive fragment-based covalent ligand library with an isotopic tandem orthogonal proteolysis-enabled activity-based protein profiling (isoTOP-ABPP) chemoproteomic platform to rapidly couple the discovery of lead small-molecules that impair pancreatic cancer pathogenicity with the identification of druggable hotspots for potential cancer therapy. Through this coupled approach, we have discovered a covalent ligand DKM
2-93 that impairs pancreatic cancer cell survival and in vivo tumor growth through covalently modifying the catalytic cysteine of the ubiquitin-like modifier activating enzyme 5 (UBA5), thereby inhibiting its activity as a protein that activates the ubiquitin-like protein UFMylate proteins. We show that UBA5 is a novel pancreatic cancer therapeutic target and show DKM 2-93 as a relatively selective lead inhibitor of UBA5. Our results underscore the utility of coupling the screening of covalent ligand libraries with isoTOP-ABPP platforms for mining the proteome for druggable hotspots for cancer therapy.

[0595] In the United States, it is estimated that over 53,000 people will be diagnosed with pancreatic cancer and over 40,000 patients will die from pancreatic cancer with a dismal overall 5-year survival rate of 7.7% (1). Current therapeutic strategies for pancreatic cancer include resection and non-specific therapies such as radiation or chemotherapy (2). Unfortunately, these treatment strategies are clearly insufficient for current pancreatic cancer therapy and better strategies are needed to discover both novel anti-cancer agents and targets for combatting pancreatic cancer.

[0596] However, a major bottleneck in this effort has been that despite the identification of many novel protein targets that control cancer, these potential cancer therapy targets have remained largely untranslated, in-part because most of these proteins are "undruggable" or difficult to target with small-molecules (3). Developing technologies that enable the coupled discovery of new cancer targets and small-molecule therapies would provide a promising platform to discover next-generation cures for cancer. Recently, chemoproteomic technologies have arisen to address this challenge, including activity-based protein profiling (ABPP), which uses activity or reactivity-based probes to map proteome-wide reactive, functional, and druggable hotspots directly in complex proteomes. Through competing small-molecules against the binding of these chemical probes to functional and ligandable hotspots in proteins, this competitive ABPP platform provides a facile strategy for developing selective modulators against new cancer targets (4-6). Another approach that has been successful at identifying new anti-cancer agents in a high throughput manner is chemical genetics, which involves small-molecule screening for anti-cancer phenotypes. However, a major challenge of chemical genetics is in identifying the target and mechanism of action of promising agents that arise from screens (7,8). To address this challenge, we have coupled the screening of a fragment-based cysteine-reactive ligand library with competitive isotopic tandem orthogonal proteolysis-enabled ABPP (isoTOP-ABPP) platforms to couple the identification of covalent ligands that impair pancreatic cancer pathogenicity with the
discovery of druggable hotspots that can be targeted for potential pancreatic cancer therapy (FIG. 1A).

[0597] We screened 85 acrylamide and chloroacetamide cysteine-reactive ligands to identify small-molecules that impair PaCa2 pancreatic cancer cell serum-free cell survival or proliferation by >70% (FIG. IB, Table 1). To rule out compounds that may non-specifically cause toxicity, we also counterscreened any leads to eliminate any compounds that impair survival or proliferation in immortal human pancreatic ductal epithelial (HPDE) cells by >50% (FIG. 1C, Table 1). Through this screening effort, we identified three main chloroacetamide leads DKM 2-67, DKM 2-83, and DKM 2-93 (FIG. ID). Interestingly, these three compounds were all based on similar scaffolds with DKM 2-93 being the most complex structure of these three compounds. We thus chose to pursue DKM 2-93 for target identification using isoTOP-ABPP approaches.

[0598] Table 1. Screening of cysteine-reactive covalent ligand libraries in pancreatic cancer cells. A library of cysteine-reactive acrylamides and chloroacetamides were screened in PaCa2 pancreatic cancer cells or HPDE pancreatic ductal epithelial cells (50 μM) to assess 48 h serum-free cell survival. Cell survival was assessed using Hoescht staining. Data are presented as mean ± sem, n=3/group.

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Table 2. IsoTOP-ABPP Data for DKM 2-93 Target Identification and Cysteine Profiling in Primary Human Pancreatic Tumors. IsoTOP-ABPP analysis of DKM2-93 in PaCa2 cells. PaCa2 proteomes were pre-treated with DMSO or DKM2-93 (50 µM) prior to labeling proteomes with IAyne and appending a biotin-azide handle bearing a TEV protease recognition site and an isotopically light (for DMSO-treated) and heavy (for DKM2-93-treated) tag. DMSO and DKM2-93-treated proteomes were then mixed in a 1:1 ratio and subsequently avidin-enriched, tryptically digested, and then probe-modified tryptic peptides were released by TEV protease and analyzed using quantitative proteomic approaches. Peptide ratios shown are average ratios for those probe-modified peptides that were identified in at least 2 out of 3 biological replicates. A light to heavy ratio of 1 indicates that the probe-labeled cysteine-bearing peptide was not bound by DKM2-93, whereas a ratio >3 indicates bound sites. If a top hit showing >3 ratio showed more than 1 ratio greater than 3, the average of the top 2 ratios was kept. If a top hit showing >3 ratio had only one out of 3 or 1 out of 2 ratios that showed >3, the ratio was replaced with the lowest of the ratios.
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[0600] We show that DKM 2-93 not only impairs PaCa2 pancreatic cancer cell survival, but also Panel pancreatic cancer cell survival (FIG. 2A). Surprisingly, even though the structure of DKM 2-93 is quite simple, we show that DKM 2-93 daily treatment significantly impairs tumor growth of PaCa2 cells in vivo in tumor xenograft studies in immune-deficient mice without causing any weight loss or overt toxicity (FIG. 2B; FIG. 4).

[0601] Next, we used competitive isoTOP-ABPP platforms to identify the specific druggable hotspot targeted by DKM 2-93 to impair pancreatic cancer pathogenicity. We competed DKM 2-93 directly against labeling of PaCa2 pancreatic cancer cell proteomes with the broad cysteine-reactive iodoacetamide-alkyne (IAyne) probe for subsequent isoTOP-ABPP quantitative proteomic analysis. Through this study, we identified cysteine 250 (C250) on ubiquitin-like modifier activating enzyme 5 (UBA5) as the primary target of DKM 2-93, showing the highest light (vehicle-treated) to heavy (DKM 2-93 treated) isotopic ratio of 4.2 (FIG. 2C). C250 is the catalytic cysteine on UBA5, suggesting that DKM 2-93 is a direct inhibitor of UBA5 (9,10). UBA5 is a protein involved in activating a ubiquitin-like protein UFM1 to UFMylate proteins (9,11). While UBA5 and UFMylation has been shown to be important in breast cancer through UFM1 conjugation of a nuclear receptor coactivator ASCI.
that modulates estrogen receptor signaling (12), UBA5 has not been previously attributed to pancreatic cancer pathogenicity, thus making it a potentially novel pancreatic cancer therapeutic target. We show validation of UBA5 as a target of DKM 2-93 through competition of DKM 2-93 against IAyne labeling of pure human UBA5 using gel-based ABPP methods (FIG. 2D). Consistent with our data showing that DKM 2-93 binds to the catalytic cysteine of UBA5, we also show that UBA5 activity, represented by activation and conjugation of UFMI on C250 on UBA5 (UFM1-UBA5 complex), is inhibited by DKM 2-93 (FIG. 2E).

[0602] We also performed isoTOP-ABPP profiling to quantitatively map proteome-wide cysteine reactivity in pooled primary human pancreatic tumors to determine whether UBA5 exists in pancreatic cancer and also to ascertain the relative reactivity of UBA5 C250 within the proteome. To map the relative reactivity of each cysteine in primary pancreatic tumors, we labeled pooled pancreatic tumor proteomes with either a high (100 µM, heavy) versus low (10 µM, light) concentration of IAyne and assessed the quantitative heavy to light ratios of probe-labeled peptides. Previous studies mapping cysteine-reactivity in this manner have shown that a ratio of <3 would indicate a hyper-reactive and likely functional cysteine, whereas a ratio >10 would not be considered particularly reactive (13). We indeed showed that UBA5 protein is present in primary human pancreatic tumors and that C250 of UBA5 shows a heavy (100 µM) to light (10 µM) ratio of 4.7, indicating that this cysteine is just moderately hyper-reactive, despite C250 representing the catalytic cysteine of this enzyme (FIG. 2F). This lack of hyper-reactivity may be possibly due to the exquisite substrate specificity of UBA5 for a large protein substrate such as UFMI, where the reactivity of C250 on UBA5 may be tempered to prevent promiscuous substrate recognition. Nonetheless, we show that UBA5 is present in primary human pancreatic tumors and that the catalytic C250 is accessible in these tumors.

[0603] To further confirm that UBA5 inactivation impairs pancreatic cancer pathogenicity, we also knocked down the expression of UBA5 in PaCa2 cells (FIG. 3A). We show that short interfering RNA (siRNA)-mediated transient or short hairpin RNA (shRNA)-mediated stable genetic knockdown of UBA5 in PaCa2 cells phenocopies DKM 2-93 in impairing PaCa2 serum-free cell survival and in vivo tumor xenograft growth (FIGS. 3B, 3C).

[0604] Here, we have coupled chemical genetic screening of a covalent ligand library with isoTOP-ABPP platforms to discover a covalent ligand DKM 2-93 that inhibits UBA5 to
impair pancreatic cancer pathogenicity. A previous study has reported another organometallic UBA5 inhibitor that acts through non-competitive mechanisms (14), DKM 2-93 represents another potential lead inhibitor scaffold that acts through covalent modification of the catalytic cysteine that can potentially be used to generate more potent and selective UBA5 inhibitors. It will be of future interest to determine of the UFMylation protein substrates of UBA5 that are responsible for the effects observed here, towards better understanding the mechanism through which UBA5 controls pancreatic cancer pathogenicity. Taken more broadly, our results underscore the utility of combining covalent ligand screening with chemoproteomic to rapidly mine the proteome for druggable hotspots that can be exploited for potential cancer therapy.

[0605] Materials. IAYne was obtained from CHESS Gmbh. HIS$_6$-UBA5 and HISE-UFMI were purchased from Boston Biochem. shRNA constructs were obtained from Sigma Aldrich. Primers were obtained from Elim Pharmaceuticals. Description of part of the cysteine-reactive library of covalent ligands is described in a previous paper (15). Additional cysteine-reactive covalent ligands screened herein are described following.

[0606] Cell Culture. Mia-PaCa2 and Panel cells were purchased from ATCC and were grown in DMEM with 10% FBS. HPDE cells were obtained from Rushika Perera's laboratory at UCSF and grown in Life Technologies Keratinocyte SFM combo (cat no: 17005042). The generation of these cells have been previously described (16).

[0607] Survival and Proliferation Assays. Cells were plated the evening before the experiment, and allowed to adhere overnight. For both survival and proliferation assays, cells were plated in regular media. Before dosing, the media was aspirated from all wells and replaced with the appropriate media and drug dosage. For the chemical genetics screen, cells were treated with either DMSO or the cysteine-reactive fragment for 48 h and cell viability was assessed by Hoescht stain using our previously described methods (17).

[0608] Tumor Xenografts. C.B17 SCID male mice (6-8 weeks old) were injected subcutaneously into the flank with 2,000,000 cells as previously described (17). After three days, the mice were exposed by intraperitoneal (ip) injection with either vehicle (18:1:1 PBS/ethanol/PEG40) or 50mg/kg DKM-293 once per day, each day for the duration of the study. Tumors were measured every 3 days by caliper measurements. Animal experiments were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee of the University of California, Berkeley.
Proteomic Analysis. IsoTOP-ABPP analyses were performed as previously described (6,13). PaCa2 cell lysates were pre-incubated with DMSO vehicle or DKM 2-93 (50 μM) for 30 min at 37°C, and then labeled with IAyne (100 μM) for 1 h at room temperature. They were subsequently treated with isotopically light (control) or heavy (treated) TEV-biotin 100 μM and click chemistry was performed as previously described (6,13). Proteins were precipitated over one hour and pelleted by centrifugation at 6500 x g. Proteins were washed 3 times with cold methanol then denatured and resolubilized by heating in 1.2% SDS/PBS to 85°C for 5 min. Insoluble components were precipitated by centrifugation at 6500 x g and soluble proteome was diluted in 5 ml PBS, for a final concentration of 0.2% SDS. 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-Aldrich) and reduced in dithiothreitol (1 mM, Sigma-Aldrich), alkylated with iodoacetamide (18 mM, Sigma-Aldrich), then washed and resuspended in 2 M urea/PBS with 1 mM calcium chloride and trypsinized overnight with 0.5 ug/ul sequencing grade trypsin (Promega). Tryptic peptides were discarded and beads were washed three times each in PBS and water, then washed with one wash of TEV buffer containing 1 μM DTT. TEV-biotin tag was digested overnight in TEV buffer containing 1 μM DTT and 5 μl Ac-TEV protease at 29°C. Peptides were diluted in water and acidified with final concentration of 5% formic acid (1.2 M, Spectrum).

Peptides from all proteomic experiments were pressure-loaded onto a 250 mm 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 μm 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 Multidimensional Protein Identification Technology (MudPIT) program as previously described (6,13). Data was collected in data-dependent acquisition mode with dynamic exclusion enabled (60 s). One full MS (MSI) 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.
For MudPIT runs, samples were run with the following 5-step MudPIT program (using 0%, 10%, 25%, 80%, and 100% salt bumps). Data was extracted in the form of MSI and MS2 files using Raw Extractor 1.9.9.2 (Scripps Research Institute) and searched against the Uniprot mouse database using ProLuCID search methodology in IP2 v.3 (Integrated Proteomics Applications, Inc) (18). Cysteine residues were searched with a static modification for carboxyamidomethylation (+57.02146) and up to two differential modifications for 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 1%.

Gel-Based ABPP. Gel-based ABPP methods were performed as previously described (19). HIS$_6$-UBA5 (0.06 µg) protein were pre-treated with DMSO or DKM 2-93 for 30 min at room temperature in an incubation volume of 50 µL PBS, and were subsequently treated with IAyne (10 µM final concentration) for 30 min at 37°C. Copper-catalyzed azide-alkyne cycloaddition "click chemistry" was performed to append rhodamine-azide onto IAyne probe-labeled proteins. The samples were separated by SDS/PAGE and scanned using a ChemiDoc MP (Bio-Rad Laboratories, Inc). Inhibition of target labeling was assessed by densitometry using ImageStudio Light software.

UBA5 activity assay. HIS$_6$-UBA5 and HIS$_6$-UFM1 were purchased from Boston Biochem. UBA5 (1.25 µM) was pre-incubated for 30 min with either DMSO or DKM 2-93 in buffer (50 mM Tris-HCl, pH 7, 5 mM MgCb), and then incubated with UFM1 (52.5 µM) ATP (1 µM) for 90 min at room temperature, after which the reaction was quenched in 6x non-reducing loading dye, and proteins were separated on a 4-20% TGX non-reducing denaturing gel, followed by Western blot analysis using anti-HIS6 antibody (Abeam, 4bl8184).

UBA5 Knockdown. UBA5 was knocked down transiently with siRNA or stably with shRNA as previously described (17,20). For siRNA studies, PaCa2 cells (200,000 cells/well) were seeded overnight after which siControl (non-targeting siRNA) or siUBA5 siRNA oligonucleotides (5 pooled siRNAs targeting UBA5 purchased from Dharmacon) were transfected into cells using Dharmafect 2. Cells were harvested after 48 h for qPCR and for seeding for cell viability assays.
For shRNA studies, shControl (targeting GFP) and shUBA5 constructs (purchased from Sigma) were transfected into HEK293T cells alongside lentiviral vectors using Lipofectamine 2000. Lentivirus was collected from filtered cultured medium 48 h post-transfection and used to infect the target cancer cell line with Polybrene (0.01 mg/ml). Target cells were selected over 3 days with 1 mg/ml puromycin. The short-hairpin sequence used for generation of the UBA5 knockdown lines was:

CCGGCCTCAGTGATGACAGAAATCTCGAGATTTCTGTCATCACACTGAGGTTT (SEQ ID NO:335). The control shRNA was targeted against GFP with the target sequence GCAAGCTGACCCTGAAGTTCAT (SEQ ID NO:336). Knockdown was confirmed by qPCR.

qPCR. qPCR was performed using the manufacturer's protocol for Fisher Maxima SYBR Green with 10 mM primer concentrations or for Bio-Rad SsoAdvanced Universal Probes Supermix. Primer sequences for Fisher Maxima SYBR Green were derived from Primer Bank. Primer sequences for Bio-Rad SsoAdvanced Universal Probes Supermix were designed with Primer 3 Plus.

Primary Human Pancreatic Tumors. Eligible patients completed written consent for our tissue banking protocol that is approved by the University of Alabama at Birmingham Institutional Review Board. During the pancreatic tumor resection, a 1 cm^3 portion of the tumor was dissected free of the fresh resection specimen, divided into 4-5 aliquots, placed into 1.5 mL cryovials, flash frozen, and stored at -80°C. Adjacent non-tumor bearing pancreatic tissue was also collected and banked in a similar manner.

**Example 2 - Synthetic Methods and Results**

General Procedure A. The amine (1 eq.) was dissolved in DCM (5 mL/mmol) and cooled to 0°C. To the solution was added acryloyl chloride (1.2 eq.) followed by triethylamine (1.2 eq.). The solution was warmed to room temperature and stirred overnight. The solution was then washed with brine and the crude product was purified by silica gel chromatography (and recrystallization if necessary) to afford the corresponding acrylamide.

General Procedure B. The amine (1 eq.) was dissolved in DCM (5 mL/mmol) and cooled to 0°C. To the solution was added chloroacetyl chloride (1.2 eq.) followed by triethylamine (1.2 eq.). The solution was warmed to room temperature and stirred overnight. The solution was then washed with brine and the crude product was purified by silica gel chromatography (and recrystallization if necessary) to afford the corresponding acrylamide.
N-(4-phenoxyphenyl)acrylamide (DKM 2-1 19). Following General Procedure A starting from 4-phenoxyaniline (571 mg, 3.1 mmol), product was obtained after silica gel chromatography (10% to 30% ethyl acetate in hexanes) in 69% yield as a white solid (512 mg). 1H NMR (400MHz, CDCb): δ 8.17 (s, 1H), 7.55 (d, J = 8.9 Hz, 2H), 7.33-7.29 (m, 2H), 7.08 (t, J = 7.4 Hz, 1H), 6.98-6.94 (m, 4H), 6.42 (dd, J = 1.4, 16.9 Hz, 1H), 6.31 (dd, J = 10.0, 16.9 Hz, 1H), 5.73 (dd, J = 1.4, 10.0 Hz, 1H). 13C NMR (100MHz, CDCb): δ 16.0, 157.5, 153.8, 13.4, 131.2, 129., 12.8, 123.3, 122.1, 119.6, 118.6. HRMS (+ESI): Calculated: 240.1019 (C15H14NO2). Observed: 240.1015.

[0621] 2-chloro-l-(indolin-l-yl)ethan-l-one (DKM 2-79). Following General Procedure B starting from indoline (331 mg, 2.8 mmol) product was obtained after silica gel chromatography (0% to 20% ethyl acetate in hexanes) in 51% yield as a pale brown solid (278 mg). 1H NMR (400MHz, CDCb): δ 8.17 (d, J = 8.0 Hz, 1H), 7.20-7.16 (m, 2H), 7.04 (t, J = 7.4 Hz, 1H), 4.09 (s, 2H), 4.05 (t, J = 8.4 Hz, 2H), 3.17 (t, J = 8.4 Hz, 2H). 13C NMR (100MHz, CDCb): δ 164.0, 142.4, 131.3, 127.6, 124.7, 124.5, 117.1, 47.7, 43.02, 28.1. HRMS (+ESI): Calculated: 196.0524 (C10H11CINO). Observed: 196.0523.

[0622] 2-Chloro-N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acetamide (DKM 2-90). Following General Procedure B starting from 1,4-benzodioxan-6-amine (457 mg, 3.0 mmol) product was obtained after silica gel chromatography (0% to 60% ethyl acetate in hexanes) in 8% yield as an off-white solid (56 mg). 1H NMR (400MHz, CDCb): δ 8.1 1 (s, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 2.4, 8.7 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 4.25 (s, 4H), 4.17 (s, 2H). 13C NMR (100MHz, CDCb): δ 163.8, 143.7, 141.3, 130.4, 117.5, 114.0, 110.2, 64.5, 64.4, 43.0. HRMS (+ESI): Calculated: 228.0422 (C10H11CINO3). Observed: 228.0421.
[0623] N-(4-Benzoylphenyl)-2-chloroacetamide (DKM 3-22). Following General Procedure B starting from 4-aminobenzophenone (590 mg, 3.0 mmol) product was obtained after silica gel chromatography (30% to 50% ethyl acetate in hexanes) in 83% yield as a light brown solid (679 mg). ¾ NMR (400MHz, CDCb): δ 8.48 (s, 1H), 7.85-7.83 (m, 2H), 7.78-7.76 (m, 2H), 7.61-7.57 (m, 1H), 7.50-7.46 (m, 2H), 4.22 (s, 2H). ¹³C NMR (100MHz, CDCb): δ 195.7, 164.2, 140., 137.7, 134.1, 132.5, 131.7, 130.0, 128.5, 119.3, 43.0. HRMS (-ESI): Calculated: 272.0484 (C₁₅H₁₁NO₂CI). Observed: 272.0482.

[0624] N-(3',5'-dichloro-[1,1'-biphenyl]-4-yl)acrylamide (DKM 3-3). Following General Procedure A starting from 4-amino-3,5-dichlorobiphenyl (717 mg, 3.0 mmol), product was obtained after silica gel chromatography (20% to 45% ethyl acetate in hexanes) and recrystallization from toluene in 23% yield as a white solid (203 mg). ¾ NMR (600MHz, MeOD): δ 7.77 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 1.7 Hz, 2H), 7.37 (t, J = 1.7 Hz, 1H), 6.46 (dd, J = 9.9, 17.0 Hz, 1H), 6.39 (dd, J = 1.7, 17.0 Hz, 1H), 5.80 (dd, J = 1.7, 9.9 Hz, 1H). ¹³C NMR (150MHz, MeOD): δ 166.2, 145.2, 140.4, 136.5, 135.2, 132.4, 128.5, 128.0, 127.7, 126.2, 121.7. HRMS (-ESI): Calculated: 290.0145 (C₁₅H₁₁NO₂CI₂). Observed: 290.0143.

[0625] Ethyl 4-(2-chloroacetamido)benzoate (TRH 1-17). Following General Procedure B starting from benzocaine (498 mg, 3.0 mmol) product was obtained after silica gel chromatography (2% to 20% ethyl acetate in hexanes) in 68% yield as a white solid (494 mg). ¾ NMR (400MHz, CDCb): δ 8.67 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 4.33 (q, J = 8.0 Hz, 2H), 4.15 (s, 2H), 1.34 (t, J = 6.0 Hz, 3H). ¹³C NMR (100MHz,
CDCb): δ 166.1, 164.5, 141.0, 130.7, 126.7, 119.3, 61.1, 43.0, 14.3. HRMS (-ESI):

Calculated: 240.0433 (C11H11NO3Cl). Observed: 240.0430.

[0626] N-(2,3-dihydrobenzo[\b][1,4]dioxin-6-yl)acrylamide (DKM 2-87).

Following General Procedure A starting from 1,4-benzodioxan-6-amine (462 mg, 3.1 mmol), product was obtained after silica gel chromatography (40% ethyl acetate in hexanes) in 38% yield as a light yellow solid (239 mg). 1H NMR (400MHz, (CD3)2SO): δ 9.97 (s, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 2.4, 8.7 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 6.38 (dd, J = 10.0, 17.0 Hz, 1H), 6.22 (dd, J = 2.1, 17.0 Hz, 1H), 5.71 (dd, J = 2.1, 10.0 Hz, 1H), 4.23-4.18 (m, 4H). 13C NMR (100MHz, (CD3)2SO): δ 162.7, 142.9, 139.5, 132.7, 131.9, 126.4, 116.8, 112.5, 108.4, 64.2, 63.9. HRMS (+ESI): Calculated: 206.0812 (C11H12NO3). Observed: 206.0807.

[0627] N-((tetrahydrofuran-2-yl)methyl)acrylamide (DKM 3-15). Following General Procedure A starting from tetrahydrofurfuryl amine (294 mg, 2.9 mmol), product was obtained after silica gel chromatography (20% to 70% ethyl acetate in hexanes) in 55% yield as a pale yellow oil (246 mg). 1H NMR (400MHz, CDCb): 6.48 (s, 1H), 6.20 (dd, J = 1.7, 17.0 Hz, 1H), 6.07 (dd, J = 10.1, 17.0 Hz, 1H), 5.54 (dd, J = 1.7, 10.1 Hz, 1H), 3.96-3.90 (m, 1H), 3.80-3.75 (m, 1H), 3.70-3.64 (m, 1H), 3.58-3.52 (m, 1H), 3.17-3.11 (m, 1H), 1.95-1.87 (m, 1H), 1.86-1.78 (m, 2H), 1.53-1.44 (m, 1H). 13C NMR (100MHz, CDCb): δ 165.7, 130.8, 126.3, 77.7, 68.0, 43.2, 28.7, 25.7. HRMS (+ESI): Calculated: 156.1019 (C6H14NO2). Observed: 156.1017.
N-(5,6,7,8-tetrahydronaphthalene-1-yl)acrylamide (TRH 1-56). Following General Procedure A starting from 5,6,7,8-tetrahydronaphthalene-1-amine (277 mg, 2.0 mmol), product was obtained after silica gel chromatography (30% ethyl acetate in hexanes) in 34% yield as a white solid (190 mg). ¹H NMR (400MHz, MeOD): δ 7.16 (d, J = 7.8 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.48 (dd, J = 17.1, 10.2 Hz, 1H), 6.33 (dd, J = 16.9, 1.8 Hz, 1H), 5.75 (dd, J = 10.1, 1.8 Hz, 1H), 2.78-2.75 (m, 2H), 2.62-2.60 (m, 2H), 1.80-1.73 (m, 4H). ¹³C NMR (100MHz, MeOD): δ 166.7, 139.3, 136.2, 133.3, 132.1, 128.5, 127.7, 126.5, 124.4, 30.7, 25.8, 24.0, 23.9. HRMS (+ESI): Calculated: 202.1226 (CisHieNO). Observed: 202.1224.

N-(7-bromo-2,3-dihydro-1H-inden-4-yl)acrylamide (TRH 1-65). To a solution of N-(2,3-dihydro-1H-inden-4-yl)acrylamide (DKM 2-84, 469 mg, 2.5 mmol) in acetic acid (10 mL) was added ammonium bromide (305 mg, 3.1 mmol) followed by dropwise addition of hydrogen peroxide solution (50% in water, 1.90 mL). The reaction was stirred overnight, after which it was carefully neutralized with a solution of saturated sodium bicarbonate and extracted with ethyl acetate (3x20 mL). The combined organics were then evaporated and the resulting crude was purified via silica gel chromatography (20% ethyl acetate in hexanes) to give 621 mg of the product as a white solid (93%). ¾ NMR (400MHz, MeOD): δ 7.36 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 6.49 (dd, J = 10.2, 17.0 Hz, 1H), 6.35 (dd, J = 1.8, 17.0 Hz, 1H), 5.77 (dd, J = 1.8, 10.2 Hz, 1H), 2.95 (q, J = 8.0 Hz, 4H), 2.08 (quint, J = 7.5 Hz, 2H). ¹³C NMR (100MHz, MeOD): δ 146.5, 140.2, 134.2, 132.0, 130.8, 128.1, 124.3, 116.9, 101.4, 35.8, 32.9, 24.9. HRMS (+ESI): Calculated: 287.9994 (Ci₂H₂NOBrNa). Observed: 287.9992.
[0631] N-methyl-N-(2,3-dihydro-lH-inden-4-yl)acrylamide  (TRH 1-1 15). To a solution of sodium hydride (60% dispersion in mineral oil, 167 mg, 4.0 mmol) in tetrahydrofuran (8 mL) under nitrogen atmosphere at 0 °C was added a solution N-(2,3-dihydro-lH-inden-4-yl)acrylamide (DKM 2-84, 188 mg, 1.0 mmol) in tetrahydrofuran (2 mL). After stirring for 30 minutes, methyl iodide (0.25 mL, 4.0 mmol) was added. The solution was allowed to warm to room temperature and stirred overnight. The solution was quenched with water and extracted with three times with ethyl acetate. The combined organics were washed with brine, dried with magnesium sulfate, filtered, and evaporated, and the resulting crude product was purified via silica gel chromatography (20% ethyl acetate in hexanes) to afford the product in 35% yield as a clear oil (71 mg). 1H NMR (400MHz, CDCB): δ 7.19-7.13 (m, 2H), 6.90 (d, J = 7.4 Hz, 1H), 6.32 (dd, J = 2.0, 16.8 Hz, 1H), 5.96 (dd, J = 10.3, 16.8 Hz, 1H), 5.43 (dd, J = 2.0, 10.3 Hz, 1H), 3.24 (s, 3H), 2.93 (t, J = 7.5 Hz, 2H), 2.81-2.66 (m, 2H), 2.08-2.00 (m, 2H). 13C NMR (100MHz, CDCB): δ 165.6, 146.6, 141.7, 139.3, 128.2, 127.7, 127.4, 125.1, 124.2, 36.0, 33.2, 30.5, 24.9. HRMS (+ESI): Calculated: 202.1226 (C_{13}H_{16}NO). Observed: 202.1224.

[0632] General synthetic methods

[0633] Chemicals and reagents were purchased from major commercial suppliers and used without further purification. Reactions were performed under a nitrogen atmosphere unless otherwise noted. Silica gel flash column chromatography was performed using EMD or Sigma Aldrich silica gel 60 (230-400 mesh). Proton and carbon nuclear magnetic resonance (1H NMR and 13C NMR) data was acquired on a Bruker AVB 400, AVQ 400, or AV 600 spectrometer at the University of California, Berkeley. High resolution mass spectrum were obtained from the QB3 mass spectrometry facility at the University of California, Berkeley using positive or negative electrospray ionization (+ESI or -ESI). Yields are reported as a single run.

[0634] General Procedure A. The amine (1 eq.) was dissolved in DCM (5 mL/mmol) and cooled to 0°C. To the solution was added acryloyl chloride (1.2 eq.) followed by
triethylamine (1.2 eq.). The solution was warmed to room temperature and stirred overnight. The solution was then washed with brine and the crude product was purified by silica gel chromatography (and recrystallization if necessary) to afford the corresponding acrylamide.

[0635] General Procedure B. The amine (1 eq.) was dissolved in DCM (5 mL/mmol) and cooled to 0°C. To the solution was added chloroacetyl chloride (1.2 eq.) followed by triethylamine (1.2 eq.). The solution was warmed to room temperature and stirred overnight. The solution was then washed with brine and the crude product was purified by silica gel chromatography (and recrystallization if necessary) to afford the corresponding chloroacetamide.

\[
\text{N-(4-benzoylphenyl)acrylamide (DKM 2-117). Following General Procedure A starting from 4-aminobenzophenone (587 mg, 3.0 mmol), product was obtained after silica gel chromatography (10% to 30% ethyl acetate in hexanes) in 37% yield as a yellow solid (275 mg).}
\]

\[\text{\quad \text{\textsuperscript{1}H NMR (400MHz, CDC\textsubscript{b}):} \delta 8.77 (s, 1H), 7.80-7.73 (m, 6H), 7.57 (tt, J = 1.5, 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 6.46 (dd, J = 1.6 16.9 Hz, 1H), 6.37 (dd, J = 9.9, 16.9 Hz, 1H), 5.75 (dd, J = 1.3, 9.9 Hz, 1H).} \]

\[\text{\quad \text{\textsuperscript{13}C NMR (100MHz, CDC\textsubscript{b}):} \delta 196.3, 164.4, 142.3, 137.8, 133.0, 132.5, 131.7, 131.0, 130.0, 128.8, 128.4, 119.3.} \]

\[\text{\quad \text{HRMS (+ESI): Calculated: 252.1019 (C\textsubscript{16}H\textsubscript{14}NO\textsubscript{2}). Observed: 252.1014.} \]

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\text{N-([l,l'-biphenyl]-4-ylmethyl)acrylamide (DKM 2-37). Following General Procedure A starting from 4-phenylbenzylamine (552 mg, 3.0 mmol), product was obtained after silica gel chromatography (0% to 80% ethyl acetate in hexanes) in 10% yield as an off-white solid (73 mg).}
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\[\text{\quad \text{\textsuperscript{1}H NMR (400MHz, CDC\textsubscript{b}):} \delta 7.58-7.55 (m, 4H), 7.44 (t, J = 7.5 Hz, 2H), 7.38-7.33 (m, 3H), 6.35 (dd, J = 1.3, 17.0 Hz, 1H), 6.13 (dd, J = 10.3, 17.0 Hz, 1H), 6.01 (s, 1H), 5.68 (dd, J = 1.3, 10.3 Hz, 1H), 4.56 (d, J = 5.8 Hz, 2H).} \]

\[\text{\quad \text{\textsuperscript{13}C NMR (100MHz,} \]

254
CDCb): δ 165.5, 140.77, 140.73, 137.2, 130.7, 128.9, 128.5, 127.6, 127.5, 127.1, 43.5.

**[0638]** 2-Chloro-N-(4-phenylbutan-2-yl)acetamide (DKM 2-76). Following General Procedure B starting from 1-methyl-3-phenylpropylamine (614 mg, 4.1 mmol) product was obtained after silica gel chromatography (0% to 30% ethyl acetate in hexanes) in 81% yield as a white solid (662 mg). ¾ NMR (400MHz, CDCb): δ 7.34-7.31 (m, 2H), 7.24-7.21 (m, 3H), 6.55 (d, J = 7.4 Hz, 1H), 4.15-4.07 (m, 1H), 4.04 (s, 2H), 2.70 (t, J = 8.2 Hz, 2H), 1.89-1.83 (m, 2H), 1.26 (d, J = 6.4 Hz, 3H). ¹³C NMR (100MHz, CDCb): δ 165.1, 141.3, 128.4, 128.2, 125.9, 45.7, 42.7, 38.1, 32.3, 20.7. HRMS (+ESI): Calculated: 226.0993 (C₁₂H₁₇ClNO). Observed: 226.0992.

**[0639]** 2-chloro-N-(4-fluorobenzyl)acetamide (DKM 2-80). Following General Procedure B starting from 4-fluorobenzylamine (369 mg, 2.9 mmol) product was obtained after silica gel chromatography (0% to 30% ethyl acetate in hexanes) in 77% yield as a white solid (452 mg). ¾ NMR (400MHz, CDCb): δ 7.28-7.24 (m, 2H), 7.05-7.01 (m, 2H), 6.97 (s, 1H), 4.45 (d, J = 5.6 Hz, 2H), 4.09 (s, 2H). ¹³C NMR (100MHz, CDCb): δ 166.1, 163.6, 161.2, 133.20, 133.17, 129.64, 129.56, 115.9, 115.7, 43.2, 42.7. HRMS (-ESI): Calculated: 200.0284 (C₁₀H₈NOC₁F). Observed: 200.0284.

**[0640]** N-(benzo[d][1,3]dioxol-5-yl)acrylamide (DKM 2-86). Following General Procedure A starting from 3,4-(methylenedioxy)aniline (486 mg, 2.9 mmol), product was obtained after silica gel chromatography (0% to 30% ethyl acetate in hexanes) in 68% yield as a white solid (438 mg). ¾ NMR (400MHz, (CD₃)₂SO): δ 10.05 (s, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.02 (dd, J = 2.0, 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.38 (dd, J = 10.1, 17.0 Hz,
1H), 6.22 (dd, $J = 2.1$, 17.0 Hz, 1H), 5.99 (s, 2H), 5.72 (dd, $J = 7.2$, 10.1 Hz, 1H). $^{13}$C NMR (100MHz, (CD$_3$)$_2$SO): $\delta$ 162.8, 147.0, 143.1, 133.4, 131.8, 126.5, 112.1, 108.1, 101.4, 101.0. HRMS (+ESI): Calculated: 192.0655 (C$^{10}$H$^{10}$N$^{0}$). Observed: 192.0651.

[0641] 2-chloro-N-(2,3-dihydro-lH-inden-4-yl)acetamide (DKM 2-91). Following General Procedure B starting from 4-aminoindan (372 mg, 2.8 mmol) product was obtained after silica gel chromatography (0% to 40% ethyl acetate in hexanes) in 49% yield as an off-white solid (289 mg). $^{3}$H NMR (400MHz, CDC$_3$)$_3$: $\delta$ 8.19 (s, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.15 (t, $J = 7.8$ Hz, 1H), 7.05 (d, $J = 7.6$ Hz, 1H), 4.16 (s, 2H), 2.94 (t, $J = 7.4$ Hz, 2H), 2.82 (t, $J = 7.4$ Hz, 2H). $^{13}$C NMR (100MHz, CDC$_3$): δ 163.8, 145.5, 134.5, 132.8, 127.3, 121.6, 118.5, 43.1, 33.2, 29.8, 41.6. HRMS (+ESI): Calculated: 210.0680 (C$^{10}$H$^{10}$Cl$^{1}$NO). Observed: 210.0680.

[0642] 2-Chloro-N-(2-chlorobenzyl)acetamide (DKM 2-94). Following General Procedure B starting from 2-chlorobenzylamine (432 mg, 3.1 mmol) product was obtained after silica gel chromatography (0% to 30% ethyl acetate in hexanes) in 67% yield as a white solid (443 mg). $^{3}$H NMR (400MHz, CDC$_3$): $\delta$ 7.36-7.18 (m, 5H), 4.51 (d, $J = 6.4$ Hz, 2H), 4.01 (s, 2H). $^{13}$C NMR (100MHz, CDC$_3$): δ 166.1, 134.5, 132.8, 127.3, 121.6, 118.5, 43.1, 33.2, 29.8, 41.6. HRMS (-ESI): Calculated: 215.9988 (C$^{9}$H$^{8}$N$^{0}$Cl$^{2}$). Observed: 215.9988.

[0643] N-(4'-cyano-[1 ,r-biphenyl]-4-yl)acrylamide (DKM 2-98). Following General Procedure A starting from 4-(4-aminophenyl)benzonitrile (387 mg, 2.0 mmol), product was obtained after silica gel chromatography (1% to 2% ethyl methanol in DCM) in 70% yield as a yellow solid (348 mg). $^{3}$H NMR (600MHz, (D$_3$C)$_2$CO): 9.52 (s, 1H), 7.90-7.89 (m, 2H), 7.21 (t, $J = 7.4$ Hz, 2H), 5.99 (s, 2H), 5.72 (dd, $J = 2.1$, 17.0 Hz, 1H), 6.22 (dd, $J = 2.1$, 17.0 Hz, 1H), 5.99 (s, 2H), 5.72 (dd, $J = 7.2$, 10.1 Hz, 1H). $^{13}$C NMR (100MHz, (CD$_3$)$_2$SO): δ 162.8, 147.0, 143.1, 133.4, 131.8, 126.5, 112.1, 108.1, 101.4, 101.0. HRMS (+ESI): Calculated: 192.0655 (C$^{10}$H$^{10}$N$^{0}$). Observed: 192.0651.
7.87-7.86 (m, 2H), 7.84-7.82 (m, 2H), 7.73-7.71 (m, 2H), 6.49 (d, \( J = 10.0, 16.9 \) Hz, 1H), 6.39 (d, \( J = 2.0, 16.9 \) Hz, 1H), 5.76 (d, \( J = 2.0, 10.0 \) Hz, 1H). 13C NMR (150MHz, \( (D_3)C_2CO \)): \( \delta \) 164.3, 145.7, 140.9, 134.8, 133.6, 132.7, 128.5, 128.2, 127.6, 120.8, 119.5, 111.3. HRMS (+ESI): Calculated: 247.0877 (C_{6}H_{10}N_{2}O). Observed: 247.0875.

N-(4-(methylthio)phenyl)acrylamide (DKM 3-10). Following General Procedure A starting from 4-(methylthio)aniline (405 mg, 2.9 mmol), product was obtained after silica gel chromatography (10% to 40% ethyl acetate in hexanes) in 64% yield as a clear oil (362 mg).

\( ^1H \) NMR (400MHz, MeOD): \( \delta \) 7.59-7.56 (m, 2H), 7.26-7.22 (m, 2H), 6.42 (d, \( J = 9.6, 17.0 \) Hz, 1H), 6.34 (d, \( J = 2.3, 17.0 \) Hz, 1H), 5.75 (d, \( J = 2.3, 9.6 \) Hz, 1H), 2.45 (s, 3H). 13C NMR (100MHz, MeOD): \( \delta \) 166.0, 137.2, 135.4, 132.4, 128.6, 127.7, 121.9, 16.4. HRMS (+ESI): Calculated: 194.0634 (C_{10}H_{12}NO). Observed: 194.0631.

N-(4'-ethyl-[1, r'-biphenyl]-4-yl)acrylamide (DKM 3-16). Following General Procedure A starting from 4-amino-4-ethylbiphenyl (386 mg, 2.0 mmol), product was obtained after silica gel chromatography (10% to 70% ethyl acetate in hexanes) in 65% yield as a white solid (164 mg).

\( ^1H \) NMR (400MHz, \( (CD_3)_{2}CO \)): \( \delta \) 7.82 (d, \( J = 8.2 \) Hz, 2H), 7.62-7.59 (m, 2H), 7.58-7.54 (m, 2H), 7.29 (d, \( J = 8.2 \) Hz, 2H), 6.47 (d, \( J = 9.9, 16.9 \) Hz, 1H), 6.36 (d, \( J = 2.2, 16.9 \) Hz, 1H), 5.72 (d, \( J = 2.2, 9.9 \) Hz, 1H), 2.67 (q, \( J = 7.6 \) Hz, 2H), 1.24 (t, \( J = 7.6 \) Hz, 3H). 13C NMR (100MHz, \( (CD_3)_2CO \)): \( \delta \) 164.1, 144.0, 139.5, 13.9, 137.1, 132.9, 129.3, 127.9, 127.4, 127.2, 120.7, 29.2, 16.2. HRMS (+ESI): Calculated: 252.1383 (C_{19}H_{21}NOS). Observed: 252.1379.

2-Chloro-N-(4-phenoxyphenyl)acetamide (TRH 1-23). Following General Procedure B starting from 4-phenoxyaniline (370 mg, 2.0 mmol) product was obtained after silica gel chromatography (10% to 30% ethyl acetate in hexanes) in 46% yield as a white
solid (315 mg). ¾ NMR (400MHz, CDCb): δ 8.42 (s, 1H), 7.52-7.48 (m, 2H), 7.35-7.31 (m, 2H), 7.10 (t, J = 7.3 Hz, 1H), 7.01-6.98 (m, 4H), 4.17 (s, 2H). 

13C NMR (100MHz, CDCb): δ 164.2, 157.2, 154.4, 132.1, 129.8, 123.4, 122.2, 119.4, 118.7, 42.9. HRMS (-ESI): Calculated: 260.0484 (C14HnN02Cl). Observed: 260.0482.

[0647] 2-Chloro-N-(2-methylbenzyl)acetamide (TRH 1-55). Following General Procedure B starting from 2-methylbenzylamine (239 mg, 2.0 mmol) product was obtained after silica gel chromatography (30% ethyl acetate in hexanes) and recrystallization from 5% ethyl acetate in hexanes in 64% yield as a white solid (191 mg). ¾ NMR (400 MHz, CDCb): δ 7.25-7.19 (m, 4H), 6.85 (s, 1H), 4.46 (d, J = 5.6 Hz, 2H), 4.04 (s, 2H), 2.33 (s, 3H). 

13C NMR (100MHz, CDCb): δ 165.8, 136.4, 135.0, 130.6, 128.4, 128.0, 126.3, 42.6, 42.0, 19.0. HRMS (+ESI): Calculated: 196.0535 (C10HnNOCl). Observed: 196.0534.

[0648] N-benzylacryl amide (DKM 2-31). Following General Procedure A starting from benzyamine (334 mg, 3.1 mmol), product was obtained after silica gel chromatography (0% to 50% ethyl acetate in hexanes) in 75% yield as a white solid (376 mg). ¾ NMR (400MHz, CDCb): δ 7.28-7.18 (m, 6H), 6.19-6.16 (m, 2H), 5.53 (dd, J = 4.6, 7.3 Hz, 1H), 4.36 (d, J = 5.9 Hz, 2H). 

13C NMR (100MHz, CDCb): δ 165.8, 138.1, 130.8, 128.6, 127.7, 127.3, 126.5, 43.5. HRMS (+ESI): Calculated: 162.0913 (C10HnNO). Observed: 162.0912.

[0649] N-(4-phenylbutan-2-yl)acrylamide (DKM 2-32). Following General Procedure A starting from 1-methyl-3-phenylpropylamine (606 mg, 4.0 mmol), product was obtained after silica gel chromatography (0% to 50% ethyl acetate in hexanes) in 89% yield as a clear oil (735 mg). ¾ NMR (400MHz, CDCb): δ 7.32-7.29 (m, 2H), 7.23-7.20 (m, 3H), 6.84 (d, J =
8.4 Hz, 1H), 6.36-6.24 (m, 2H), 5.64 (dd, J = 2.8, 9.2 Hz, 1H), 4.21-4.14 (m, 1H), 2.70 (t, J = 7.8 Hz, 2H), 1.93-1.77 (m, 2H), 1.24 (d, J = 6.4 Hz, 3H). 13C NMR (100MHz, CDCl3): δ 165.1, 141.7, 131.3, 128.3, 128.2, 125.80, 125.77, 45.1, 38.4, 32.5, 20.8. HRMS (+ESI): Calculated: 204.1383 (C12H13NO). Observed: 204.1380.

N-(4-methoxybenzyl)acrylamide (DKM 2-33). Following General Procedure A starting from 4-methoxybenzylamine (424 mg, 3.1 mmol), product was obtained after silica gel chromatography (0% to 50% ethyl acetate in hexanes) in 60% yield as a clear oil (343 mg). 1H NMR (400MHz, CDCl3): δ 7.14 (d, J = 8.8 Hz, 2H), 6.85 (s, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.24-6.14 (m, 2H), 5.56 (dd, J = 2.0, 9.6 Hz, 1H), 4.33 (d, J = 5.6 Hz, 2H), 3.73 (s, 3H). 13C NMR (100MHz, CDCl3): δ 165.6, 158.9, 130.9, 130.3, 129.1, 126.4, 113.9, 55.2, 42.9. HRMS (+ESI): Calculated: 192.1019 (C11H14NO2). Observed: 192.1017.

N-(4-fluorobenzyl)acrylamide (DKM 2-34). Following General Procedure A starting from 4-fluorobenzylamine (368 mg, 2.9 mmol), product was obtained after silica gel chromatography (0% to 60% ethyl acetate in hexanes) in 52% yield as an off-white solid (276 mg). 1H NMR (400MHz, CDCl3): δ 7.24-7.19 (m, 2H), 6.97 (t, J = 8.5 Hz, 2H), 6.42 (s, 1H), 6.27 (d, J = 17.0 Hz, 1H), 6.12 (dd, J = 17.0, 10.2 Hz, 1H), 5.63 (d, J = 10.2 Hz, 1H), 4.42 (d, J = 5.8 Hz, 2H). 13C NMR (100MHz, CDCl3): δ 165.7, 163.5, 134.0, 130.6, 129.6, 129.5, 127.0, 115.7, 115.5, 43.0. HRMS (+ESI): Calculated: 180.0819 (C11H14NOF). Observed: 180.0818.

Ethyl 4-acryloylpiperazine-l-carboxylate (DKM 2-39). Following General Procedure A starting from ethyl 1-piperazinecarboxylate (477 mg, 3.0 mmol), product was
obtained after silica gel chromatography (0% to 70% ethyl acetate in hexanes) in 58% yield as a yellow oil (372 mg). ¾NMR (400MHz, CDCb): δ 6.46 (dd, J = 10.5, 16.8 Hz, 1H), 6.18 (dd, J = 1.9, 16.8 Hz), 5.60 (dd, J = 1.9, 10.5 Hz), 4.03 (q, J = 7.1 Hz, 2H), 3.54 (s, 2H), 3.44 (s, 2H), 3.39-3.36 (m, 4H), 1.15 (t, J = 7.1 Hz, 3H). ¹³C NMR (100MHz, CDCb): δ 165.3, 155.1, 128.2, 127.1, 61.5, 45.4, 43.6, 43.3, 41.5, 14.5. HRMS (+ESI): Calculated: 213.1234 (C₁₀H₁₇N₂O₃). Observed: 213.1232.

[0653] N-(2,5-difluorophenyl)acrylamide (DKM 2-40). Following General Procedure A starting from 2,5-difluoroaniline (369 mg, 2.9 mmol), product was obtained after silica gel chromatography (0% to 15% ethyl acetate in hexanes) in 27% yield as a white solid (141 mg). ¾ NMR (400MHz, (CD₃)₂CO): δ 9.26 (s, 1H), 8.29-8.24 (m, 1H), 7.24-7.18 (m, 1H), 6.90-6.84 (m, 1H), 6.67 (dd, J = 10.2, 16.9 Hz, 1H), 6.41 (dd, J = 1.9, 16.9 Hz, 1H), 5.79 (dd, J = 1.9, 10.2 Hz, 1H). ¹³C NMR (100MHz, (CD₃)₂CO): δ 164.6, 160.4, 151.0, 148.7, 132.0, 128.9, 128.8, 128.5, 116.7, 116.6, 116.5, 116.4, 111.1, 111.0, 110.8, 110.7, 110.0, 109.7. HRMS (+ESI): Calculated: 184.0568 (C₉H₈F₂NO). Observed: 184.0567.

[0654] N-phenethylacrylamide (DKM 2-42). Following General Procedure A starting from phenylethylamine (367 mg, 3.0 mmol), product was obtained after silica gel chromatography (0% to 50% ethyl acetate in hexanes) in 85% yield as a yellow oil (450 mg). ¾ NMR (400MHz, CDC1₃): δ 7.30-7.18 (m, 5H), 6.63 (s, 1H), 6.25 (dd, J = 1.8, 17.0 Hz, 1H), 6.13 (dd, J = 10.0, 17.0 Hz 1H), 5.59 (dd, J = 1.6, 10.0 Hz, 1H), 3.56 (q, J = 6.8 Hz, 2H), 2.85 (t, J = 7.3 Hz, 2H). ¹³C NMR (100MHz, CDCb): δ 165.8, 138.8, 131.0, 128.7, 128.6, 126.4, 126.1, 40.8, 35.6. HRMS (+ESI): Calculated: 176.1070 (C₁₁H₁₄NO). Observed: 176.1068.
N-(4-bromobenzyl)acrylamide (DKM 2-43). Following General Procedure A starting from 4-bromobenzylamine (535 mg, 2.9 mmol), product was obtained after silica gel chromatography (0% to 50% ethyl acetate in hexanes) in 59% yield as a white solid (407 mg). ³¹NMR (400MHz, CDCl₃): δ 7.37 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.00 (s, 1H), 6.24-6.10 (m, 2H), 5.59 (dd, J = 2.0, 9.7 Hz, 1H), 4.32 (d, J = 6.0 Hz, 2H). ¹³C NMR (100MHz, CDCl₃): δ 165.9, 137.2, 131.7, 130.6, 129.4, 126.9, 121.2, 42.8. HRMS (+ESI): Calculated: 240.0019 (C₁₀H₇BrNO). Observed: 240.0016.

N-(3,5-dimethylbenzyl)acrylamide (DKM 2-47). Following General Procedure A starting from 3,5-dimethylbenzylamine (257 mg, 1.9 mmol), product was obtained after silica gel chromatography (0% to 40% ethyl acetate in hexanes) in 77% yield as a white solid (276 mg). ³¹NMR (400MHz, CDCl₃): δ 6.89-6.87 (m, 4H), 6.26 (dd, J = 2.1, 17.0 Hz, 1H), 6.18 (dd, J = 9.7, 17.0 Hz, 1H), 5.59 (dd, J = 2.1, 9.7 Hz, 1H), 4.35 (d, J = 6.0 Hz, 2H), 2.28 (s, 6H). ¹³C NMR (100MHz, CDCl₃): δ 165.6, 138.1, 138.0, 130.9, 129.0, 126.3, 125.6, 43.4, 12.2. HRMS (+ESI): Calculated: 190.1226 (C₆H₁₀NO). Observed: 190.1225.

1-(pyrrolidin-1-yl)prop-2-en-1-one (DKM 2-48). Following General Procedure A starting from pyrrolidine (223 mg, 3.1 mmol), product was obtained after silica gel chromatography (0% to 80% ethyl acetate in hexanes) in 38% yield as a pale yellow oil (148 mg). ³¹NMR (400MHz, CDCl₃): δ 6.40 (dd, J = 10.0, 16.8 Hz, 1H), 6.29 (dd, J = 2.4, 16.8 Hz, 1H), 5.60 (dd, J = 2.4, 10.0 Hz, 1H), 3.48 (t, J = 6.8 Hz, 4H), 1.91 (quint, J = 6.7 Hz,
2H), 1.82 (quint, J = 6.7 Hz, 2H). $^{13}$C NMR (100MHz, CDCb): δ 164.4, 128.8, 127.2, 46.6, 45.9, 26.1, 24.3. HRMS (+ESI): Calculated: 126.0913 (C7H12NO). Observed: 126.0912.

[0658] l-morpholinoprop-2-en-l-one (DKM 2-49). Following General Procedure A starting from morpholine (273 mg, 3.1 mmol), product was obtained after silica gel chromatography (0% to 80% ethyl acetate in hexanes) in 46% yield as a yellow oil (205 mg).

$^{1}$$^{1}$$^{H}$NMR (400MHz, CDCb): δ 6.45 (dd, J = 10.5, 16.8 Hz, 1H), 6.20 (dd, J = 1.9, 16.8 Hz, 1H), 5.61 (dd, J = 1.9, 10.5 Hz, 1H), 5.38 (s, 6H), 3.46 (s, 2H). $^{13}$C NMR (100MHz, CDCb): δ 165.3, 128.1, 126.9, 66.6, 46.0, 42.1. HRMS (+ESI): Calculated: 142.0863 (C7H12NO2). Observed: 142.0861.

[0659] N-(3-phenylpropyl)acrylamide (DKM 2-50). Following General Procedure A starting from 3-phenyl-1-propylamine (275 mg, 2.0 mmol), product was obtained after silica gel chromatography (0% to 60% ethyl acetate in hexanes) in 58% yield as a yellow oil (223 mg).

$^{1}$$^{H}$NMR (400MHz, CDCb): δ 7.29-7.25 (m, 2H), 7.20-7.16 (m, 3H), 6.99 (s, 1H), 6.29-6.17 (m, 2H), 5.59 (dd, J = 2.6, 9.0 Hz, 1H), 3.34 (q, J = 6.7 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 1.87 (quint, J = 7.4 Hz, 2H). $^{13}$C NMR (100MHz, CDCb): δ 166.0, 141.4, 131.1, 128.33, 128.26, 125.9, 39.2, 33.2, 31.0. HRMS (+ESI): Calculated: 190.1226 (C12H16NO). Observed: 190.1225.

[0660] N-(2-(2-methoxyphenoxy)ethyl)acrylamide (DKM 2-58). Following General Procedure A starting from 2-(2-methoxyphenoxy)ethanamine (509 mg, 3.0 mmol), product was obtained after silica gel chromatography (0% to 30% ethyl acetate in hexanes) in 70%
yield as a yellow oil (470 mg). ³¹NMR (400MHz, CDCb): δ 6.95-6.84 (m, 4H), 6.77 (s, 1H), 6.26 (d, J = 17.1 Hz, 1H), 6.11 (dd, J = 10.2, 17.1 Hz, 1H), 5.59 (d, J = 10.2 Hz, 1H), 4.07 (t, J = 5.2 Hz, 2H), 3.79 (s, 3H), 3.69 (q, J = 5.4 Hz, 2H). ¹³C NMR (100MHz, CDCb): δ 165.7, 149.6, 147.7, 130.8, 126.4, 122.1, 121.0, 114.8, 111.8, 68.5, 55.7, 38.9. HRMS (+ESI): Calculated: 244.0944 (C₁₂H₁₅N₀₃Na). Observed: 244.0940.

[0661] N-([1,r-biphenyl]-2-ylmethyl)acrylamide (DKM 2-59). Following General Procedure A starting from 2-phenylbenzylamine (202 mg, 1.1 mmol), product was obtained after silica gel chromatography (0% to 40% ethyl acetate in hexanes) in 70% yield as a yellow oil (184 mg). ³¹NMR (400MHz, CDCb): δ 7.41-7.22 (m, 9H), 6.16 (dd, J = 1.2, 17.2 Hz, 1H), 6.03-5.97 (m, 2H), 5.55 (dd, J = 1.2, 10.0 Hz, 1H), 4.44 (d, J = 5.6 Hz, 2H). ¹³C NMR (100MHz, CDCb): δ 165.3, 141.6, 140.6, 135.2, 130.6, 130.2, 129.0, 128.7, 128.4, 127.8, 127.4, 127.3, 126.4, 41.4. HRMS (+ESI): Calculated: 238.1226 (C₁₀H₁₀ClNO). Observed: 238.1223.

[0662] N-(2-chlorobenzyl)acrylamide (DKM 2-60). Following General Procedure A starting from 2-chlorobenzylamine (406 mg, 2.9 mmol), product was obtained after silica gel chromatography (0% to 30% ethyl acetate in hexanes) in 34% yield as a white solid (162 mg). ³¹NMR (400MHz, CDCb): δ 7.34-7.30 (m, 2H), 7.20-7.16 (m, 2H), 6.84 (s, 1H), 6.25 (dd, J = 2.0, 17.0 Hz, 1H), 6.16 (dd, J = 9.7, 17.0 Hz, 2H), 5.60 (dd, J = 2.0, 9.7 Hz, 1H), 4.52 (d, J = 6.1 Hz, 2H). ¹³C NMR (100MHz, CDCb): δ 165.9, 135.5, 133.5, 130.6, 129.8, 129.5, 128.8, 127.1, 126.8, 41.4. HRMS (+ESI): Calculated: 196.0524 (C₁₀H₉ClNO). Observed: 196.0521.
N-(2,3-dihydro-1H-inden-4-yl)acrylamide (DKM 2-84). Following General Procedure A starting from 4-aminoindan (402 mg, 3.0 mmol), product was obtained after silica gel chromatography (30% ethyl acetate in hexanes) in 59% yield as a white solid (332 mg). ¾ NMR (400MHz, CDCl₃): δ 7.72 (d, J = 7.5 Hz, 1H), 7.54 (s, 1H), 7.10 (t, J = 7.7 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.40-6.26 (m, 2H), 5.69 (dd, J = 1.9, 9.7 Hz, 1H), 2.91 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 2.05 (quint, J = 7.4 Hz, 2H). ¹³C NMR (100MHz, CDCl₃): 163.5, 145.3, 134.4, 133.6, 131.2, 127.5, 127.2, 12.0, 19.2, 33.2, 30.1, 24.8. HRMS (+ESI): Calculated: 188.1070 (C₁₂H₁₄NO). Observed: 188.1069.

Ethyl 4-acrylamidobenzoate (DKM 2-85). Following General Procedure A starting from benzocaine (486 mg, 2.9 mmol), product was obtained after silica gel chromatography (0% to 30% ethyl acetate in hexanes) in 68% yield as a white solid (438 mg). ¹H NMR (400MHz, CDCl₃): δ 9.39 (s, 1H), 7.95 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 6.43-6.41 (m, 2H), 5.71 (dd, J = 4.7, 6.9 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.33 (s, J = 7.1 Hz, 3H). ¹³C NMR (100MHz, CDCl₃): δ 166.5, 164.6, 142.5, 131.0, 130.6, 128.4, 125.7, 119.4, 61.0, 14.2. HRMS (-ESI): Calculated: 218.0823 (C₁₂H₁₂NO₃). Observed: 218.0822.

N-benzyl-N-methylacrylamide (DKM 2-95). Following General Procedure A starting from N-methylbenzylamine (350 mg, 2.9 mmol), product was obtained after silica gel chromatography (20% ethyl acetate in hexanes) in 60% yield as a clear oil (304 mg). ¾ NMR (-48:52 rotamer ratio, asterisks denote minor peaks, 400MHz, CDCl₃): δ 7.34-7.23 (m,
4H), 7.16 (s, 1H), 7.14 (s, 1H), 6.61 (dd, J = 10.4, 16.8 Hz, 1H), 6.57 (dd, J = 10.4, 16.8 Hz, 1H), 6.38 (dd, J = 1.9, 16.8 Hz, 1H), 6.36 (dd, J = 1.9, 16.8 Hz, 1H), 5.71 (dd, J = 1.9, 10.4 Hz, 1H), 5.64 (dd, J = 1.9, 10.4 Hz), 4.63 (s, 2H), 4.56 (s, 2H), 2.98 (s, 3H), 2.96 (s, 3H).

13C NMR (100MHz, CDCl3): δ 167.0, 166.4, 137.1, 136.5, 128.8, 128.5, 128.2, 128.0, 17.62, 127.59, 127.3, 126.3, 53.3, 51.0, 34.8, 34.0.


[0666] 1-(4-phenylpiperidin-1-yl)prop-2-en-1-one (DKM 2-97). Following General Procedure A starting from 4-phenylpiperidine (331 mg, 2.1 mmol), product was obtained after silica gel chromatography (0% to 50% ethyl acetate in hexanes) in 86% yield as a yellow oil (379 mg). 1H NMR (400MHz, CDCl3): δ 7.32-7.28 (m, 2H), 7.22-7.17 (m, 3H), 6.62 (dd, J = 10.6, 16.8 Hz, 1H), 6.30 (dd, J = 1.9, 16.8 Hz, 1H), 5.68 (dd, J = 1.9, 10.6, Hz, 1H), 4.82 (d, J = 12.9 Hz, 1H), 4.11 (d, J = 13.2 Hz, 1H), 3.15 (t, J = 8.5 Hz, 1H), 2.78-2.67 (m, 2H), 1.90 (d, J = 12.9 Hz, 2H), 1.64 (quint, J = 12.3 Hz, 2H). 13C NMR (100MHz, CDCl3): 165.3, 145.0, 128.5, 127.8, 127.4, 126.6, 126.4, 46.4, 42.7, 33.9, 32.7. HRMS (+ESI): Calculated: 216.1383 (C14H19NO). Observed: 216.1383.

[0667] N-(2-morpholinoethyl)acrylamide (DKM 2-100). Following General Procedure A starting from 2-morpholinoethylamine (580 mg, 3.0 mmol), product was obtained after silica gel chromatography (2% to 6% methanol in dichloromethane) in 33% yield as a white solid (184 mg). 1H NMR (400MHz, CDCl3): δ 6.39 (s, 1H), 6.21 (dd, J = 1.7, 17.0 Hz, 1H), 6.08 (dd, J = 10.1, 17.0 Hz, 1H), 5.56 (dd, J = 1.7, 10.1 Hz, 1H), 3.63 (t, J = 4.6 Hz, 4H), 3.36 (q, J = 6.2 Hz, 2H), 2.45 (t, J = 6.2 Hz, 2H), 2.40-2.38 (m, 4H). 13C NMR (100MHz, CDCl3): δ 165.5, 130.9, 126.2, 66.9, 57.0, 53.3, 35.7. HRMS (+ESI): Calculated: 185.1285 (C9H17N2O2). Observed: 185.1280.
l-(indolin-l-yl)prop-2-en-l-one (DKM 2-101). Following General Procedure A starting from indoline (580 mg, 3.0 mmol), product was obtained after silica gel chromatography (0% to 20% ethyl acetate in hexanes) in 56% yield as a green solid (285 mg). ³¹ NMR (400MHz, CDCl₃): δ 8.30 (d, J = 7.7 Hz, 1H), 7.22-7.17 (m, 2H), 7.03 (t, J = 7.9 Hz, 1H), 6.60-6.48 (m, 2H), 5.79 (dd, J = 2.6, 9.5 Hz, 1H), 4.15 (t, J = 8.5 Hz, 2H), 3.20 (t, J = 8.1, 2H). ¹³C NMR (100MHz, CDCl₃): δ 163.6, 142.6, 131.5, 129.0, 128.6, 127.2, 124.4, 123.8, 117.2, 47.8, 27.7. HRMS (+ESI): Calculated: 174.0913 (C₁₁H₁₂NO). Observed: 174.0911.

N-butylacrylamide (DKM 2-102). Following General Procedure A starting from butylamine (223 mg, 3.0 mmol), product was obtained after silica gel chromatography (20% ethyl acetate in hexanes) in 61% yield as a clear oil (237 mg). ³¹ NMR (400MHz, CDCl₃): δ 6.81 (s, 1H), 6.21-6.10 (m, 2H), 5.52 (dd, J = 3.6, 8.3 Hz, 1H), 3.26-3.21 (m, 2H), 1.48-1.41 (m, 2H), 1.33-1.23 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H). ¹³C NMR (100MHz, CDCl₃): δ 166.0, 131.2, 125.6, 39.3, 31.5, 20.1, 13.7. HRMS (+ESI): Calculated: 128.1070 (C₇H₁₄NO). Observed: 128.1068.

N-(3-methoxypropyl)acrylamide (DKM 2-103). Following General Procedure A starting from 3-methoxypropylamine (274 mg, 3.1 mmol), product was obtained after silica gel chromatography (35% to 60% ethyl acetate in hexanes) in 54% yield as a clear oil (236 mg). ³¹NMR (400MHz, CDCl₃): δ 6.84 (s, 1H), 6.15 (dd, J = 2.0, 17.0 Hz, 1H), 6.07 (dd, J = 9.8, 17.0 Hz, 1H), 5.51 (dd, J = 2.0, 9.8 Hz, 1H), 3.39 (t, J = 5.9 Hz, 2H), 3.33 (q, J = 6.3 Hz, 2H), 3.25 (s, 3H), 1.72 (quint, J = 6.3 Hz, 2H). ¹³C NMR (100MHz, CDCl₃): δ 165.8, 131.2, 125.7, 71.3, 58.7, 37.7, 29.0. HRMS (+ESI): Calculated: 144.1019 (C₇H₁₄NO₂). Observed: 144.1017.
N-cyclohexylacrylamide (DKM 2-106). Following General Procedure A starting from cyclohexylamine (292 mg, 2.9 mmol), product was obtained after silica gel chromatography (20% to 30% ethyl acetate in hexanes) in 86% yield as a white solid (313 mg). ³¹NMR (400MHz, (CDCl₃): δ 6.55 (d, J = 6.7 Hz, 1H), 6.21-6.09 (m, 2H), 5.51 (dd, J = 2.5, 9.1 Hz, 1H), 3.79-3.70 (m, 1H), 1.86-1.82 (m, 2H), 1.67-1.63 (m, 2H), 1.56-1.52 (m, 1H), 1.28-1.21 (m, 2H), 1.16-1.05 (m, 3H). ¹³C NMR (100MHz, CDCl₃): δ 164.8, 131.5, 125.7, 48.3, 32.9, 25.5, 24.9. HRMS (+ESI): Calculated: 154.1226 (C₇H₆NO). Observed: 154.1224.

N-(4-chlorophenyl)acrylamide (DKM 2-107). Following General Procedure A starting from 4-chloroaniline (386 mg, 3.0 mmol), product was obtained after silica gel chromatography (0% to 40% ethyl acetate in hexanes) followed by recrystallization from toluene in 31% yield as a white solid (168 mg). ³¹NMR (400MHz, (CDCl₃): δ 9.47 (s, 1H), 7.77-7.74 (m, 2H), 7.35-7.31 (m, 2H), 6.43 (dd, J = 9.6, 16.9 Hz, 1H), 6.35 (dd, J = 2.5, 16.9 Hz, 1H), 5.73 (dd, J = 2.5, 9.6 Hz, 1H). ¹³C NMR (100MHz, (CDCl₃): δ 164.1, 139.0, 132.5, 129.5, 128.7, 127.5, 121.7. HRMS (-ESI): Calculated: 180.0222 (C₉H₇NOCl). Observed: 180.0221.

N-cyclopentylacrylamide (DKM 2-108). Following General Procedure A starting from cyclopentylamine (257 mg, 3.0 mmol), product was obtained after silica gel chromatography (20% to 30% ethyl acetate in hexanes) in 55% yield as a colorless oil (229 mg). ³¹NMR (400MHz, (CDCl₃): δ 6.70 (s, 1H), 6.21-6.10 (m, 2H), 5.51 (dd, J = 3.5, 8.5 Hz, 1H), 5.53-5.50 (sex, J = 7.1 Hz, 1H), 1.94-1.86 (m, 2H), 1.65-1.46 (m, 4H), 1.41-1.32 (m, 2H). ¹³C NMR (100MHz, CDCl₃): δ 165.4, 131.3, 125.7, 51.1, 32.9, 23.8. HRMS (+ESI): Calculated: 140.1070 (C₆H₄NO). Observed: 140.1067.
1-(4-methoxypiperidin-1-yl)prop-2-en-1-one (DKM 2-109). Following General Procedure A starting from 4-methoxypiperidine (461 mg, 3.0 mmol), product was obtained after silica gel chromatography (40% to 60% ethyl acetate in hexanes) in 75% yield as a pale yellow oil (386 mg). ³¹NMR (400MHz, CDCb): δ 6.45 (dd, J = 10.6, 16.8 Hz, 1H), 6.09 (dd, J = 2.0, 16.8 Hz, 1H), 5.51 (dd, J = 2.0, 10.6 Hz, 1H), 3.80-3.74 (m, 1H), 3.65-3.58 (m, 1H), 3.33-3.17 (m, 6H), 1.74-1.67 (m, 2H), 1.47-1.39 (m, 2H). ¹³C NMR (100MHz, CDCb): δ 165.1, 127.6, 127.2, 75.0, 55.5, 42.7, 38.9, 31.1, 29.9. HRMS (+ESI): Calculated: 170.1176 (C9H16NO2). Observed: 170.1176.

N-(3,4-dimethoxybenzyl)acrylamide (DKM 2-110). Following General Procedure A starting from 3,4-dimethoxybenzylamine (497 mg, 3.0 mmol), product was obtained after silica gel chromatography (30% to 40% ethyl acetate in hexanes) in 65% yield as a white solid (425 mg). ³¹NMR (400MHz, CDCb): δ 7.07 (s, 1H), 6.70-6.64 (m, 3H), 6.18-6.08 (m, 2H), 5.50 (dd, J = 3.1, 8.8 Hz, 1H), 4.26 (d, J = 5.8 Hz, 2H), 3.70 (d, J = 7.8 Hz, 6H). ¹³C NMR (400MHz, CDCb): δ 165.5, 148.7, 148.0, 130.73, 130.67, 126.2, 119.9, 110.98, 110.96, 55.64, 55.55, 43.12. HRMS (+ESI): Calculated: 222.1125 (C₁₂H₁₆N₀₃). Observed: 222.1121.

tert-butyl 4-acryloypiperazine-1-carboxylate (DKM 2-111). Following General Procedure A starting from 1-boc-piperazine (552 mg, 3.0 mmol), product was obtained after silica gel chromatography (50% to 70% ethyl acetate in hexanes) in 75% yield as a pale yellow oil (534 mg). ¹³H NMR (400MHz, CDCb): δ 6.48 (dd, J = 10.5, 16.8 Hz, 1H), 6.20 (dd, J = 1.8, 16.8 Hz, 1H), 5.60 (dd, J = 1.8, 10.5 Hz, 1H), 3.55 (s, 2H), 3.44 (s, 2H), 3.36-
3.34 (m, 4H), 1.37 (s, 9H). 13C NMR (100MHz, CDCb): δ 165.4, 154.4, 128.2, 127.2, 80.2, 45.5, 41.7, 28.3. HRMS (+ESI): Calculated: 241.1547 (C12H21N2O3). Observed: 241.1543.

[0677] N-(2-phenoxyethyl)acrylamide (DKM 2-13). Following General Procedure A starting from 2-phenoxyethyamine (279 mg, 2.0 mmol), product was obtained after silica gel chromatography (30% to 70% ethyl acetate in hexanes) in 61% yield as a white solid (239 mg). 1H NMR (400MHz, CDCb): δ 7.31-7.25 (m, 2H), 6.98-6.94 (m, 1H), 6.90-6.87 (m, 2H), 6.58 (s, 1H), 6.31 (dd, J = 1.6, 17.0 Hz, 1H), 6.17 (dd, J = 10.2, 17.0 Hz, 1H), 5.64 (dd, J = 1.6, 10.2 Hz, 1H), 4.05 (t, J = 5.2 Hz, 2H), 3.73 (q, J = 5.4 Hz, 2H). 13C NMR (100MHz, CDCb): δ 165.9, 158.4, 130.7, 129.6, 126.7, 121.2, 114.4, 66.5, 39.1. HRMS (+ESI): Calculated: 192.1019 (C11H14NO2). Observed: 192.1016.

[0678] N,N'-dicyclohexylacrylamide (DKM 2-14). Following General Procedure A starting from dicyclohexylamine (537 mg, 3.0 mmol), product was obtained after silica gel chromatography (20% to 40% ethyl acetate in hexanes) in 55% yield as a white solid (382 mg). 1H NMR (400MHz, CDCb): δ 6.49 (dd, J = 10.6, 16.8 Hz, 1H), 6.11 (dd, J = 1.9, 16.8 Hz, 1H), 5.49 (dd, J = 2.0, 10.6 Hz, 1H), 3.45 (s, 1H), 3.22 (s, 1H), 2.22 (s, 2H), 1.74-1.49 (m, 12H), 1.22-1.07 (m, 6H). 13C NMR (100MHz, CDCb): δ 166.2, 130.9, 125.5, 57.5, 55.6, 31.6, 30.1, 26.4, 26.0, 25.3. HRMS (+ESI): Calculated: 236.2009 (C15H26NO). Observed: 236.2004.

[0679] N-(4-(trifluoromethyl)benzyl)acrylamide (DKM 2-16). Following General Procedure A starting from 4-(trifluoromethyl)benzylamine (516 mg, 2.9 mmol), product was
obtained after silica gel chromatography (20% to 30% ethyl acetate in hexanes) in 24% yield as a white solid (165 mg). ¾ NMR (600MHz, CDCb): δ 7.53 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 6.58 (s, 1H), 6.28 (dd, J = 1.5, 17.0 Hz, 1H), 6.14 (dd, J = 10.1, 17.0 Hz, 1H), 5.64 (dd, J = 1.5, 10.1 Hz, 1H), 4.50 (d, J = 6.0 Hz, 2H). ¹³C NMR (150MHz, CDCb): δ 165.9, 142.3, 130.5, 130.0, 129.7, 128.0, 127.3, 125.73, 125.69, 125.66, 125.62, 43.1.


[0680] Ethyl l-acryloylpiperidine-4-carboxylate (DKM 2-120). Following General Procedure A starting from ethyl isonipecotate (459 mg, 2.9 mmol), product was obtained after silica gel chromatography (20% to 45% ethyl acetate in hexanes) in 71% yield as a pale yellow liquid (440 mg). ¾NMR (400MHz, CDCb): δ 6.40 (dd, J = 10.6, 16.8 Hz, 1H), 6.04 (dd, J = 2.0, 16.8 Hz, 1H), 5.47 (dd, J = 2.0, 10.6 Hz, 1H), 4.23 (d, J = 13.2 Hz, 1H), 3.93 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 14.0 Hz, 1H), 2.99 (t, J = 11.0 Hz, 1H), 2.70 (t, J = 11.0 Hz, 1H), 2.27 (tt, J = 4.1, 10.7 Hz, 1H), 1.77-1.73 (m, 2H), 1.51-1.42 (m, 2H), 1.05 (t, J = 7.1 Hz, 3H). ¹³C NMR (100MHz, CDCb): δ 173.7, 165.0, 127.5, 127.2, 60., 44.7, 41.0, 40.5, 28.2, 27.4, 13.8. HRMS (+ESI): Calculated: 212.1281 (C₉H₉NO). Observed: 212.1276.

[0681] N-benzhydrylacryl amide (DKM 3-4). Following General Procedure A starting from benzhydrylamine (459 mg, 3.0 mmol), product was obtained after silica gel chromatography (0% to 20%, ethyl acetate in hexanes) and recrystallization from toluene in 15% yield as a white solid (110 mg). ¾ NMR (400MHz, (CD₃)₂CO): δ 7.35-7.23 (m, 10H), 6.45 (dd, J = 10.2, 17.0 Hz, 1H), 6.36-6.34 (m, 1H), 6.25 (dd, J = 2.2, 17.0 Hz, 1H), 5.61 (dd, J = 2.2, 10.2 Hz, 1H). ¹³C NMR (100MHz, (CD₃)₂CO): δ 164.84, 164.76, 143.51, 143.48, 132.51, 132.47, 129.4, 128.5, 128.0, 126.3, 57.5, 57.4. HRMS (+ESI): Calculated: 238.1226 (C₁₉H₁₈N₂O). Observed: 238.1222.
l-(4-phenylpiperazin-l-yl)prop-2-en-l-one (DKM 3-5). Following General Procedure A starting from 1-phenylpiperazine (479 mg, 3.0 mmol), product was obtained after silica gel chromatography (30% to 70% ethyl acetate in hexanes) in 87% yield as a yellow oil (555 mg). ¾ NMR (400MHz, CDCb): δ 7.30-7.25 (m, 2H), 6.92-6.87 (m, 3H), 6.60 (dd, J = 10.5, 16.8 Hz, 1H), 5.72 (dd, J = 2.0, 10.5 Hz, 1H), 6.33 (dd, J = 2.0, 16.8 Hz, 1H), 5.72 (dd, J = 2.0, 10.5 Hz, 1H), 3.81 (s, 2H), 3.66 (s, 2H), 3.14 (t, J = 5.2 Hz, 4H). ¹³C NMR (100MHz, CDCb): δ 165.0, 150.6, 18.9, 127.8, 127.1, 120.2, 116.3, 49.4, 48.9, 45.3, 41.5. HRMS (+ESI): Calculated: 217.1335 (C13H17N2O). Observed: 217.1332.

N-(4-acetylphenyl)acrylamide (DKM 3-7). Following General Procedure A starting from 4-aminoacetophenone (398 mg, 2.9 mmol), product was obtained after silica gel chromatography (20% to 50% ethyl acetate in hexanes) in 45% yield as a white solid (253 mg). ¾ NMR (400MHz, CDCb): δ 8.40 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 8.7 Hz, 2H), 6.46 (dd, J = 1.3, 16.9 Hz, 1H), 6.34 (dd, J = 10.1, 16.9 Hz, 1H), 5.79 (dd, J = 1.3, 10.1 Hz, 1H), 2.57 (s, 3H). ¹³C NMR (100MHz, CDCb): δ 197.5, 164.1, 142.5, 133.0, 130.9, 129.9, 128.9, 119.4, 26.6. HRMS (+ESI): Calculated: 190.0863 (C11H12NO2). Observed: 190.0858.

l-(4-methylpiperidin-l-yl)prop-2-en-l-one (DKM 3-8). Following General Procedure A starting from 4-methylpiperidine (295 mg, 3.0 mmol), product was obtained after silica gel chromatography (10% to 30% ethyl acetate in hexanes) in 84% yield as a yellow oil (385 mg). ¹HNMR (400MHz, CDCb): δ 6.51 (dd, J = 10.6, 16.5 Hz, 1H), 6.16
(dd, \( J = 2.0, 16.5 \) Hz, 1H), 5.57 (dd, \( J = 2.0, 10.6 \) Hz, 1H), 4.53 (d, \( J = 13.1 \) Hz, 1H), 3.88 (d, \( J = 13.3 \) Hz, 1H), 2.99-2.92 (m, 1H), 2.55 (td, \( J = 2.1, 12.8 \) Hz, 1H), 1.62 (d, \( J = 13.1 \) Hz, 2H), 1.57-1.49 (m, 1H), 1.10-0.98 (m, 2H), 0.87 (d, \( J = 6.5 \) Hz, 3H). \(^{13}\)C NMR (100MHz, CDCb): \( \delta \) 165.2, 128.0, 127.0, 46.2, 42.4, 34.7, 33.7, 31.1, 21.7. HRMS (+ESI): Calculated: 154.1226 (\( \text{C}_9\text{H}_{16}\text{NO} \)). Observed: 154.1224.

![N-(2,2-diethoxyethyl)acrylamide](image)

\[0685\] N-(2,2-diethoxyethyl)acrylamide (DKM 3-9). Following General Procedure A starting from aminoacetaldehyde diethyl acetal (402 mg, 3.0 mmol), product was obtained after silica gel chromatography (10% to 40% ethyl acetate in hexanes) in 75% yield as a clear oil (313 mg). ^{1}H NMR (400MHz, CDCb): 6.25-6.19 (m, 2H), 6.09 (dd, \( J = 10.1, 17.0 \) Hz, 1H), 5.56 (dd, \( J = 1.7, 10.1 \) Hz, 1H), 4.48 (t, \( J = 5.3 \) Hz, 1H), 3.64 (dq, \( J = 7.1, 9.4 \) Hz, 2H), 3.47 (dq, \( J = 7.1, 9.4 \) Hz, 2H), 3.38 (t, \( J = 5.6 \) Hz, 2H), 1.13 (t, \( J = 7.1 \) Hz, 6H). \(^{13}\)C NMR (100MHz, CDCb): \( \delta \) 165.7, 130.6, 126.4, 100.6, 62.8, 42.0, 15.2. HRMS (+ESI): Calculated: 188.1281 (\( \text{C}_9\text{H}_{18}\text{NO}_3 \)). Observed: 188.1278.

![1-acryloylpiperidine-4-carbonitrile](image)

\[0686\] 1-acryloylpiperidine-4-carbonitrile (DKM 3-11). Following General Procedure A starting from piperidine-4-carbonitrile (329 mg, 3.0 mmol), product was obtained after silica gel chromatography (30% to 70% ethyl acetate in hexanes) in 48% yield as a colorless oil (234 mg). ^{1}H NMR (400MHz, CDCb): 6.49 (dd, \( J = 10.6, 16.8 \) Hz, 1H), 6.19 (d, \( J = 1.9 \), 16.8 Hz, 1H), 5.64 (dd, \( J = 1.9, 10.6 \) Hz, 1H), 3.77-3.46 (m, 4H), 2.88-2.82 (sept, \( J = 3.9 \) Hz, 1H), 1.90-1.73 (m, 4H). \(^{13}\)C NMR (100MHz, CDCb): \( \delta \) 165.4, 128.3, 127.3, 120.8, 43.8, 39.9, 29.1, 28.1, 26.3. HRMS (+ESI): Calculated: 165.1022 (\( \text{C}_9\text{H}_{13}\text{N}_2\text{O} \)). Observed: 165.1020.
N-(3-(methylthio)propyl)acrylamide (DKM 3-12). Following General Procedure A starting from 3-(methylthio)propylamine (313 mg, 3.0 mmol), product was obtained after silica gel chromatography (20% to 60% ethyl acetate in hexanes) in 69% yield as a colorless oil (328 mg). ¾ NMR (400MHz, CDCb): δ 6.79 (s, 1H), 6.19 (dd, J = 2.2, 17.0 Hz, 1H), 6.11 (dd, J = 9.6, 17.0 Hz, 1H), 5.55 (dd, J = 2.2, 9.6 Hz, 1H), 3.35 (q, J = 6.5 Hz, 2H), 2.47 (t, J = 7.2 Hz, 2H), 2.02 (s, 3H), 1.78 (quint, J = 7.0 Hz, 2H). 13C NMR (100MHz, CDCb): δ 165.9, 131.0, 126.1, 38.6, 31.6, 28.6, 15.4. HRMS (+ESI): Calculated: 160.0791 (C7H14NOS). Observed: 160.0788.

N-(cyclohexylmethyl)acrylamide (DKM 3-13). Following General Procedure A starting from cyclohexanemethylamine (331 mg, 2.9 mmol), product was obtained after silica gel chromatography (10% to 50% ethyl acetate in hexanes) in 67% yield as a pale yellow solid (330 mg). ¾ NMR (400MHz, CDCb): δ 6.51 (s, 1H), 6.22 (dd, J = 2.5, 17.0 Hz, 1H), 6.15 (dd, J = 9.3, 17.0 Hz, 1H), 5.55 (dd, J = 2.5, 9.3 Hz, 1H), 3.11 (t, J = 6.5 Hz, 2H), 1.70-1.58 (m, 5H), 1.51-1.40 (m, 1H), 1.22-1.04 (m, 3H), 0.93-0.83 (m, 2H). 13C NMR (100MHz, CDCb): δ 165.9, 131.2, 125.9, 45.9, 38.0, 30.9, 26.4, 25.8. HRMS (+ESI): Calculated: 168.1383 (C10H14NOS). Observed: 168.1380.

1-(4-(4-acetylphenyl)piperazin-1-yl)prop-2-en-1-one (DKM 3-29). Following General Procedure A starting from 4'-piperazinoacetophenone (607 mg, 3.0 mmol), product was obtained after silica gel chromatography (50% to 85% ethyl acetate in hexanes) in 65% yield as a yellow solid (496 mg). ¾ NMR (400MHz, CDCb): δ 7.79 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 9.0 Hz, 2H), 7.42 (s, 2H), 7.32 (d, J = 9.0 Hz, 2H), 7.14 (t, J = 9.0 Hz, 2H), 6.91 (t, J = 9.0 Hz, 2H), 6.86 (s, 1H), 3.93-3.82 (m, 2H), 3.61-3.50 (m, 2H), 3.03-2.91 (m, 2H), 2.78-2.68 (m, 2H), 1.72 (s, 3H), 1.41-1.30 (m, 2H), 0.91-0.80 (m, 2H). HRMS (+ESI): Calculated: 326.1059 (C15H16N2OS). Observed: 326.1052.
6.78 (d, J = 9.0 Hz, 2H), 6.54 (dd, J = 10.5, 16.8 Hz, 1H), 6.25 (dd, J = 1.9, 16.8 Hz, 1H), 5.66 (dd, J = 1.9, 10.5 Hz, 1H), 3.75 (s, 2H), 3.66 (s, 2H), 3.31-3.29 (m, 4H), 2.42 (s, 3H). 

$^{13}$C NMR (100MHz, CDCb): δ 196.3, 165.2, 153.4, 130.2, 128.3, 127.9, 127.0, 113.5, 47.3, 47.0, 45.0, 41.2, 26.0. HRMS (+ESI): Calculated: 259.1441(C$_{15}$H$_{11}$NO$_{2}$Cl). Observed: 259.1436.

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**[0690]** N-(4-(4-chlorophenoxy)phenyl)acrylamide (DKM 3-30). Following General Procedure A starting from 4-(4-chlorophenoxy)aniline (440 mg, 2.0 mmol), product was obtained after silica gel chromatography (10% to 30% ethyl acetate in hexanes) in 33% yield as a white solid (180 mg). ¾ NMR (400MHz, CDCb): δ 8.00 (s, 1H), 7.56 (d, J = 8.9 Hz, 2H), 7.29-7.25 (m, 2H), 6.96-6.88 (m, 4H), 6.43 (dd, J = 1.4, 16.9 Hz, 1H), 6.30 (dd, J = 10.1, 16.9 Hz, 1H), 5.75 (dd, J = 1.4, 10.1 Hz, 1H). 

$^{13}$C NMR (100MHz, CDCb): δ 163.9, 156.2, 153.4, 133.7, 131.2, 129.8, 128.2, 128.0, 122.1, 119.8, 119.7. HRMS (+ESI): Calculated: 272.0484 (C$_{15}$H$_{11}$NO$_{2}$Cl). Observed: 272.0479.

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**[0691]** N-(4-fluorophenyl)acrylamide (DKM 3-31). Following General Procedure A starting from 4-fluoroaniline (239 mg, 2.2 mmol), product was obtained after silica gel chromatography (20% to 30% ethyl acetate in hexanes) in 16% yield as a white solid (56 mg). ¾ NMR (600MHz, MeOD): δ 7.64-7.60 (m, 2H), 7.07-7.03 (m, 2H), 6.41 (dd, J = 9.8, 17.0 Hz, 1H), 6.35 (dd, J = 2.1, 17.0 Hz, 1H), 5.76 (dd, J = 2.1, 9.8 Hz, 1H). 

$^{13}$C NMR (150MHz, MeOD): δ 166.0, 161.56, 160.0, 135.93, 135.91, 132.3, 127.8, 123.2, 123.1, 116.4, 116.2. HRMS (-ESI): Calculated: 164.0517 (C$_{9}$H$_{7}$NOC). Observed: 164.0517.
N-(sec-butyl)acrylamide (DKM 3-32). Following General Procedure A starting from sec-butylamine (222 mg, 3.0 mmol), product was obtained after silica gel chromatography (10% to 40% ethyl acetate in hexanes) in 74% yield as a yellow oil (287 mg). ¾ NMR (400MHz, CDCl₃): δ 6.56 (d, J = 5.6 Hz, 1H), 6.17 (s, 1H), 6.16 (d, J = 3.5 Hz, 1H), 5.51 (dd, J = 4.3, 7.6 Hz, 1H), 3.93-3.83 (m, 1H), 1.47-1.36 (m, 2H), 1.06 (d, J = 6.6 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H). ¹³C NMR (100MHz, CDCl₃): δ 165.2, 131.4, 125.6, 46.6, 29.5, 20.2, 10.4. HRMS (+ESI): Calculated: 128.1070 (C₇H₁₄NO). Observed: 128.1069.

1-(4-(4-methoxyphenyl)piperazin-1-yl)prop-2-en-1-one (DKM 3-36). Following General Procedure A starting from 1-(4-methoxyphenyl)piperazine (388 mg, 2.0 mmol), product was obtained after silica gel chromatography (20% to 80% ethyl acetate in hexanes) in 29% yield as a white solid (143 mg). ¾ NMR (400MHz, CDCl₃): δ 6.87-6.79 (m, 4H), 6.57 (dd, J = 10.5, 16.8 Hz, 1H), 6.28 (dd, J = 1.9, 16.8 Hz, 1H), 5.68 (dd, J = 1.9, 10.5 Hz, 1H), 3.79 (s, 2H), 3.72 (s, 3H), 3.66 (s, 2H), 3.01 (t, J = 5.1 Hz, 4H). ¹³C NMR (100MHz, CDCl₃): δ 165.2, 154.3, 145.1, 128.0, 127.3, 118.8, 114.4, 55.4, 51.3, 50.7, 45.8, 41.9. HRMS (+ESI): Calculated: 247.1441 (C₁₄H₁₉N₂O₂). Observed: 247.1443.

N-tritylacrylamide (DKM 3-41). Following General Procedure A starting from triphenylmethylamine (386 mg, 1.5 mmol), product was obtained after silica gel chromatography (5% to 30% ethyl acetate in hexanes) in 74% yield as a white solid (346
mg). ¾ NMR (400MHz, CDCl₃): δ 7.38-7.27 (m, 15H), 6.83 (s, 1H), 6.28-6.26 (m, 2H), 5.66 (dd, J = 3.9, 7.2 Hz, 1H). ¹³C NMR (100MHz, CDCl₃): δ 164.6, 144.6, 131.5, 128.8, 128.1, 127.2, 127.1, 70.7. HRMS (+ESI): Calculated: 314.1539 (C₂₂H₂₀NO). Observed: 314.1542.

[0695] (E)-N-(3,7-dimethylocta-2,6-dien-1-yl)acrylamide (DKM 3-42). Following General Procedure A starting from geranylamine (462 mg, 3.0 mmol), product was obtained after silica gel chromatography (10% to 40% ethyl acetate in hexanes) in 23% yield as a colorless oil (141 mg). ¾NMR (400MHz, CDCl₃): δ 6.25 (dd, J = 1.5, 17.0 Hz, 1H), 6.09 (dd, J = 10.2, 17.0 Hz, 1H), 5.83 (s, 1H), 5.59 (dd, J = 1.5, 10.2 Hz, 1H), 5.22-5.18 (m, 1H), 5.07-5.03 (m, 1H), 3.90 (t, J = 6.2 Hz, 2H), 2.09-2.03 (m, 2H), 2.00-1.97 (m, 2H), 1.65 (s, 6H), 1.57 (s, 3H). ¹³C NMR (100MHz, CDCl₃): δ 165.5, 140.2, 131.8, 131.0, 126.2, 123.9, 119.7, 39.6, 37.6, 265, 25.8, 17.8, 16.4. HRMS (+ESI): Calculated: 208.1696 (C₁₃H₂₂NO). Observed: 208.1697.

[0696] N-(benzo[d][1,3]dioxol-5-ylmethyl)acrylamide (DKM 3-43). Following General Procedure A starting from piperonylamine (312 mg, 2.1 mmol), product was obtained after silica gel chromatography (20% to 50% ethyl acetate in hexanes) in 74% yield as a white solid (315 mg). ¾ NMR (400MHz, CDCl₃): δ 6.78 (s, 1H), 6.71 (s, 1H), 6.68 (s, 2H), 6.22 (dd, J = 1.9, 17.0 Hz, 1H), 6.13 (dd, J = 9.9, 17.0 Hz, 1H), 5.87 (s, 2H), 5.58 (dd, J = 1.9, 9.9 Hz, 1H), 4.30 (d, J = 5.8 Hz, 2H). ¹³C NMR (100MHz, CDCl₃): δ 165.7, 147.8, 146.9, 132.0, 130.8, 126.6, 121.1, 108.4, 108.2, 101.0, 43.4. HRMS (+ESI): Calculated: 206.0812 (C₁₁H₁₂NO₃). Observed: 206.0808.

[0697] N-decylacrylamide (TRH 1-12). Following General Procedure A starting from decylamine (479 mg, 3.0 mmol), product was obtained after silica gel chromatography (20%
to 40% ethyl acetate in hexanes) in 26% yield as a white solid (163 mg). ¾ NMR (400MHz, CDCb): δ 6.54 (s, 1H), 6.21 (dd, J = 2.0, 16.9 Hz, 1H) 6.13 (dd, 7 = 9.7, 16.9 Hz, 1H), 5.55 (dd, 7 = 2.0, 9.7 Hz, 1H), 3.25 (q, 7 = 6.7 Hz, 2H), 1.50-1.45 (m, 2H), 1.29-1.20 (m, 14H), 0.83 (t, 7 = 6.7 Hz, 3H). ¹³C NMR (100MHz, CDCb): δ 165.8, 131.2, 125.9, 71.9, 39.7, 31.9, 29.6, 29.6, 29.38, 29.35, 27.0, 22.7, 14.1. HRMS (+ESI): Calculated: 212.2009 (C₉H₁₈O₂N). Observed: 212.2009.

[0698] N-(2,4-dimethoxybenzyl)acrylamide (TRH 1-13). Following General Procedure A starting from 2,4-dimethoxybenzylamine (514 mg, 3.0 mmol), product was obtained after silica gel chromatography (20% to 60% ethyl acetate in hexanes) in 11% yield as a white solid (73 mg). ¾ NMR (400MHz, CDCb): δ 7.17 (d, 7 = 8.1 Hz, 1H), 6.43-6.39 (m, 2H), 6.26-6.22 (m, 2H), 6.07 (dd, 7 = 10.7, 17.0 Hz, 1H), 5.57 (dd, 7 = 1.4, 10.7 Hz, 1H), 4.41 (d, 7 = 5.8 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H). ¹³C NMR (100MHz, CDCb): δ 165.2, 160.6, 158.6, 131.1, 130.7, 126.2, 118.7, 104.0, 98.6, 55.5, 55.4, 39.0. HRMS (+ESI): Calculated: 222.1 125 (C₁₂H₁₆N₂O₃). Observed: 222.1 124.

[0699] N-Phenylacrylamide (TRH 1-19). Following General Procedure A starting from aniline (277 mg, 3.0 mmol), product was obtained after recrystallization from a 1:20 ethyl acetate:hexanes mixture in 46% yield as a white solid (200 mg). ¾ NMR (400MHz, CDCb): δ 8.59 (s, 1H), 7.63 (d, 7 = 7.9 Hz, 2H), 7.30 (t, 7 = 7.9 Hz, 2H), 7.1 1 (t, 7 = 7.4 Hz, 1H), 6.44-6.33 (m, 2H), 5.70 (dd, 7 = 2.8, 8.9 Hz, 1H). ¹³C NMR (100MHz, CDCb): δ 164.3, 138.0, 131.4, 129.0, 127.7, 124.6, 120.5. HRMS (+ESI): Calculated: 148.0757 (C₉H₁₀NO). Observed: 148.0754.
N-(1-phenyl ethyl)acrylamide (TRH 1-20). Following General Procedure A starting from 1-phenylethan-1-amine (387 mg, 3.0 mmol), product was obtained after silica gel chromatography (5% to 20% ethyl acetate in hexanes) in 46% yield as a white solid (315 mg). ³¹NMR (400MHz, CDCb): δ 7.61 (d, J = 7.8 Hz, 1H) 7.37-7.24 (m, 5H), 6.33-6.24 (m, 2H), 5.57 (dd, J = 4.8, 7.9 Hz, 1H), 5.20 (quint, J = 7.2 Hz, 1H), 1.49 (d, J = 7.0 Hz, 3H). ¹³C NMR (100MHz, CDCb): δ 165.0, 143.4, 131.1, 128.4, 126.9, 126.0, 126.0, 48.7, 21.8. HRMS (+ESI): Calculated: 176.1070 (C11H14NO). Observed: 176.1067.

N-(4-methoxyphenyl)acrylamide (TRH 1-32). Following General Procedure A starting from p-anisidine (258 mg, 2.0 mmol), product was obtained after silica gel chromatography (10% to 50% ethyl acetate in hexanes) in 58% yield as a white solid (216 mg). ³¹NMR (400MHz, CDCb): δ 8.94 (s, 1H), 7.48 (d, J = 9.1 Hz, 2H), 6.78 (d, J = 9.1 Hz, 2H), 6.34 (d, J = 5.6 Hz, 2H), 5.61 (t, J = 5.9 Hz, 1H), 3.73 (s, 3H). ¹³C NMR (100MHz, CDCb): δ 164.3, 156.4, 131.4, 131.1, 127., 122.3, 114.0, 55.4. HRMS (+ESI): Calculated: 178.0863 (C10H12O2N). Observed: 178.0859.

N-(2-methylbenzyl)acrylamide (TRH 1-54). Following General Procedure A starting from 2-methylbenzylamine (240 mg, 2.0 mmol), product was obtained after silica gel chromatography (30% to 40% ethyl acetate in hexanes) in 73% yield as a white solid (257 mg). ³¹NMR (400MHz, CDCb): δ 7.26-7.12 (m, 4H), 6.66 (s, 1H), 6.24-6.12 (m, 2H), 5.57 (dd, J = 9.5, 2.2 Hz, 1H), 4.39 (d, J = 5.4 Hz, 2H), 2.27 (s, 3H). ¹³C NMR (100MHz, CDCb): δ 165.6, 136.3, 135.7, 130.7, 130.4, 128.4, 127.6, 126.4, 126.1, 41.6, 19.0. HRMS (+ESI): Calculated: 176.1070 (C11H14NO). Observed: 176.1067.
Ethyl 4-(2-chloroacetyl)piperazine-1-carboxylate (DKM 2-52). Following General Procedure B starting from ethyl 1-piperazinecarboxylate (477 mg, 3.0 mmol) product was obtained after silica gel chromatography (0% to 80% ethyl acetate in hexanes) in 80% yield as a pale yellow oil (569 mg). ³¹NMR (400MHz, CDCb): δ 4.04-3.99 (m, 4H), 3.48-3.34 (m, 8H), 1.14 (t, J = 7.1 Hz, 3H). ¹³C NMR (100MHz, CDCb): δ 165.1, 155.0, 61.5, 45.8, 43.3, 43.0, 41.7, 40.7, 14.4. HRMS (+SI): Calculated: 235.0844 (C₉H₁₆CIN₂O₃). Observed: 235.0842.

N-benzyl-2-chloroacetamide (DKM 2-67). Following General Procedure B starting from benzylamine (430 mg, 3.1 mmol) product was obtained after silica gel chromatography (0% to 30% ethyl acetate in hexanes) in 70% yield as a white solid (416 mg). ³¹NMR (400MHz, CDCb): δ 7.40-7.31 (m, 5H), 7.08 (s, Is), 4.50 (d, J = 5.8 Hz, 2H), 4.09 (s, 2H). ¹³C NMR (100MHz, CDCb): δ 166.0, 137.4, 128.8, 127.8, 43.8, 42.6. HRMS (-ESI): Calculated: 182.0378 (C₉H₉NOCI). Observed: 182.0378.

2-Chloro-l-(pyrrolidin-l-yl)ethan-l-one (DKM 2-71). Following General Procedure B starting from pyrrolidine (511 mg, 3.0 mmol) product was obtained after silica gel chromatography (0% to 30% ethyl acetate in hexanes) in 83% yield as a clear oil (368 mg). ³¹NMR (400MHz, CDCb): δ 3.94 (s, 2H), 3.41 (quint, J = 7.2 Hz, 4H), 1.91 (quint, J = 6.3 Hz, 2H), 1.80 (quint, J = 6.6 Hz, 2H). ¹³C NMR (100MHz, CDCb): δ 164.7, 46.5, 46.3, 42.1, 26.1, 24.1. HRMS (+ESI): Calculated: 170.0343 (C₉H₁₀ClNNaO). Observed: 170.0343.
[0706] 2-Chloro-N-decylacetamide (DKM 2-72). Following General Procedure B starting from decylamine (472 mg, 3.0 mmol) product was obtained after silica gel chromatography (0% to 40% ethyl acetate in hexanes) in 81% yield as a white solid (555 mg). ¾ NMR (400MHz, CDCl₃): δ 6.71 (s, 1H), 3.97 (s, 2H), 3.22 (q, J = 6.8 Hz, 2H), 1.51-1.44 (m, 2H), 1.24-1.19 (m, 14 H), 0.81 (t, J = 6.8 Hz, 3H). ¹³C NMR (100MHz, CDCl₃): δ 165.8, 42.7, 39.9, 31.9, 29.5, 29.29, 29.27, 29.22, 26.8, 22.6, 14.1. HRMS (+ESI): Calculated: 234.1619 (C₁₂H₂₅CINO). Observed: 234.1618.

[0707] 2-chloro-N-(4-methoxybenzyl)acetamide (DKM 2-83). Following General Procedure B starting from 4-methoxybenzylamine (430 mg, 3.1 mmol) product was obtained after silica gel chromatography (0% to 40% ethyl acetate in hexanes) in 55% yield as an off-white solid (369 mg). ¾ NMR (400MHz, CDCl₃): δ 7.20 (d, J = 8.6 Hz, 2H), 6.91 (s, 1H), 6.86 (d, J = 8.6 Hz, 2H), 4.40 (d, J = 5.7 Hz, 2H), 4.05 (s, 2H), 3.78 (s, 3H). ¹³C NMR (100MHz, CDCl₃): δ 165.9, 159.2, 129.4, 129.2, 114.2, 55.3, 43.4, 42.7. HRMS (+ESI): Calculated: 214.0629 (C₁₀H₁₃CINO₂). Observed: 214.0627.

[0708] References (Example 1)


ProLuCID: An improved SEQUEST-like algorithm with enhanced sensitivity and specificity.


[0710] 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.
WHAT IS CLAIMED IS:

1. A method of treating cancer, said method comprising administering to a subject in need thereof an effective amount of a compound having the formula:

\[
\begin{array}{c}
\text{(I),}
\end{array}
\]

wherein,

- \( R^1 \) is independently halogen, -CX, -CHX, -CH2X, -OCX, -
- OCH2X, -OCHX, -CN, -SONHR, -SOiNR, -NHC(0)NR, -N(0)m, -NR
- C(0)R, -C(0)-OR, -C(0)NR, -OR, -NR, -NRC(0)R, -NR, -NR
- R, substituted 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;
- \( z_1 \) is an integer from 0 to 5;
- \( L^1 \) is a bond, -S(0)2, -NR, -0, -S, -C(0), -C(0)NR, -NR4
- C(0)(0)NH, -NHC(0)NR, -C(0)0, -OC(O), -CH2NR, substituted or unsubstituted
- alkylene, substituted or unsubstituted heteroalkyl ene, substituted or unsubstituted
cycloalkyl ene, substituted or unsubstituted heterocycloalkyl ene, substituted or unsubstituted
arylene, or substituted or unsubstituted heteroarylene;

- \( R^4 \) is hydrogen, -CX3, -CHX2, -CH2X, -OCX3, -OCH2X,
- OCHX, -CN, -C(0)R4C, -C(0)-OR4C, -C(0)NR4A4R4B, -OR4D, substituted or unsubstituted
alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
- substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
- or unsubstituted heteroaryl;

- \( L^2 \) is a bond, -S(0)2, -NR5, -0, -S, -C(0), -C(0)NR5, -NR5C(0),
- NR5C(0)NH, -NHC(0)NR5, -C(0)0, -OC(O), -CH2NR5, substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkyl ene, substituted or unsubstituted
cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted
arylene, or substituted or unsubstituted heteroarylene;
R^5 is hydrogen, -CX\textsubscript{3}, -CHX\textsubscript{2}, -CH\textsubscript{2}X\textsubscript{5}, -OCX\textsubscript{5},

OCH\textsubscript{2}X\textsubscript{5}, -OCHX\textsubscript{5}, -CN, -C(0)R \textsuperscript{SC}, -C(0)-OR \textsuperscript{SC}, -C(0)NR \textsuperscript{SA}R \textsuperscript{SB}, -OR \textsuperscript{SD}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

Each R\textsuperscript{1A}, R\textsuperscript{1B}, R\textsuperscript{1C}, R\textsuperscript{1D}, R\textsuperscript{4A}, R\textsuperscript{4B}, R\textsuperscript{4C}, R\textsuperscript{4D}, R\textsuperscript{5A}, R\textsuperscript{5B}, R\textsuperscript{5C}, and R\textsuperscript{5D} is independently hydrogen, -CX\textsubscript{3}, -CN, -COOH, -CONH\textsubscript{2}, -CH\textsubscript{2}X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R\textsuperscript{1A} and R\textsuperscript{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R\textsuperscript{4A} and R\textsuperscript{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R\textsuperscript{5A} and R\textsuperscript{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

each X, X\textsubscript{1}, X\textsubscript{4}, and X\textsubscript{5} is independently -F, -Cl, -Br, or -I;

n\textsubscript{l}, n\textsubscript{4}, and n\textsubscript{5} are independently an integer from 0 to 4; and

m\textsubscript{l}, m\textsubscript{4}, m\textsubscript{5}, v\textsubscript{l}, v\textsubscript{4}, and v\textsubscript{5} are independently an integer from 1 to 2.

2. The method of claim 1, wherein the compound has the formula:

(\textit{R}^1)_{z1}\textsuperscript{L^2}\textsuperscript{E}

(Ia).

3. The method of claim 1, wherein the compound has the formula:

(\textit{R}^1)_{z1}\textsuperscript{N}\textsuperscript{L^2}\textsuperscript{E}

(lb).

4. The method of claim 1, wherein the compound has the formula:
The method of claim 1, wherein the compound has the formula:

(Ii).

The method of claim 1, wherein the compound has the formula:

(Iia).

The method of claim 1, wherein R₁ is independently halogen, -CX₁, -CH₂X₁, -OCX₁, -OCH₂X₁, -OCH₃X₁, -CN, -SR₁, -NR₁A₁R₁B₁, substituted or unsubstituted alky, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The method of claim 1, wherein R₁ is independently halogen, -CX₁, -CH₂X₁, -OCX₁, -OCH₂X₁, -OCH₃X₁, -CN, -SH, -NH₂, -C(0)OH, -C(0)NH₂, -OH, -OCH₃, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆-C₁₂ cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

The method of claim 1, wherein R₁ is independently halogen, -CX₁, -CH₂X₁, -OCX₁, -OCH₂X₁, -OCH₃X₁, -CN, -SH, -NH₂, -C(0)OH, -C(0)NH₂, -OH, -OCH₃, substituted or unsubstituted Ci-Cs alkyl, or substituted or unsubstituted 2 to 8 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.
11. The method of claim 1, wherein $R^1$ is independently
- $\text{OCH}_3$.

12. The method of claim 1, wherein $z_1$ is 0.

13. The method of claim 1, wherein the compound has the formula:

$$
R^{1.2}_1 - L^1 - L^2 - E
$$

wherein

- $R^{1.1}$ and $R^{1.2}$ are independently hydrogen, halogen, $-\text{CX}_3^1$, $-\text{CHX}^\Delta$,
- $-\text{CH}_2^\Delta$, $-\text{OCX}_1^1$, $-\text{OCH}_2^\Delta$, $-\text{CN}$, $-\text{ONiR}_{\text{D}^\Delta}$, $-\text{SO}_i\text{NR}^1\text{A}^\text{R}^1\text{B}^\text{B}^\text{D}^\text{D}^\text{E}^\text{E}^\text{F}^\text{F}^\text{G}^\text{G}^\text{H}^\text{H}^\text{I}^\text{I}^\text{J}^\text{J}^\text{K}^\text{K}$,
- $-\text{N}(0)\text{i}_1$, $-\text{NR}^1\text{A}^\text{R}^1\text{B}^\text{B}^\text{D}^\text{D}^\text{E}^\text{E}^\text{F}^\text{F}^\text{G}^\text{G}^\text{H}^\text{H}^\text{I}^\text{I}^\text{J}^\text{J}^\text{K}^\text{K}$,
- substituted 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 $R^{1.1}$ and $R^{1.2}$ may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

14. The method of claim 13, wherein the compound has the formula:

$$
R^{1.2}_1 - L^2 - E
$$

(IIIa).

15. The method of claim 13, wherein the compound has the formula:

$$
R^{1.2}_1 - N - L^2 - E
$$

(IIIb).

16. The method of claim 13, wherein $R^{1.1}$ and $R^{1.2}$ are independently
- halogen, $-\text{CX}^\Delta$, $-\text{CHX}^\Delta$, $-\text{CH}_2^\Delta$, $-\text{OCX}^\Delta$, $-\text{OCH}_2^\Delta$, $-\text{CN}$, $-\text{SR}^\Delta$, $-\text{NR}^1\text{AR}^1\text{BR}^1\text{D}^\text{D}^\text{E}^\text{E}^\text{F}^\text{F}^\text{G}^\text{G}^\text{H}^\text{H}^\text{I}^\text{I}^\text{J}^\text{J}^\text{K}^\text{K}$,
- substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

17. The method of claim 13, wherein $R^{1,1}$ and $R^{1,2}$ are independently halogen, -CX\(^\wedge\), -CHX\(^\wedge\), -CH\(_2\)X\(^1\), -OCX\(^\wedge\), -OCH\(_2\)X\(^1\), -OCHX\(^\wedge\), -CN, -SH, -NH\(_2\), -C(0)OH, -C(0)NH\(_2\), -OH, -OCH\(_3\), substituted or unsubstituted Ci-C\(_8\) alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C3-C\(_8\) cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C\(_6\)-C\(_2\) cycloalkyl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

18. The method of claim 13, wherein $R^{1,1}$ and $R^{1,2}$ are independently halogen, -CX\(^\wedge\), -CHX\(^\wedge\), -CH\(_2\)X\(^1\), -OCX\(^\wedge\), -OCH\(_2\)X\(^1\), -OCHX\(^\wedge\), -CN, -SH, -NH\(_2\), -C(0)OH, -C(0)NH\(_2\), -OH, -OCH\(_3\), substituted or unsubstituted Ci-C\(_8\) alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl; substituted or unsubstituted C3-C\(_8\) cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

19. The method of claim 13, wherein $R^{1,1}$ and $R^{1,2}$ are independently -OR\(^{1,1}\).

20. The method of claim 13, wherein $R^{1,1}$ and $R^{1,2}$ are independently -OCH\(_3\).

21. The method of claim 1, wherein L\(^1\) is a bond, substituted or unsubstituted Ci-C\(_8\) alkyne, substituted or unsubstituted 2 to 8 membered heteroalkyne, substituted or unsubstituted C3-C\(_8\) cycloalkylene, substituted or unsubstituted 3 to 8 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

22. The method of claim 1, wherein L\(^1\) is a bond.

23. The method of claim 1, wherein L\(^1\) is -CH\(_2\)NR\(^4\).-

24. The method of claim 1, wherein L\(^2\) is -NR\(^5\).-

25. The method of claim 24, wherein R\(^5\) is hydrogen, substituted or unsubstituted Ci-C\(_6\) alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.
26. The method of claim 24, wherein R⁵ is hydrogen or unsubstituted C₃ alkyl.

27. The method of claim 24, wherein R⁵ is hydrogen, unsubstituted methyl, unsubstituted ethyl, unsubstituted hexyl, or unsubstituted benzyl.

28. The method of claim 24, wherein R⁵ is hydrogen.

29. The method of claim 1, wherein E is a covalent cysteine modifier moiety.

30. The method of claim 1, wherein E is:

\[ \text{R}^{15} \text{ is independently hydrogen, halogen, } \text{C}^{15}_{X} \text{, } -\text{CH}^{15}_{X} \text{, } \]
\[ \text{CH}_{2}^{15} \text{X}^{15}_{X}, -\text{CN}, -\text{SO} \text{i}^{15}_{iR} \text{NR}^{15}_{AR} \text{R}^{15}_{B}, -\text{NHNR}^{15}_{AR} \text{R}^{15}_{B}, -\text{ONR}^{15}_{AR} \text{R}^{15}_{B}, \]
\[ -\text{NHC}(0)\text{NHNR}^{15}_{AR} \text{R}^{15}_{B}, -\text{NHC}(0)\text{NR}^{15}_{AR} \text{R}^{15}_{B}, -\text{N}(0)_{n}^{15}_{n}, -\text{NR}^{15}_{AR} \text{R}^{15}_{B}, -\text{C}(0)\text{R}^{15}_{C}, \]
\[ -\text{C}(0)\text{OR}^{15}_{D}, -\text{C}(0)\text{NR}^{15}_{AR} \text{R}^{15}_{B}, -\text{NR}^{15}_{AR} \text{SO} \text{R}^{15}_{D}, -\text{NR}^{15}_{AR} \text{C}(0)\text{R}^{15}_{C}, \]
\[ -\text{NR}^{15}_{AR} \text{OR}^{15}_{C}, -\text{NR}^{15}_{AR} \text{OR}^{15}_{C}, -\text{OCX}^{15}_{X}, -\text{OCHX}^{15}_{X}, \text{substituted or unsubstituted alkyl,} \]
\[ \text{substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;} \]
\[ \text{R}^{16} \text{ is independently hydrogen, halogen, } \text{C}^{16}_{X}, -\text{CH}^{16}_{X}, \]
\[ \text{CH}_{2}^{16} \text{X}^{16}_{X}, -\text{CN}, -\text{SO} \text{i}^{16}_{iR} \text{NR}^{16}_{AR} \text{R}^{16}_{B}, -\text{NHNR}^{16}_{AR} \text{R}^{16}_{B}, -\text{ONR}^{16}_{AR} \text{R}^{16}_{B}, \]
\[ -\text{NHC}(0)\text{NHNR}^{16}_{AR} \text{R}^{16}_{B}, -\text{NHC}(0)\text{NR}^{16}_{AR} \text{R}^{16}_{B}, -\text{N}(0)_{n}^{16}_{n}, -\text{NR}^{16}_{AR} \text{R}^{16}_{B}, \]
\[ -\text{C}(0)\text{R}^{16}_{C}, -\text{C}(0)\text{OR}^{16}_{D}, -\text{C}(0)\text{NR}^{16}_{AR} \text{R}^{16}_{B}, -\text{NR}^{16}_{AR} \text{SO} \text{R}^{16}_{D}, -\text{NR}^{16}_{AR} \text{C}(0)\text{R}^{16}_{C}, \]
\[ -\text{NR}^{16}_{AR} \text{OR}^{16}_{C}, -\text{NR}^{16}_{AR} \text{OR}^{16}_{C}, -\text{OCX}^{16}_{X}, \]
\[ -\text{OCHX}^{16}_{X}, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,} \]
substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

\[ R^{17} \text{ is independently hydrogen, halogen, } \text{CX}^{17}, \text{-CHX}^{17}, \]

\[ \text{CH}_2X^{17}, \text{-CN, -SOnivR}^{17A}, \text{-SO}_{2}X^{17A}R^{17B}, \text{-NHR}^{17A}R^{17B}, \text{-ONR}^{17A}R^{17B}, \]

\[-\text{NHC}=(0)\text{NHNR}^{17A}R^{17B}, \text{-NHRC}=(0)\text{NR}^{17A}R^{17B}, \text{-N(O)_{m}j}_{17}, \text{-NR}^{17A}R^{17B}, \text{-C(0)R}^{17C}, \]

\[-\text{C(0)-OR}^{17C}, \text{-C(O)NR}^{17B}, \text{-OR}^{17D}, \text{-NRC(0)SO}_{2}X^{17D}, \text{-NR}^{17A}C(0)\text{R}^{17C}, \]

\[-\text{NR}^{17A}C(0)\text{OR}^{17C}, \text{-NR}^{17A}\text{OR}^{17C}, \text{-OCX}^{17}, \text{-OCHX}^{17}, \text{substituted or unsubstituted alkyl}, \text{substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl}; \]

\[ R^{18} \text{ is independently hydrogen, -CX}^{18}, \text{-CHX}^{18}, \]

\[ \text{CH}_2X^{18}, \text{-C(O)R}^{18C}, \text{-C(O)OR}^{18C}, \text{-C(O)NR}^{18A}R^{18B}, \text{substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl}; \]

\[ R^{15A}, R^{15B}, R^{15C}, R^{15D}, R^{16A}, R^{16B}, R^{16C}, R^{16D}, R^{17A}, R^{17B}, R^{17C}, R^{17D}, R^{18A}, \]

\[ R^{18B}, R^{18C}, R^{18D}, \text{are independently hydrogen, -CX}_{3}, \text{-CN, -COOH, -CONH}_{2}, \text{-CHX}_{2}, \text{-CH}_{2}X, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; } R^{15A} \text{ and } R^{15B} \text{ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; } R^{16A} \text{ and } R^{16B} \text{ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; } \]

\[ \text{each } X, X^{15}, X^{16}, X^{17} \text{ and } X^{18} \text{ is independently -F, -Cl, -Br, or -I; } \]

\[ \text{nl}5, \text{nl}6, \text{nl}7, \text{vl}5, \text{vl}6, \text{ and vl}7, \text{ are independently an integer from 0 to 4; } \]

\[ \text{and } \]

\[ \text{m}15, \text{m}16, \text{ and m}l7 \text{ are independently and integer from 1 to 2}. \]

31. The method of claim 30, wherein \( R^{15}, R^{16}, R^{17}, \text{ and } R^{18} \text{ are hydrogen.} \)
32. The method of claim 30, wherein E is:

33. The method of claim 30, wherein E is:

34. The method of claim 1, wherein the compound has the formula:
36. The method of claim 1, wherein the cancer is pancreatic cancer.

37. The use of a compound for the preparation of a medicament for the treatment of cancer, wherein the compound has the formula:

\[
\begin{align*}
\text{(I),} \\
\text{wherein,} \\
R^1 &\text{ is independently halogen, } -\text{CX}^\alpha, -\text{CHX}^\alpha, -\text{CH}_2X^\alpha, -\text{OCX}^\alpha, - \\
\text{OCH}_2X^\alpha, -\text{OCHX}^\alpha_2, -\text{CN}, -\text{SONiR}^\alpha_d, -\text{SO}\text{viNR}^\alpha_{\alpha}R^\alpha_{\beta}, -\text{NHC}(0)_\text{NR}^\alpha_{\alpha}R^\alpha_{\beta}, -\text{N}(0)_\text{NR}^\alpha_{\alpha}R^\alpha_{\beta}, -\text{NR}^\alpha_{\alpha}R^\alpha_{\beta}, \\
-\text{C}(0)R^\alpha_{\alpha}C^\alpha, -\text{C}(0)R^\alpha_{\alpha}C^\beta, -\text{C}(0)R^\alpha_{\alpha}C^\gamma, -\text{C}(0)R^\alpha_{\alpha}C^\delta, -\text{R}^\alpha_{\alpha}C^\gamma, -\text{R}^\alpha_{\alpha}C^\delta, -\text{R}^\alpha_{\alpha}C^\eta, -\text{R}^\alpha_{\alpha}C^\zeta, \\
R^\alpha_{\alpha} &\text{ substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,} \\
\text{substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,} \\
\end{align*}
\]
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; two adjacent $R$ substituents may optionally be joined to form a substitute of unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
or unsubstituted heteroaryl;

$z_1$ is an integer from 0 to 5;

$L^1$ is a bond, $-S(0)\_2$, $-NR^4$, $-O$, $-S$, $-C(0)\_2$, $-C(0)NR^4$, $-NR^4C(0)$,

$-NR^4C(0)NH$, $-NHC(0)NR^4$, $-C(0)O$, $-OC(0)$, $-CH_2NR^4$, substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted
aryl, or substituted or unsubstituted heteroaryl;

$R^4$ is hydrogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$,
$-OCHX^4_2$, $-CN$, $-C(0)R^4C^4$, $-C(0)OR^4C^4$, $-C(0)NR^4R^4$, $-OR^4D$, substituted or unsubstituted
alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
or unsubstituted heteroaryl;

$L^2$ is a bond, $-S(0)\_2$, $-NR^5$, $-C^5_\_2$, $-C$, $-C(0)\_2$, $-C(0)NR^5$, $-NR^5C(0)$,

$-NR^5C(0)NH$, $-NHC(0)NR^5$, $-C(0)O$, $-OC(0)$, $-CH_2NR^5$, substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted
aryl, or substituted or unsubstituted heteroaryl;

$R^5$ is hydrogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$,
$OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-C(0)R^5C^5$, $-C(0)OR^5C^5$, $-C(0)NR^5R^5$, $-OR^5D$, substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

$E$ is an electrophilic moiety;

Each $R^{1A}$, $R^{1B}$, $R^{1C}$, $R^{1D}$, $R^{4A}$, $R^{4B}$, $R^{4C}$, $R^{4D}$, $R^{5A}$, $R^{5B}$, $R^{5C}$, and $R^{5D}$ is
independently hydrogen, $-CX_3$, $-CN$, $-COOH$, $-CONH_2$, $-CHX_2$, $-CH_2X$, substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl; $R^{1A}$ and $R^{1B}$ substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; $R^{4A}$ and $R^{4B}$ substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; $R^{4A}$ and $R^{5B}$ substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl;

- each $X$, $X^1$, $X^4$, and $X^5$ is independently -F, -Cl, -Br, or -I;
- $n_1$, $n_4$, and $n_5$ are independently an integer from 0 to 4; and
- $m_1$, $m_4$, $m_5$, $v_1$, $v_4$, and $v_5$ are independently an integer from 1 to 2.

38. A pharmaceutical composition comprising a Ubiquitin-like modifier
activating enzyme 5 (UBA5) inhibitor and a pharmaceutically acceptable excipient.

39. The pharmaceutical composition of claim 38, wherein the Ubiquitin-like modifier activating enzyme 5 (UBA5) inhibitor has the formula:

![Formula Image](image)

wherein,

- $R^1$ is independently halogen, -CX^A, -CHX^A, -CH2X^1, -OCX^A, -
- OCH2X^1, -OCHX^1, -CN, -SO_{1R}^{1D}, -SO_{2R}^{1D}, -NHC(0)NR^{1A} R^{1B}, -N(0)^m_i, -NR^{1A} R^{1B},$
- C(0)R^{1C}, -C(0)-OR^{1C}, -C(0)NR^{1A} R^{1B}, -OR^{1D}, -NR^{1A} SO_2 R^{1D}, -NR^{1A} C(0)R^{1C}, -NR^{1A} C(0)0
- $R^{1C}, -NR^{1A} R^{1C}$, substituted 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;
- $z_1$ is an integer from 0 to 5;
- $L^1$ is a bond, -S(0)$_2$, -NR$_4$, -O-, -C(O)-, -C(0)NR$_4$, -NR$_4$C(0)-,
- NR$_4$C(0)NH-, -NH(C(0))NR$_4$, -C(0)0-, -OC(O)-, -CH2NR$_4$, substituted or unsubstituted
- alkyene, substituted or unsubstituted heteroalkyl ene, substituted or unsubstituted
cycloalkyl ene, substituted or unsubstituted heterocycloalkyl ene, substituted or unsubstituted
- arylene, or substituted or unsubstituted heteroarylene;
- $R^4$ is hydrogen, -CX$_3$, -CHX$_2$, -CH$_2$X$^4$, -OCX$_3$, -OCH$_2$X
- -OCHX$_4$, -CN, -C(0)R$_{4C}$, -C(0)-OR$_{4C}$, -C(0)NR$_{4A}$R$_{1B}$, -OR$_{4D}$, substituted or unsubstituted
alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
or unsubstituted heteroaryl;

L² is a bond, -S(0)_2-, -NR^5-, -O-, -S-, -C(O)-, -C(0)NR^5-, -NR^5C(0)-,
-NR^5C(0)NH-, -NHC(0)NR^5-, -C(0)0-, -OC(O)-, -CH₂NR^5-, substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted
arylene, or substituted or unsubstituted heteroarylene;

R^5 is hydrogen, -CX^5, -CHX^5, -CH₂X^5, -OCX^5, -
OCH₂X^5, -OCHX^5, -CN, -C(0)R^5C, -C(0)OR^5C, -C(0)NR^5A, -OR^5B, substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

Each R^1A, R^1B, R^1C, R^1D, R^4A, R^4B, R^4C, R^4D, R^5A, R^5B, R^5C, and R^5D is
independently hydrogen, -CX^3, -CN, -COOH, -CONH^₂, -CHX^2, -CH₂X, substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl; R^1A and R^1B substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; R^4A and R^4B substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; R^5A and R^5B substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl;

each X, X^1, X^4, and X^5 is independently -F, -Cl, -Br, or -I;
n, n4, and n5 are independently an integer from 0 to 4; and
m, m4, m5, v, v4, and v5 are independently an integer from 1 to 2.

40. A method of inhibiting ubiquitin-like modifier activating enzyme 5
protein (UBA5) activity, said method comprising contacting a UBA5 protein with an
effective amount of a UBA5 inhibitor, wherein the UBA5 inhibitor contacts one or more
amino acids corresponding to N210, E209, L254, S253, and A251 of SEQ ID NO:337.
41. The method of claim 40, wherein the UBA5 inhibitor is an antisense nucleic acid, antibody, or compound.

42. The method of claim 40, said method comprising contacting a UBA5 protein with an effective amount of a compound having the formula:

\[ \text{(I),} \]

wherein,

\[ \text{R}^1 \text{ is independently halogen, -CX}^\land, \text{-CHX}^\land, \text{-CH2X}^\land, \text{-OCX}^\land, - \]

\[ \text{OCH2X}^\land, \text{-OCHX}^\land, \text{-CN, } \text{-SO}_{\text{i}}\text{NR}^{\text{A}}\text{R}^{\text{B}}, \text{-NHC(O)(0)NR}^{\text{A}}\text{R}^{\text{B}}, \text{-N(O)}_{\text{i}}\text{iNR}^{\text{A}}\text{R}^{\text{B}}, \]

\[ \text{-C(O)R}^{\text{IC}}, \text{-C(O)NR}^{\text{IC}}, \text{-C(O)NR}^{\text{A}}\text{R}^{\text{IB}}, \text{-OR}^{\text{IA}}, \text{-NR}^{\text{A}}\text{SO}_{\text{2}}\text{R}^{\text{ID}}, \text{-NR}^{\text{A}}\text{C(0)R}^{\text{IC}}, \text{-NR}^{\text{A}}\text{C(0)0} \]

\[ \text{R}^{\text{IC}}, \text{-NR}^{\text{A}}\text{R}^{\text{IC}}, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted unsubstituted heteroaryl;} \]

\[ \text{z}^2 \text{ is an integer from 0 to 5;} \]

\[ \text{L}^1 \text{ is a bond, -S(O)}_{\text{2}}, \text{-NR}^{\text{4}}, \text{-O}, \text{-S}, \text{-C(O)}, \text{-C(O)NR}^{\text{4}}, \text{-NR}^{\text{4}}\text{C(0)}, \]

\[ \text{-NR}^{\text{4}}\text{C(0)NH}, \text{-NHC(O)NR}^{\text{4}}, \text{-C(O)0}, \text{-OC(O)}, \text{-CH2NR}^{\text{4}}, \text{substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkyl ene, substituted or unsubstituted cycloalkyl ene, substituted or unsubstituted heterocycloalkyl ene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;} \]

\[ \text{R}^{\text{4}} \text{ is hydrogen, -CX}^\land, \text{-CHX}^\land, \text{-CH2X}^\land, \text{-OCX}^\land, \text{-OCH2X}^\land, \]

\[ \text{-OCHX}^\land, \text{-CN, } \text{-C(O)R}^{\text{4C}}, \text{-C(O)OR}^{\text{4C}}, \text{-C(O)NR}^{\text{4A}}\text{R}^{\text{IB}}, \text{-OR}^{\text{ID}}, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted unsubstituted heteroaryl;} \]

\[ \text{L}^2 \text{ is a bond, -S(O)}_{\text{2}}, \text{-NR}^{\text{5}}, \text{-O}, \text{-S}, \text{-C(O)}, \text{-C(O)NR}^{\text{5}}, \text{-NR}^{\text{5}}\text{C(0)}, \]

\[ \text{-NR}^{\text{5}}\text{C(0)NH}, \text{-NHC(O)NR}^{\text{5}}, \text{-C(O)0}, \text{-OC(O)}, \text{-CH2NR}^{\text{5}}, \text{substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkyl ene, substituted or unsubstituted heteroarylene;} \]
cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted
arylene, or substituted or unsubstituted heteroarylene;

\[ R^5 \text{ is hydrogen, } -\text{CX}^3, -\text{CHX}_2^5, -\text{CH}_2\text{X}_5, -\text{OCX}^5_3, - \]

OCH\(_2\)X\(_5\), -OCHX\(_2\), -CN, -C(0)R \(^5\text{C}\), -C(0)-OR \(^5\text{C}\), -C(0)NR \(^5\text{A}\)R\(^5\text{B}\), -OR \(^5\text{D}\), substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

Each R\(^{1\text{A}}\), R\(^{1\text{B}}\), R\(^{1\text{C}}\), R\(^{1\text{D}}\), R\(^{4\text{A}}\), R\(^{4\text{B}}\), R\(^{4\text{C}}\), R\(^{4\text{D}}\), R\(^{5\text{A}}\), R\(^{5\text{B}}\), R\(^{5\text{C}}\), and R\(^{5\text{D}}\) is
independently hydrogen, -CX\(_3\), -CN, -COOH, -CONH\(_2\), -CHX\(_2\), -CH\(_2\)X, substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl; R\(^{1\text{A}}\) and R\(^{1\text{B}}\) substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; R\(^{4\text{A}}\) and R\(^{4\text{B}}\) substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; R\(^{5\text{A}}\) and R\(^{5\text{B}}\) substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl;

each X, X\(^1\), X\(^4\), and X\(^5\) is independently -F, -Cl, -Br, or -I;

n\(_1\), n\(_4\), and n\(_5\) are independently an integer from 0 to 4; and

m\(_1\), m\(_4\), m\(_5\), v\(_1\), v\(_4\), and v\(_5\) are independently an integer from 1 to 2.

43. The method of claim 42, wherein the compound is covalently bonded
to the amino acid corresponding to C250 of SEQ ID NO:337.

44. The method of claim 42, wherein the compound contacts one or more
amino acids corresponding to N210, E209, L254, S253, and A251 of SEQ ID NO:337.

45. A UBA5 protein covalently bonded to a compound having the formula:

![Formula Image](I)

wherein,
R\(^1\) is independently halogen, -CX^\(^1\), -CHX^\(^1\), -CH2X^\(^1\), -OCX^\(^1\), -
OCHX^\(^1\), -OCH2X^\(^1\), -CN, -SONiR^\(1D\), -SO_iNR^\(1A\)R^\(1B\), -NHC(0)NR\(^1\)A\(^1\)R\(^1\)B\(^1\), -N(0)_\(1_m\)i, -NR\(^1\)A\(^1\)R\(^1\)B\(^1\),
-C(0)R\(^1\)C, -C(0)-OR\(^1\)C, -C(0)NR\(^1\)A\(^1\)R\(^1\)B\(^1\), -OR\(^1\)D, -NR\(^1\)A\(^1\)S0\(^2\)R\(^1\)D, -NR\(^1\)A\(^1\)C(0)R\(^1\)C, -NR\(^1\)A\(^1\)C(0)0
R\(^1\)C, -NR\(^1\)A\(^1\)0\(^1\)C, substituted 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;

z\(1\) is an integer from 0 to 5;

L\(^1\) is a bond, -S(0)\(_2\), -NR\(^4\), -O-, -S-, -C(O)-, -C(0)NR\(^4\), -NR\(^4\)C(0)-,
-NR\(^4\)C(0)NH-, -NHC(0)NR\(^4\), -C(0)0-, -OC(O)-, -CH2NR\(^4\), substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkyl ene, substituted or unsubstituted
cycloalkyl ene, substituted or unsubstituted heterocycloalkyl ene, substituted or unsubstituted
arylene, or substituted or unsubstituted heteroarylene;

R\(^4\) is hydrogen, -CX\(^4\), -CHX\(^4\), -CH2X\(^4\), -OCX\(^4\), -OCH2X\(^4\),
-OCHX\(^4\), -CN, -C(0)R\(^4\)C, -C(0)-OR\(^4\)C, -C(0)NR\(^4\)R\(^4\)B, -OR\(^4\)D, substituted or unsubstituted
alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
or unsubstituted heteroaryl;

L\(^2\) is a bond, -S(0)\(_2\), -NR\(^5\), -O-, -S-, -C(O)-, -C(0)NR\(^5\), -NR\(^5\)C(0)-,
-NR\(^5\)C(0)NH-, -NHC(0)NR\(^5\), -C(0)0-, -OC(O)-, -CH2NR\(^5\), substituted or unsubstituted
alkylene, substituted or unsubstituted heteroalkyl ene, substituted or unsubstituted
cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted
arylene, or substituted or unsubstituted heteroarylene;

R\(^5\) is hydrogen, -CX\(^5\), -CHX\(^5\), -CH2X\(^5\), -OCX\(^5\), -
OCH2X\(^5\), -OCHX\(^5\), -CN, -C(0)R\(^5\)C, -C(0)-OR\(^5\)C, -C(0)NR\(^5\)R\(^5\)B, -OR\(^5\)D, substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl;

E is an electrophilic moiety;

Each R\(^1\)A, R\(^1\)B, R\(^1\)C, R\(^1\)D, R\(^4\)A, R\(^4\)B, R\(^4\)C, R\(^4\)D, R\(^5\)A, R\(^5\)B, R\(^5\)C, and R\(^5\)D is
independently hydrogen, -CX\(^3\), -CN, -COOH, -CONH2, -CHX\(^2\), -CH2X, substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heteroaryl; \( R^{1A} \) and \( R^{1B} \) substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; \( R^{4A} \) and \( R^{4B} \) substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl; \( R^{5A} \) and \( R^{5B} \) substituents bonded to the same nitrogen
atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
substituted or unsubstituted heteroaryl;

\[
\begin{align*}
X, X^1, X^4, \text{and } X^5 \text{ is independently } &-F, \quad -Cl, \quad -Br, \text{ or } -I; \\
n, n^4, \text{and } n^5 \text{ are independently an integer from } 0 &\text{ to } 4; \text{ and} \\
m, m^4, m^5, v, v^4, \text{and } v^5 \text{ are independently an integer from } 1 &\text{ to } 2; \\
\text{wherein the UBA5 protein is covalently bonded to the compound through the} \\
\text{reacted residue of said electrophilic moiety.}
\end{align*}
\]

46. The UBA5 protein of claim 45, wherein the compound is bonded to a
cysteine residue of the protein.

47. The UBA5 protein of claim 45, irreversibly covalently bonded to the
compound.

48. The UBA5 protein of claim 45, wherein the compound is covalently
bonded to an amino acid corresponding to C250 of SEQ ID NO:337.
FIG. 1A

cysteine-reactive fragment libraries

chemical genetics

plated cells

add targeted reactive libraries

screen for anti-cancer phenotypes

lead identification
FIG. 1A - cont'd.

1. mix
2. avidin enrichment
3. tryptic digestion
4. TEV digestion

protein 1: YWKDAC*SHR
protein 2: SYC*WHIL

light/heavy: 1
inhibited
not inhibited

Target identification of lead fragments
FIG. 1B

Survival screen in PaCa2 pancreatic cancer cells

FIG. 1C

Counterscreen in human pancreatic ductal epithelial (HPDE) cells

FIG. 1D

Leads

\[
\begin{align*}
\text{DKM 2-67} \\
\text{DKM 2-83} \\
\text{DKM 2-93}
\end{align*}
\]
FIG. 2A

DKM 2-93 anti-survival effects in pancreatic cancer cells
PaCa2 cells

FIG. 2B

DKM 2-93 anti-tumorigenic effects in PaCa2 cells

- control
- DKM 2-93 (50 mg/kg ip)
FIG. 2C

isoTOP-ABPP analysis of DKM 2-93 in PaCa2 pancreatic cancer cell proteomes

FIG. 2D

DKM 2-93 inhibits UBA5 activity

<table>
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<tr>
<th>DKM 2-93 (mM)</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>3</th>
<th>1</th>
<th>0.3</th>
<th>0.1</th>
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<td>UBA5-UFM1&gt;</td>
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</tr>
</tbody>
</table>
FIG. 2E

UBA5 knockdown impairs PaCa2 cell survival

UBA5 expression

survival

FIG. 2F

isoTOP-ABPP analysis of cysteine-reactivity in primary human pancreatic tumors
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/016649

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61 K 31/275; A61 K 31/277; A61 P 35/00; C07C 255/23; C07C 255/31; C07C 317/32 (2018.01)
CPC - A61 K 31/275; A61 K 31/277; A61 P 35/00; C07C 255/23; C07C 255/31; C07C 317/32; C07C 317/40; C07C 323/41; C07D 213/75; C07D 317/40; C07D 317/58 (2018.05)

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/482; 514/519; 514/19.2; 514/19.3 (keyword delimited)

Electronic data base consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US 5,312,830 A (KUO) 17 May 1994 (17.05.1994) entire document</td>
<td>1, 12, 13, 29-32, 34, 36-48</td>
</tr>
<tr>
<td>A</td>
<td>US 2017/0029373 A1 (NANYANG TECHNOLOGICAL UNIVERSITY) 02 February 2017 (02.02.2017) entire document</td>
<td>1, 12, 13, 29-32, 34, 36-48</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

"A" Special categories of cited documents:
"X" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"T" document referring to an oral disclosure, use, exhibition or other means
"Y" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
23 May 2018

Date of mailing of the international search report
11 JUN 2018

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Facsimile No. 571-273-8300

Authorized officer
Blaine R. Copenhaver
PCT Hipdork: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/2 16 (second sheet) (January 2015)
**INTERNATIONAL SEARCH REPORT**

<table>
<thead>
<tr>
<th>Box No. 1</th>
<th>Nucleotide and/or amino acid sequence(s) (Continuation of item l.c. of the first sheet)</th>
</tr>
</thead>
</table>

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ☒ forming part of the international application as filed:
      - ☒ in the form of an Annex C/ST.2.5 text file.
      - ☑ on paper or in the form of an image file.
   b. ☑ furnished together with the international application under PCT Rule 13(1)(a) for the purposes of international search only in the form of an Annex C/ST.2.5 text file.
   c. ☑ furnished subsequent to the international filing date for the purposes of international search only:
      - ☑ in the form of an Annex C/ST.2.5 text file (Rule 33er. 1(a)).
      - ☑ on paper or in the form of an image file (Rule 33er. 1(b) and Administrative Instructions, Section 7.13).

2. ☑ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:
   SEQ ID NO: 337 was searched.

Form PCT/ISA/2 10 (continuation of first sheet (1)) (January 2015)
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/016649

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

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

1. □ Claims Nos.:
   because they relate to subject matter not required to be searched by the Authority, namely:

2. □ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

See extra sheet(s).

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
   1, 12, 13, 29-32, 34, and 36-48 to the extent that they read on N-(4-phenoxyphenyl)prop-2-enamide.

Remark on Protest
□ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
□ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
□ No protest accompanied the payment of additional search fees.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US201 8/01 6649

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

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

Group l+: claims 1-48 are drawn to compounds of Formula (I), compositions and methods comprising the same.

The first invention of Group l+ is restricted to a compound of Formula (I), compositions and methods comprising the same, wherein the
compound of Formula (I) is selected to be N-(4-phenoxyphenyl)prop-2-enamide (first structure in instant claim 34). It is believed that
claims 1, 12, 13, 29-32, 34, and 36-48 read on this first named invention and thus these claims will be searched without fee to the extent
that they read on N-(4-phenoxyphenyl)prop-2-enamide.

Applicant is invited to elect additional compounds of Formula (I), each with specified chemical structure, to be searched in a specific
combination by paying an additional fee for each set of election. A n exemplary election would be a compound of Formula (I),
compositions and methods comprising the same, wherein the compound of Formula (I) is selected to be
2-chloro-N-(2,3-dihydro-1,4-benzodioxin-6-yl)acetamide.
Additional compounds of Formula (I) will be searched upon the payment of
additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if
applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly
identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be
searched/examined.

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

The Groups l+ formulas do not share a significant structural element for treating cancer, requiring the selection of alternatives for the
chemical structure of the ubiquitin-like modifier 2 activating enzyme 5 (UBA5) inhibitor, where "the ubiquitin-like modifier activating
enzyme 5 (UBA5) inhibitor has the formula (I), wherein R 1 is independently halogen, -C(X1 )3, -CH(X1)2, -CH2X1 , -OC(X1)3, -OCH2X1 ,
-OCH(X1)2, -CN, -SOn1 R1D, -SOv1NR1AR1B, -NHC(0)NR1AR1B, -N(0)m1 , -NR1AR1B, -C(0)R1C, -C(0)-OR1C, -C(0)NR1AR1B,
-OR1D, -NR1AS02R1D, -NR1AC(0)R1C, -NR1AC(0)OR1C, -NR1AOR1C, substituted 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; z 1 is an integer from 0 to 5; L 1 is a bond, -S(0)2-, -NR4-, -0-, -S-, -C(O)-, -C(0)NR4-, -NR4C(0)-, -NR4C(0)NH-, -NHC(O)
NR4-, -C(0)0-, -OC(O)-, -CH2NR4-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or
unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or
unsubstituted heteroaryl; R4 is hydrogen, -C(X4)3, -CH(X4)2, -CH2X4, -OC(X4)3, -OCH2X4, -OCH(X4)2, -CN, -C(0)R4C, -C(0)-OR4C,
-C(0)NR4AR4B, -OR4D, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; L2
is a bond, -S(0)2-, -NR5-, -0-, -S-, -C(O)-, -C(0)NR5-, -NR5C(0)-, -NR5C(0)NH-, -NHC(0)NR5-, -C(0)0-, -OC(O)-, -CH2NR5-,
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 hydrogen,
-C(X5)3, -CH(X5)2, -CH2X5, -OC(X5)3, -OCH2X5, -OCH(X5)2, -CN, -C(0)R5C, -C(0)-OR5C, -C(0)NR5AR5B, -OR5D, substituted or
unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; E is an electrophilic moiety; Each R1A,
R1B, R1C, R1D, R4A, R4B, R4C, R4D, R5A, R5B, R5C, and R5D is independently hydrogen, ...or substituted or unsubstituted
heteroaryl; R1A and R1B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted
heterocycloalkyl or substituted or unsubstituted heteroaryl; R4A and R4B substituents bonded to the same nitrogen atom may optionally
be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R5A and R5B substituents
bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
unsubstituted heteroaryl; each X , X 1 , X4, and X5 is independently -F, -CI, -Br, or -I; n 1 , n4, and n5 are independently an integer from 0
to 4 ; and m 1, m4, m5, v 1 , v4, and v5 are independently an integer from 1 to 2".
Additionally, even if Groups l+ were considered to share the technical features of a method of treating cancer; use of a compound for the
preparation of a medicament for the treatment of cancer; a pharmaceutical composition comprising a UBA5 inhibitor; a method of
inhibiting UBA5 activity; and a UBA5 protein covalently bonded to a UBA5 inhibitor; said methods and compositions comprising a UBA5
inhibitor formula (I), wherein R 1 is independently halogen, -C(X1 )3, -CH(X1 )2, -CH2X1, -OC(X1)3, -OCH2X1 , -OCH(X1)2, -CN,
-SOMR1D, -SOV1NR1AR1B, -NHC(0)NR1AR1 B, -N(0)m1 , -NR1AR1B, -C(0)R1C, -C(0)-OR1C, -C(0)NR1AR1B, -OR1 D,
-NR1AS02R1D, -NR1AC(0)R1C, -NR1AC(0)OR1C, -NR1AOR1C, substituted or unsubstituted alkyl, substituted or unsubstituted
heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
substituted or unsubstituted heternaryl; 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; z 1 is
an
frnm Π tn 5 I 1 is a hnn . -S(0)2-. -NR4-. -0-. -S-. -C(
-C(0)NR4-, -NR4C(0)-, -NR4C(0)NH-, -NHC(0)NR4-, -C(0)0-,
-OC(O)-, -CH2NR4-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted
heteroaryl; R4 is hydrogen, -C(X4)3, -CH(X4)2, -CH2X4, -OC(X4)3, -OCH2X4, -OCH(X4)2, -CN, -C(0)R4C, -C(0)-OR4C, -C(O)
NR4AR4B, -OR4D, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; L2 is a bond,
-S(0)2-, -NR5-, -0-, -S-, -C(O)-, -C(0)NR5-, -NR5C(0)-, -NR5C(0)NH-, -NHC(0)NR5-, -C(0)0-, -OC(O)-, -CH2NR5-, substituted or

Form PCT/ISA/2 10 (extra sheet) (January 20 15)


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 hydrogen, -C(X)53, -CH(X)52, -CH2X5, -OC(X)53, -OCH2X5, -OCH(X)52, -CN, -C(0)RSC, -C(0)ORSC, -C(0)NR5ARB, -OR5D, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; E is an electrophilic moiety; Each R1A, R1B, R1C, R1D, R4A, R4B, R4C, R4D, R5A, RSB, RSC, and R5D is independently hydrogen, ...or substituted or unsubstituted heteroaryl; R1A and R1B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroarylene; R4A and R4B substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroarylene; R5A and RSB substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroarylene; each X, X1, X4, and X5 is independently -F, -Cl, -Br, or -I; n1, n4, and n5 are independently an integer from 0 to 4; and mL, m4, m5, n1, v1, v4, and v5 are independently an integer from 1 to 2. These shared technical features do not represent a contribution over the prior art.

Specifically, WO 2015/1 79953 A1 to The Governing Council of the University of Toronto discloses a method of treating cancer (a method of treating or preventing a disease or condition mediated by the UBAS enzyme, Para. [0091]); the compounds of the Formula (I) are useful for treating or preventing conditions of a condition or disease mediated by the UBAS enzyme. ...the condition or disease is cancer, Para. [0010]), said method comprising administering to a subject in need thereof an effective amount of a compound having a formula (administering a pharmaceutically effective amount of a compound of the Formula (I) ...to a subject in need thereof, Para. [0091]); the use of a compound for the preparation of a medicament for the treatment of cancer (methods for the preparation of pharmaceutically acceptable compositions which can be administered to subjects, Para. [0068]); a method of treating or preventing a disease or condition mediated by the UBAS enzyme, Para. [0091]); a pharmaceutical composition comprising a UBAS inhibitor and a pharmaceutically acceptable excipient (the present disclosure also includes pharmaceutical compositions comprising compounds of the Formula (I) and pharmaceutically acceptable excipients, carriers and/or additives, Para. [0099]); a method of inhibiting UBAS activity (a method of treating or preventing a disease or condition mediated by the UBAS enzyme, Para. [0091]); the compounds of the Formula (I) are useful for treating or preventing conditions of a condition or disease mediated by the UBAS enzyme. Para. [0010]), said method comprising contacting a UBAS protein with an effective amount of a UBAS inhibitor (administering a pharmaceutically effective amount of a compound of the Formula (I) ...to a subject in need thereof, Para. [0091]), wherein the UBAS inhibitor contacts one or more amino acids UBAS (1.5.Zn is proposed to bind to the nucleotide binding pocket, as well as an electropositive zinc (II) coordination complex bound to electronegative residues on UBAS, Para. [00129]); a UBAS protein covalently bonded to a UBAS inhibitor ([complex] 1.5.Zn is proposed to bind to the nucleotide binding pocket, as well as an electropositive zinc (II) coordination complex bound to electronegative residues on UBAS... compound 1.5.Zn to inhibit UBAS and block subsequent UB 1 transfer to its E2, Para. [00129] and Fig. 3B).

Further, US 2017/0029373 A1 to Nanyang Technological University discloses a compound of instant formula (I), where z1 is 0; L1 is -CH2NR4; R4 is H; L2 is a bond; and E is buta-2,3-dierioyl (N-benzylbuta-2,3-dienamide, see first compound (a) shown in Para. [0069]), wherein the compound reacts with cysteine amino acid residues on polypeptides (there is provided a use of a compound of formula I as an irreversible binder to a free thiol group, Para. [0039]); selective modification of cysteine residue in proteins, Para. [0010]; and Fig. 1).

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